Communicating post-market safety risks of medicines with regulatory safety advisories: an international comparison of policy and perceptions

Alice Bhasale

A thesis submitted in fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Charles Perkins Centre

School of Pharmacy, Faculty of Medicine and Health

University of Sydney

2021

Candidate's declaration

I, Alice Bhasale, hereby declare that the work described in this thesis is my own. I am the principal researcher of all work contained in this thesis, including work conducted in association with my PhD supervisor and other co-authors. This thesis does not contain written or published materials prepared by others except where acknowledged within the text and has not been submitted to any other university or institution as a part or whole requirement for any higher degree.

I, Alice Bhasale, understand that if I am awarded a higher degree for my thesis entitled '*Communicating Post-Market Safety Risks of Medicines Using Regulatory Safety Advisories: An International Comparison of Policy and Perceptions'*, being lodged for examination, the thesis will be lodged in the University Library and be available immediately for use. I agree that the University Librarian (or in the case of a department, the Head of Department) may supply a photocopy or microform of the thesis to an individual for research or study or to a library.

Alice Bhasale Date: 12 April 2021

Contributions and publications

This dissertation includes two published manuscripts and two submitted manuscripts.

Chapter 2 includes the publication:

1. Bhasale AL, Sarpatwari A, De Bruin ML, Lexchin J, Lopert R, Bahri P, and Mintzes BJ. Postmarket safety communication for protection of public health: A comparison of regulatory policy in Australia, Canada, the European Union, and the United States. Clinical Pharmacology and Therapeutics 2020. doi: 10.1002/cpt.2010

I developed the analysis framework, abstracted the data, analysed the findings, prepared the figures/tables, and wrote the drafts of the manuscript.

Chapter 3: includes the publication:

2. Bhasale A, Mintzes B, and Sarpatwari A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. BMJ 369: m1107, 2020. doi: 10.1136/bmj.m1107

I developed the analysis framework, abstracted the data, analysed the findings, prepared the figures/tables, and wrote the drafts of the manuscript.

Chapter 4: includes the submitted publication:

Bhasale A.L., Perry L., McEwin E. J., Mohammad A., Hooimeyer A., Huisman A., Mintzes B.J. Post-market safety communication for new drugs approved in Australia, 2010-2016. Unpublished manuscript (2021)

Submitted to British Journal of Clinical Pharmacology 27 March 2021

I designed the coding instrument with co-authors, trained coders and coded some of the data, analysed the data using SPSS, prepared the figures/tables, and wrote the drafts of the manuscript.

Chapter 5: includes the publication:

3. Bhasale A.L., Sarpatwari A, Lipworth W, Mollebaek M, McEwin E. J., Gautam N, Santiago O.A., Mintzes B.J. Regulatory authority and clinical acceptability: Physicians' responses to regulatory drug safety warnings. Unpublished manuscript (2021)

   Accepted by British Journal of Clinical Pharmacology 17 July 2021

I designed the interview questionnaire, conducted 20/40 interviews, developed the coding framework and conducted the analysis using NVivo software in consultation with co-authors, prepared the figures/tables, and wrote the drafts of the manuscript.

Appendix 1

Includes additional publications on which I was co-author related to this research including:

- Torka M, Mintzes B, Bhasale A, Fabbri A, Perry L, and Lexchin J. Secret safety warnings on medicines: A case study of information access requests. Pharmacoepidemiology and Drug Safety 28: 551-555, 2019.
- Perry LT, Bhasale A, Fabbri A, Lexchin J, Puil L, Joarder M, and Mintzes B. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. JAMA Intern Med 179: 982-984, 2019.

- Perry LT, Bhasale A, Fabbri A, Lexchin J, Puil L, Joarder M, and Mintzes B. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. Pharmacoepidemiology and Drug Safety 29: 1054-1063, 2020.
- Hooimeyer A, Bhasale A, Perry L, Fabbri A, Mohammad A, McEwin E, and Mintzes B. Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. Pharmacology Research & Perspectives 8: e00680, 2020.

I participated in database design, development of coding instrument and specifications, training of coders, coding and reviewed and commented on draft manuscripts. (For further details see Appendix 1)

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Supervisor Name: Barbara Mintzes

Date: 12 April 2021

Acknowledgements

Writing this thesis has taken me to many new places, both physically and mentally. It has introduced me to some truly wonderful people whom I would never otherwise have met, who have all played a part in achieving completion. Biggest thanks go to my supervisor, Associate Professor Barbara Mintzes who is an inspiration for her intelligence, commitment and incredible clear-sightedness. Thank you Barbara, for your constant support and excellent advice. I have never met anyone who can see to the crux of something as quickly as you can and then articulate it beautifully as well. You have guided me brilliantly and made me try things I never would have thought possible. Also thanks to Professor Joel Lexchin for sharing his enormous wisdom. Joel - you have been so generous in so many ways from day one. As I have written and rewritten my thesis I have realised how effortless you make it look to write about policy. Through a travelling scholarship to Boston I was fortunate to meet Assistant Professor Ameet Sarpatwari, who has been a supportive and thoughtful mentor ever since.

I also thank my employer, the Australian Commission on Safety and Quality in Health Care, and colleagues there for supporting me to pursue my research.

To my fellow EMCRs and co-researchers at the Charles Perkins Centre – Annim, Eliza, Alice F, Sally, Kellia, Jeff, Lisa - thanks for making it such a fun, pleasant and highly principled place to be. It was such a privilege to be with you all under the amazing guidance of Professor Lisa Bero.

Inevitably, this thesis has also taken me away, temporarily, from some of the people I love, firstly my dear parents. Thank you, Mum and Dad, for your constant patience and support for me, your encouragement of the pursuit of higher learning and everything else. I know you have both made so many sacrifices for me in my life but especially recently. I am so fortunate to have such intelligent and loving parents and siblings.

To the other dear people in my life who have kept me sane and alive – thank you! Special thanks to my special son Yogesh who has fed me and put up with me, to my dearest friend Elizabeth, for your constant encouragement, cups of tea and praise for every tiny step forward, and to my sister Esther for always being there to help me get through.

For everyone else I haven't named but who has asked me over the last four years 'how's the PhD going?' – I thank you all. And if you are still not quite sure I have been doing and what my thesis is about – here it is!

Abstract

Background and objectives

When medicines are first approved for marketing, knowledge of their safety outcomes is generally incomplete and new evidence of less frequent, serious harms often only comes to light in the post-market period. In response, regulators use post-market safety communications (safety advisories) to advise prescribers and the public about emerging potential harms, often in addition to other measures. These advisories can influence medicines use by helping users to weigh benefits and harms, particularly for new drugs for which early information may be skewed in a positive direction.

Despite the global nature of the pharmaceutical industry and harmonisation in many aspects of regulation, inconsistencies have been identified in regulators' safety communication within product information as well as in safety advisories. Between 2007 and 2016, the United Kingdom's (UK) Medicines and Healthcare products Regulatory Agency (MHRA) issued almost twice as many safety advisories as Australia's Therapeutic Goods Association (TGA), suggesting differences in both policy and practice.[1] Even when advisories are used, the evidence that they change clinical practice is mixed, raising questions about how they are used by prescribers.

This thesis aims to improve understanding of the differences amongst jurisdictions in regulatory policy for post-market safety communication, related differences in the use of advisories for newly approved medicines, and the impact of such communications on medical prescribers. To do this, I examined both policy and outcomes for post-market safety advisories in four jurisdictions – Australia, Canada, the United Kingdom (UK) (formerly part of the European Union) and the United States (US).

Methods

The methods included:

- A regulatory policy analysis comparing publicly available policy documents and legislation for post-market safety communication in four jurisdictions, using an analytical framework that included legislative authority, risk communication capacity and transparency.
- An in-depth case study of regulatory documents associated with post-market safety actions and communications for SGLT2 inhibitors in four jurisdictions, starting from the first approved medicine in the class in any included country in 2012, until June 2018.
- A content analysis of safety advisories issued for the cohort of all new drugs approved in Australia between 2010 and 2016, using a coding instrument to compare the frequency, characteristics, communication features and timing of Australian advisories with those of the other included regulators.
- A cross-country qualitative interview study examining prescribers' awareness and use of medicines safety information, in Boston US and Australia, with a focus on their interpretation and response to safety warnings on SGLT-2 inhibitors.

Results

I identified differences in regulatory policy among the included regulators, particularly in terms of their authority to issue advisories, the role of the pharmaceutical industry in post-market safety communication and regulators' legislated transparency requirements. Differences evident in the policy analysis partially explained and were expanded further by the case study of SGLT2 inhibitors and the comparison of Australian and other regulators' new drugs advisories. The use of safety advisories varied considerably between regulators, with Australia issuing fewer advisories than other regulators, often much later. In the case study of SGLT2 safety communications, the TGA and the EMA each issued two of the five advisories issued by the FDA. This case study also revealed the extent to which industry

attempts to negotiate with regulators regarding safety messages, and suggests that smaller regulators, such as Canada and Australia, may rely on their larger counterparts (US and EU) to identify and determine responses to safety issues.

Of 173 new drugs approved in Australia between 2010 and 2016, there were 51 drugs with an advisory from any of the four included regulators, with Australian advisories issued for less than a quarter of the 73 safety concerns (20.5%) communicated. These differences in the decision to issue a warning were not clearly explained by differences in the seriousness of safety concerns, drug group or the significance of regulatory changes to product information, but may be partially explained by Australian prescribers' lesser awareness of the TGA role in communicating post-market safety concerns.

The qualitative interview study found that prescribers' awareness of regulatory safety advisories varied considerably and although regulators were a trusted source of information, doctors may not find their communications readily accessible. Further, doctors perceived regulators to lack clinical authority despite respect for their role as an institutional authority. Awareness of the regulator's role in post-market safety communication was stronger amongst US doctors for the FDA, than with Australian doctors for the TGA. Prescribers sometime hesitated to communicate serious rare harms to patients, which may further limit the impact of advisories.

Conclusions

Post-market safety advisories policy and outcomes differ considerably between jurisdictions. Clear legislated responsibilities appear to result in regulatory organisational structures and processes to support those priorities in the EU and to a lesser degree in the US. Public participation and transparency of regulatory decision making are limited in most jurisdictions apart from the EU, while industry has a major role in providing post-market safety data and participates to some extent in writing and disseminating safety advisories, particularly in the

EU and Canada. US FDA policy reflects its mandate for protecting public health, with most safety advisories issued directly by the regulator, while the TGA does not control or provide industry communications. Findings about the lower frequency of TGA advisories, their timeliness and their lack of specificity, coupled with prescribers limited awareness of TGA as a post-market safety arbiter, suggest Australian consumers and prescribers may need to look beyond the Australian regulator to maintain awareness of emerging safety issues.

Table of Contents

List of Tables and Figures

The tables and figures from published papers do not contain chapter numbers; for ease of reference I have listed them in their respective chapters.

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Acronyms and abbreviations

AU	Australia
ACM	Australian Committee on Medicines
AUSPAR	Australian Product Assessment Report
BMD	Bone mineral density
CA	Canada
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures-Human
DAEN	Database of Adverse Event Notifications
DHPC	Direct Healthcare Professional Communication
DKA	Diabetic ketoacidosis
DPP-4 inhibitors	Dipeptidyl peptidase-4 inhibitors
EMA	European Medicines Agency
EPAR	European Product Assessment Report
EU	European Union
EEC	European Economic Community
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
MHRA	Medicines and Healthcare products Regulatory Authority
PRAC	Pharmacovigilance Risk Assessment Committee

REDCap	Research Electronic Data Capture
PSUR	Periodic Safety Update Report
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk management plan
SAFER	Safety Advisories For Effective Risk communication
SGLT2-inhibitor	sodium glucose co-transporter 2- inhibitor
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States

Chapter 1 Introduction

1.1 Synopsis

When medicines are first approved for marketing there is limited information available about their full range of safety outcomes, due to the limited nature of patient exposure in pre-market trials. Post-market safety advisories are used by medicines regulators to alert prescribers and the public to new safety concerns that emerge after approval. Effectively used, they may reduce patient exposure to serious potential harms and enable informed decisions by prescribers and consumers.[1] While international comparisons have identified inconsistencies in the ways that safety information is communicated in product information,[2-4] there has been less scrutiny of differences in the use of post-market safety advisories, and very little analysis of Australia's regulator, the Therapeutic Goods Administration (TGA).

Limited evidence demonstrates that regulators differ considerably in their use of safety advisories to communicate specific safety concerns. [5-8] Whether this relates to policy differences has not been systematically examined. Further while the goal of communication is to influence prescribers' knowledge, awareness and behaviour, the perceptions of safety information amongst prescribers has been less well studied, especially in Australia where no relevant study was identified.

This dissertation aims to identify differences in policy for post-market safety communication in four discrete projects – a comparative analysis of regulatory policy and legislation; a case study analysis of the use and content of safety advisories and transparency of decision making for new warnings about a class of oral hypoglycemics, the sodium glucose co-transporter 2s (SGLT2s); a content analysis comparing the use and content of safety advisories for new drugs approved in Australia between 2010 and 2016; and a qualitative study of prescribers' awareness and perceptions of post-market safety information including advisories.

1.2 Background

1.2.1 Context for this research

The research described in this dissertation was conducted as part of a broader research project known as the *Safety Advisories For Effective Risk communication* (SAFER) project, which was funded by the Australian Government National Health and Medical Research Council (NHMRC) and the Canadian Institutes of Health Research. The SAFER project is a large multi-methods international comparative study investigating the use of safety advisories by Australia's Therapeutic Goods Administration (TGA), Health Canada, the United States (US) Food and Drug Administration (FDA) and in Europe by the European Medicines Agency (EMA) and the United Kingdom's Medicines and Healthcare products Regulatory Authority (MHRA). A key aspect of this research involved compiling a database of safety advisories (the SAFER database), containing all advisories issued between 1 January 2007 and 31 December 2016, which met the study definition of a safety advisory and were available on the included regulators' websites. The author made a significant contribution towards the development of the SAFER database, which was then used directly or indirectly for 3 of the 4 studies described in this dissertation, and co-ordinated working groups on regulatory policy and qualitative research as part of the project. The studies described in this dissertation, and the co-authored studies cited in the background below, were amongst the key research outputs of the SAFER project.[6,7,9]

1.2.2 Post-market safety advisories

Communication of information about potential harms is vital to the safe use of medicines and is particularly critical when new safety concerns emerge post-market. Medicines regulators, with their mandate over medicines licensing, have a unique role in ensuring public access to such information. They are often the first to obtain the information from manufacturers about newly identified potential harms due to legislated reporting requirements. [10,11] This means

they are privy to much more comprehensive information than is available in published medical research. When post-market safety concerns are identified, regulators use various methods to communicate these safety issues to prescribers and the public so they can take any action necessary to avoid harm.

1.2.2.1 Definitions and terminology

For the purpose of this dissertation, the following definitions and terminology are used.

1.2.2.1.1 Safety advisories

Post-market safety advisories are defined as:

Risk communications issued to the public (prescribers and/or consumers) by the regulator (or by a pharmaceutical company when required by the regulator), about evidence of a possible or confirmed safety concern or a change in the risk-benefit profile, for a medicine that has received marketing approval.

This definition of safety advisories includes website notices and email alerts, direct healthcare professional communications (DHPCs) – letters issued directly to prescribers, often by industry with regulatory oversight, regulatory drug safety bulletins, and public announcements or media releases. Advisories communicating product quality issues and errors in administration or use were not included within the definition.

1.2.2.1.2 Product information

Throughout this document, the term ‘product information’ is used to refer to the prescribing information for a medicine which is approved by the regulator. Prescribing information is known in Australia as ‘Product information’, in Canada as the Product Monograph, in the EU as the ‘Summary of Product Characteristics’, and in the US as ‘Prescribing information’, or sometimes the ‘label’. While the term is used specifically to refer to the document prepared for a healthcare professional audience, it may be used to encompass general requirements

for information associated with the drug including equivalent consumer information and, in some cases, package inserts and labelling.

1.2.2.1.3 Direct Healthcare Professional Communications

The term direct healthcare professional communications (DHPCs) is used to refer to letters directly addressed to healthcare professionals. They are known in the EU as DHPCs, in the US as 'Dear Health Care Provider Letters' and in Canada as 'Dear Health Care Professional Letters'. Similar types of letters may address other audiences such as hospitals and pharmacies. DHPCs may be issued by either regulators or industry alone, but in a regulatory context are often issued by industry with the endorsement of the regulator.

1.2.3 Current and historical context for the use of advisories

The historical roots of medicines regulation lie firmly in drug safety, despite a later emphasis on efficacy. The identification of serious harms including deaths associated with the use of therapeutic agents have prompted most major changes in regulation. In 1938, deaths from elixir of sulfanilamide led to the first *US Food Drug and Cosmetic Act*, which required manufacturers to conduct tests proving a drug's safety. Formal drug approval for licensing was introduced in the US in 1962 with the Kefauver-Harris Amendments. This major change in regulation occurred after Americans narrowly escaped the birth deformities associated with thalidomide that occurred in other countries, largely through the actions of a single FDA regulator, Frances Kelsey, who resisted pressure to approve the drug without safety data. [12] Subsequently requirements for formal phase 1 to 3 trials for efficacy and safety were introduced to satisfy the legislation's requirement for "substantial evidence that the drug will have the effect it purports or is represented to have".[13,14] At the same time, thalidomide reinforced the importance of early reporting of adverse drug events, leading to formalised systems for adverse drug reporting and monitoring, with government, professional and international agencies such as the World Health Organization playing a key role.[15]

Although the science of drug safety monitoring continued to evolve throughout the 60's companies were only required to submit spontaneous adverse drug event reports to regulators, and regulators lacked authority in key areas of post-market safety including the ability to mandate post-market safety studies, or even in some countries to require changes to the product information.[16-18] It has been argued that a lack of post-market power may have contributed to an increasingly precautionary approach to new drug approval decisions by the FDA in the 1970s, which saw regulators accused of costing lives by delaying access to significant new therapeutics.[16] When the threat of AIDS emerged in the 1980s, pressure to rapidly approve new drugs increased and there was less emphasis on post-market safety until a series of crises in the early 2000's culminating in the safety-related withdrawal of rofecoxib, which led to more substantial changes in post-market regulation.[19]

After the withdrawal of rofecoxib, it emerged that delays in US and European regulators obtaining and acting on evidence of cardiovascular harm, along with commercial obfuscation may have contributed to the deaths of hundreds of thousands of people.[20,21] Amongst the resultant changes in regulation, regulatory authorities worldwide promised expanded regulation of industry in regard to post-market safety as well as improvements in regulatory transparency and post-market safety communication.[22,23]

A key change in regulation that subsequently evolved was the move to 'life-cycle regulation'. Life-cycle regulation is implemented differently according to the regulator, but its elements include:

- planning for post-market monitoring as part of the drug approval process
- 'risk management' strategies to mitigate against known safety issues where appropriate
- ongoing post-market monitoring or specific safety studies
- the ability to require information from industry about post-market safety concerns and impose additional actions
- ongoing amendments to the product information
- product suspension or cancellation of licensing.

Life-cycle regulation was originally proposed as a way to increase post-market safety controls.[24] However, lifecycle regulation also enables faster approvals of medicines with limited data,[i] with the premise being that safety can be more closely monitored post-market.[27,28] Whether this is a positive advance or a retrograde step has been argued differently according to perspective. Proponents argue that early access to potentially lifesaving medicines can be achieved with limited impact on safety. [29] Others argue that while the possibility of benefit might outweigh risks in people with few therapeutic alternatives, there is a risk of increasing permissiveness in drug approval, and 'leakage' of limited data approvals to more equivocal situations. [30] As life-cycle regulation accepts that post-market safety issues are inevitable but can be mitigated with monitoring and

[i] While there are specific Acts and Regulations pertaining to early approvals, conceptually they are enabled by a commitment to safety monitoring post-market which sometimes includes follow-up safety studies.

responsiveness, it follows that detection, communication and action on newly emerging concerns should be given equal priority to the approval of new drugs.

Post-market monitoring occurs in several ways. The mainstay of post-market monitoring continues to be voluntary spontaneous adverse event reports from individual health professionals and consumers, which industry are required to collect and report to regulators. Harm may also be detected through clinical trials carried out post-market, or through population-based pharmacoepidemiology research, often carried out after there has been a signal of potential harm either by industry or independent researchers.

As part of their risk management provisions, regulators may request or require industry to carry out additional post-market monitoring as a condition of approval, or when safety concerns emerge after approval. Post-market safety monitoring may take the form of enhanced reporting of specific types of adverse events or for certain drugs, or specific follow-up safety studies to clarify potential or recognised safety issues. The UK, Canada and Australia manage such requirements through the 'Risk Management Plan' which is developed at approval. The FDA does not have a formal risk management plan within legislation but has similar methods and controls, as discussed in Chapter 2.

In addition to monitoring, regulators may require specific risk minimisation strategies known as Risk Evaluation and Mitigation Strategies (REMS) in the US and as risk minimisation measures in Europe. These strategies are specified with the Risk Management Plan (RMP) in the EU and Australia. They may vary in intensity from educational materials to restricted prescribing programs. For example, the *iPledge* program in the US is intended to mitigate the teratogenicity of isotretinoin. It requires industry sponsors to institute training programs for prescribers, register users under a restricted prescribing program which includes compulsory pregnancy testing, and signed declaration of birth control as part of the patient consent.[31,32]

It has been argued that recent evolutions in post-market regulation have seen a shift from post-market safety initiatives being government-led to delegation of responsibility to the pharmaceutical industry.[33,34] As well as being required through regulation to collect and report post-market safety data collection and investigate issues, industry is asked to propose, plan and implement risk minimisation measures and importantly, to finance studies and interventions. [15,30,33,34]

The balance between regulatory and commercial responsibility is also reflected in the ways in which post-market safety advisories are developed and communicated, as discussed in more detail in Chapter 2. Regulators differ in their ability to regulate communication of post-market safety issues, and while most regulators rely on their institutional authority to influence the content of advisories, they do not all have a clear legislated mandate to do so. Further, some rely to a greater extent on industry to communicate using DHPCs. However, surveys and qualitative studies suggest that prescribers are more likely to trust non-industry sources. (See Chapter 5 .)

1.2.4 Types of safety advisories

The term “safety advisories” is used in this research to encompass a range of post-market communication mechanisms including regulatory drug safety bulletins, DHPCs, website alerts and notices. These communications may be promulgated through various communications channels including media releases, podcasts and social media. As noted above, our definition includes only advisories about potential harms of medicines related to their intrinsic effects, rather than error, misuse or contamination. However, the same communication channels are exclusively used for other safety issues.

When a new post-market safety issue is identified, regulators can respond by altering the prescribing (product) information to include new warnings or advice, or by requiring additional risk minimisation strategies. Safety advisories may be used to communicate these

events, including when a possible signal is first detected, known as an 'early warning' alert in the US [35] or a 'monitoring communication' in Australia.[36] Less commonly, regulators determine that a medicine's harmful effects outweigh its benefits and proceed to suspend marketing authorisation or withdraw a medicine.

DHPCs are letters or emails sent directly to prescribers which may be individually addressed. In some jurisdictions, such as Canada, the regulator may issue a DHPC themselves, but most DHPCs are issued by pharmaceutical companies. Regulators may request companies to issue a DHPC and will often review and advise on the content, for safety-related issues. However, there are grey areas in regulation as described in Chapter 2, and regulators have varying degrees of legislated authority over their use and content.

DHPCs may also be used for other reasons, such as to communicate drug shortages or to correct misleading information in advertising, or as part of a REMS, as outlined in an FDA guidance document.[37] For the purposes of the research described in this dissertation, DHPCs issued as part of an FDA REMS were not included within the definition of post-market safety advisories. These DHPCs are usually planned communications and are not used in immediate response to an emergent issue, but as a program of communication often after other regulatory actions.

1.2.5 Previous research on the use and impact of safety advisories

Safety advisories are issued for only a proportion of post-market safety signals and product information changes. A 2005 study found that 25% of changes to the text on warnings in US FDA product information led to an advisory.[38] More recently in 2018, the EMA assessed 114 confirmed signals from the Eudravigilance adverse event reporting system, 50 (44%) of which led to changes to product information, but only 6 resulted in a DHPC, the most common form of safety advisory developed by the EMA for dissemination by member national regulatory agencies. [39]

Despite resulting from only a proportion of possible signals, safety advisories remain an important and relatively common regulatory intervention. Over a ten-year period to 2009 in the Netherlands, there were 157 direct health professional communications (DHPCs) issued representing 3% of all licensed drugs at the time. 53/279.[40] In the US over a similar period (2001-2010), there were 59 safety communications for 44 of the 222 novel therapeutics approved - approximately 19.8% of all novel therapeutics[41], while the FDA issued over 250 safety advisories (FDA Drug Safety Communications) from 2010 to 2019[42]. In four European countries for the same period there were 90 DHPCs for 53 of the 185 novel medicines approved by the European Medicines Agency (28.6%).[5] Another European study examining innovative medicines found that first DHPCs were issued for 53/279 (18.9%) of new drugs approved from 1999 to 2012.[43]

One third of advisories in the Netherlands study were issued in the first 3 years after approval,[40] while in the US study post-market safety events (including safety communications) occurred within a median 4.2 years of approval (IQR, 2.5-6.0 years).[41]

Numerous studies have investigated the effects of safety advisories. Three systematic reviews have examined the impact of safety advisories on prescribing and other healthcare utilisation outcomes,[44-46] with a further two systematic reviews examining methods used to assess these impacts.[47,48], one of which considered methods alone rather than outcomes. [47] The specific regulatory interventions and jurisdictions included in scope for these reviews varied (see Table 1.1), with some including boxed warnings, product information changes or product withdrawals along with other communications.

Table 1.1: Systematic reviews assessing the impact of advisories – types of safety communications included

	Assessed outcomes			Assessed methods	
	Dusetzina 2012	Piening 2012	Weatherburn 2020	Briesacher 2013	Goedecke 2017
N	**49**	**52**	**40**	**18**	**153**
Jurisdiction	US	US - 26 EU -19 Other - 7	UK	US	US - 70 EU - 69 Other - 14
DHPC	X	X	X	X	X
Regulatory communication	X	X	X (bulletin)	X	X
Black box warning	X	X	-	X	X
Product label change	-	-	-	X	X
Risk minimisation strategy	-	-	-	-	X
Suspension/ withdrawal*	-	-	X	X	X

Risk minimisation strategy = risk minimisation measure such as restricted prescribing program
* Weatherburn assessed the impact of advisories about suspensions or withdrawals, Briesacher and Goedecke assessed the impact of the withdrawal

Two reviews were restricted to FDA communications, one review to MHRA communications and two were not restricted to specific regulators. In one systematic review which included 153 articles, 14 studies were conducted outside of the US or Europe[47], however only 8 of these examined regulatory safety communications or DHPCs (Table 1.1).

This systematic review evidence suggests that overall, advisories have the intended impact of improving prescribing and other outcomes, but that their impact varies considerably and effects are generally modest or not sustained.[44,45,48] A review limited to UK advisories identified through meta-analysis that the relative mean change in prescribing was -34% to -11% for advisories unrelated to a product withdrawal.[46] A review of FDA regulatory safety interventions assessing their multiple intended outcomes found that 50% of studies of at least moderate rigour reported little or no impact, while 61% had a significant impact on at least one of the intended outcomes.[48]

Why should some advisories be more effective than others? Factors addressed in the literature include: awareness and dissemination strategies; content and clarity of advice; and the nature of the recommendation or treatment issue. However, a limited evidence base and methodological weaknesses hamper conclusions.

Awareness of safety advisories is certainly requisite to acting on safety advice. In a multimodal study of FDA advisories for the sedative drug zolpidem, Kesselheim identified gaps in the awareness of prescribers and consumers about the advice provided in the advisory, and relatively limited impact on prescribing.[42,49-51]

Dissemination factors associated with greater impact include the use of more intensive communications[48] whether the advice was repeated,[45] and the type of communication.[46] One review found that sequential advisories repeating messages over a period of time were effective in reducing co-prescribing of interacting medicines; and noted that many studies citing successful outcomes referred to more intensive communication efforts.[45] Similarly, studies reporting media interest found that these advisories had a stronger impact, either positively or negatively.[44,45] A review restricted to UK advisories showed that DHPCs had a greater impact on prescribing than the UK regulator's drug bulletin.[46]

The content and clarity of advisories, and the impact of these factors on prescriber and consumer uptake of advice have been less frequently studied, although risk communication experts recommend that communication objectives be formulated based on the behaviour change required, taking into account the recipients of the message and any environmental or cultural issues.[52,53]

A study by Mazor - which is quoted by the FDA in its guidance on writing DHPCs [37] - found that clinicians rated more than a quarter of DHPCs advisories overall as ineffective, and in 36%, key information and advice was not readily identifiable.[38] Advice which is very specific appears more likely to achieve results. For advisories aiming to reduce serious

cardiovascular interactions with cisapride, specifically listing the names of drugs to be avoided, rather than referring to drugs in certain classes or different mechanisms of action (e.g. QT-lowering potential) had a greater effect on co-prescribing of interacting drugs.[54] After examining the impact of several warning letters for cisapride, the researcher concluded that media uptake of messages increased their impact. Other research suggests that amplification through the media can be maximised firstly by regulators issuing media releases, and secondly by providing specific advice and including that specific information in media releases. [55,56]

Similarly, there is evidence that more direct advice is more effective than general cautions. The UK review found that communications advising of restricted indications had a greater impact on the targeted prescribing than general advice to 'be aware' (−34%; 95% confidence interval [CI] −12 to −55% and −11%; 95% CI −8 to −15%).[46] Even when messages are apparently targeted, such as messages to 'increase monitoring' a review of FDA communications found such suggestions had little meaningful impact. For example despite the FDA warning to increase liver monitoring with troglitazone, deaths continued and the drug was eventually withdrawn.[45] This may also be because advice to monitor is not provided in adequate detail – studies have shown that many messages provide inadequate information about what should be monitored, when, for how long, and what to do if there is a change in monitoring parameters.[9,57]

Environmental issues that require tailoring of advice may include the therapeutic situation. The availability of alternative treatment options can influence prescriber behaviour as seen in a qualitative study with primary care doctors, which identified their perceived lack of therapeutic options as a factor in ongoing prescribing of antidepressants to adolescents. Simple advice not to prescribe was not deemed actionable by some prescribers. [58]

However, methodological weaknesses in the evidence base and a reliance on relatively weak study designs[47,48] contribute to uncertainty about the impact of advisories. For

example, many studies relate to a small number of topics, with a third of studies in one systematic review [47] describing advisories for only two groups of drugs - analgesics and the contentious and highly publicised issue of suicidality with antidepressant prescribing in children and young people.

Concerns have been raised about the unintended effects of safety advisories found in 33% of studies examined in one systematic review.[48] Such effects include the spill-over of caution or avoidance advice to populations or drugs not involved in the safety concern.[44,45,59] However, the reasons for unintended effects may relate to surrounding events such as media publicity, as well as the communications themselves.[59]. While these findings support a need for clarity in communications, it is worth noting that the methodology of these studies has not been adequately reviewed, and there is no clear definition of what constituted an unintended effect and whether it is positive or negative for the patient.[59]

1.2.6 International comparison studies of regulatory policy

As is described above, research on the effects of advisories on prescribing indicate mixed outcomes, ranging from some studies showing a strong effect on prescribing to others indicating little to no effect and/or unintended effects. These were generally studies of effects of a single advisory and/or a single regulator. In the studies conducted for this dissertation, the focus was on the use of safety advisories by four regulators – the United States Food and Drug Administration (FDA), Health Canada, the United Kingdom's Medicines and Healthcare products Regulatory Authority (MHRA) and the TGA.

Comparing international medicines regulators has a strong precedent in the literature and is an appropriate methodology for identifying the strengths and weaknesses of different regulators, which may in turn help identify opportunities for policy improvement. [15,60-62] Regulators have been seen to differ considerably in regard to safety-related actions, including drug withdrawals, product information and advice about safety.

There are major differences in the approach taken to regulation of medicines in different countries. Only 9.3% of 462 drugs withdrawn in any country due to adverse effects between 1953 and 2013 were withdrawn worldwide, with 39% withdrawn in only one country.[63] Numerous studies have established that regulatory-approved product safety information varies considerably between regulators for the same medicines, both for consumers[64] and health professionals. [2-4,65,66] These include discrepancies in the number of adverse effects listed, their reported frequency (common vs. rare), and in the listed contraindications and warnings.[3,4,66]

In one study of the content of product information documents for 20 drugs, Australian product information listed 14% fewer adverse drug reactions than the US, while Canadian documents listed 60% more.[4] Australian and UK information never or rarely included boxed warnings, while this was a key feature of North American documents.[4] An international comparison of product information from 26 countries for the same 3 drugs, found none of the countries fully agreed in their listed cautions with differences both in the number of adverse reactions described as well as their purported frequency.[2] Another study identified low levels of consistency in specific drug-drug interaction warnings for 25 drugs, with US, UK and German prescribing information containing the same warnings for less than 20% of the drug interaction warnings examined.[3]

Differences in the way harm is described have also been found. A comparative study of product information for five ADHD medicines in four countries (Australia, Canada, the UK and the US) found that the description of the causal relationship between the adverse effect and the medicine was consistent in only 60%.[67] In another study comparing 12 matched pairs of US and European product information for anticonvulsants and antidepressants marketed by the same company, US product information more often provided the source of the evidence (10 vs.5), and the size of the risk (9 vs.5), than the EU counterpart.[68]

However, there have been few comparative studies examining the use of safety advisories, the policy frameworks underlying their use or their relative impact on the behaviour of prescribers. The TGA, the Australian regulator, has been rarely examined in the published literature. The SAFER project, which is the umbrella project for the research in this dissertation, is the first research to examine the TGA's use of post-market safety communications, with no other studies on TGA safety advisories identified apart from those from the SAFER project.

1.2.6.1 International studies comparing the use of regulatory safety advisories

Few studies have compared safety advisories between countries. Zeitoun compared 4 European countries (France, Netherlands, Spain, and the UK) and found that all 4 national regulators issued advisories for 20/95 (21.1%) safety issues, while 16.8% were issued by a single regulator. All four countries are part of the EMA network of regulatory agencies.

Rates of agreement were lower in a study comparing the US, Canada and the UK, in which 9% (21/227) of safety problems were subject to DHPCs in all 3 countries, with 77% (166/227) issued in only one country.[8] This study also identified differences in the content of the DHPCs including whether scientific justification was given for the warning (ranging from 33.8% of Health Canada letters to 93.5% of US letters), whether quantitative data for adverse effects were reported (38.8% [Health Canada] to 77.6% [FDA]) and in the provision of quantitative information on efficacy (2.5% [Health Canada] to 16.8% [FDA]).[8]

As described in 1.2.1, a database was compiled by the SAFER project, consisting of safety advisories published by the US FDA, Health Canada, the TGA and the UK Medicines and Healthcare products Regulatory Agency (MHRA) between 2007-2016. [6,7] The resulting database comprised 1441 advisories describing 680 drug safety concerns.[7] If a regulatory issued multiple communications about the same issue within a 30-day period this was treated as one advisory.

Analysis of the SAFER database identified considerable variation in the use of safety advisories between countries, despite similarities in their regulatory principles. [6,7] Taking into account which regulators had approved the drug, advisories were issued for the same drug-risk issue for 10.3% of all safety concerns (70/680), while for 7% of drug safety concerns, all four countries had approved the drug and also issued an advisory. The number of regulatory safety advisories on any drug-risk issue issued per country over this 10-year period varied from 220 in Australia to 469 in the UK. [6]

1.3 Policy differences among regulators

A key focus of the work undertaken as part of this dissertation was to characterise the differences and similarities in policy amongst the included regulators. The reasons for selecting the four regulators included in this study were as follows. The US FDA and the EMA are the world's two largest and most influential regulators and their policies and decisions may have an impact on other regulators.[69] For example, Australia adopts many of the EMA regulatory guidelines. [70] The TGA and Health Canada are much smaller regulators, with more limited budgets and populations, but nonetheless have similar societal expectations of healthcare delivery as these larger jurisdictions. Canada and Australia have Commonwealth ties to the UK, and therefore the EMA system of regulation, while Canada is also geographically close to the US and has geopolitical ties with that country.

During the study period there were two regulators responsible for the regulation of medicines in the UK – the EMA and the MHRA. The EMA has an overarching responsibility for certain aspects of medicines regulation for member states of the European Union, each of which has a national regulator or 'national competent authority'. The MHRA is the national competent authority for the UK. The EMA plays a key role in authorising new medicines which are centrally authorised for marketing in EU countries, and for making safety-related decisions for most medicines. Each national competent authority is responsible for disseminating safety communication, however except for specific locally relevant issues,

most arise from EMA assessments. (See Chapter 2 for more details). Hence for this research I examined advisories issued by the UK MHRA, and these advisories were collected in the SAFER database. However I examined EMA policy because at the time of conducting this research, the UK was part of the EU.

Regulation of pharmaceuticals depends on the scientific demonstration of predictable and quantifiable outcomes. However, the fact that regulatory agencies deal with scientific processes can obscure the fact that policy and related processes can determine how evidence about pharmaceutical safety is collected, assessed, used in decision making, and communicated to the public. In turn, influences on policy implementation may come from individual, political, commercial or public actors.

Regulators responding to evidence of divergence amongst regulators' safety decisions state that concordance in regulatory decisions is not guaranteed because of differences in decision making and regulatory tools.[71,72] In other words, the legislative and regulatory authority vested in regulators may differ, but differences in regulatory culture may also influence outcomes. For example regulators may differ in the extent to which they consider post-market communication as part of their role, in their goals in communicating, their priorities or thresholds for communication, or in the extent to which they perceive their role to be that of a public health agency[16] or more narrowly related to the supply of medicines.[16,69,73]

The question of what determines a strong, powerful or effective regulator has occupied scientists from diverse disciplines. The framework in Chapter 2 lists components of regulatory power identified as important in the literature, particularly in comparative studies of more than one regulator. These include governance, the strength of regulation and law, capacity in terms of funding, manpower and technical resource, as well as the higher-level influences on regulatory decisions including economic interests and political or executive interference.[15,17,18,62,74,75].

Wiktorowicz et al characterised US, Canadian and European regulators according to the nature of their interactions with industry in terms of decision making. Firstly, in the context of new drug approval, they argue that European and Canadian regulators make decisions based on reviews of summary data provided by industry, while FDA scientists obtain the raw data and conduct their own analyses.[76] Secondly, representation of industry in decision making differs between the FDA and other regulators, with the FDA giving a right of comment to industry, in a more "judicial" process, while the EMA and Canada more directly involve industry in consultation and decision making.[76] Lexchin's analysis of Health Canada found that Health Canada portrayed its relationship with industry as an equal partnership.[18] Few have tried to characterise the Australian regulator in this way, although Maor described the TGA as a 'guardian regulator', which acknowledges its reliance on larger 'expert' regulators for identifying safety concerns, but which aims to protect its reputation by acting quickly on drug recall decisions and having strong rules for industry communication of recalls.[69] Interestingly the same provisions are not present in regulation for other forms of safety concerns, as discussed further in this dissertation (Chapter 2).

In the post-market setting, the regulations and legislative basis for regulatory action varies amongst regulators, including in the manner and extent of industry responsibility and regulatory authority over industry, and some have commented on the potential conflicts of interest in current arrangements where regulators expect industry to collect and report information which may be commercially damaging.[18,77] The characteristics of policy for post-market safety advisories and the extent to which regulators are able to require industry actions are discussed in more detail in Chapter 2.

1.4 Research questions – aims of this thesis

Regulatory authorities use post-market safety advisories to inform prescribers and the public of current and emerging safety information, to enable them to make decisions about risks and benefits.[42,78,79] Although research has examined the impact of safety advisories on prescribing outcomes, there has been no previous comparative analysis of the policy underlying such communications by regulators in Australia, Canada, the UK and the US and very little investigation of Australia's use of safety advisories, either alone or in comparison to other countries.

This thesis examines current policy and outcomes for regulatory post-market safety communications in Australia, Canada, the UK and the US and has the following aims:

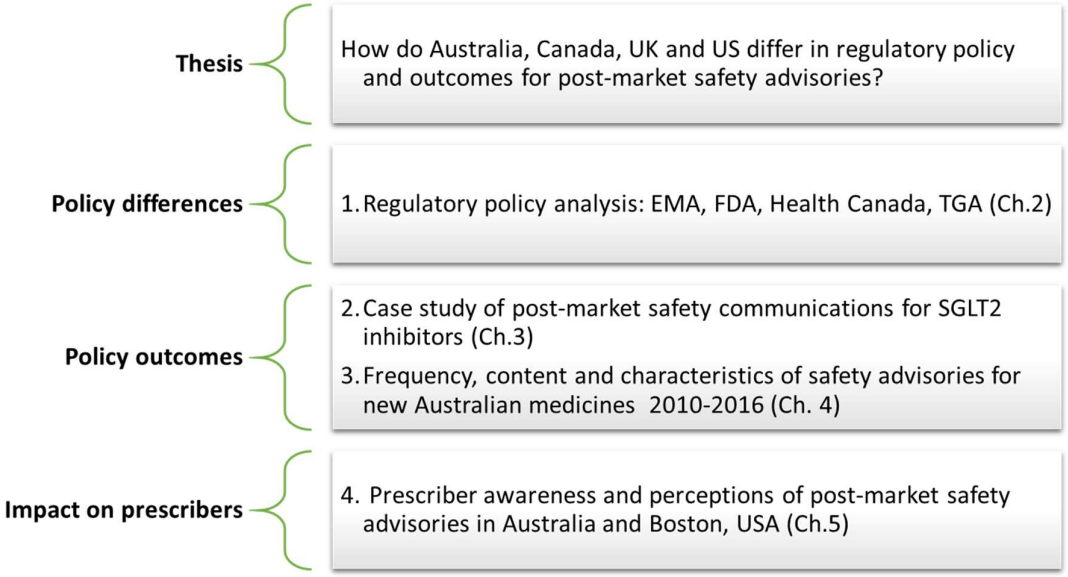
1. To compare regulatory policy for post-market safety advisories in Australia, Canada, the EU and the US using a consistent framework focusing on governance, legislated authority, capacity, and transparency.
2. To examine and compare regulatory decision making and transparency using an in-depth case study of post-market safety communication for emerging safety concerns of sodium glucose co-transporter 2 (SGLT2) inhibitor medicines for diabetes in Australia, Canada, the UK and the EU.
3. To investigate the frequency, timing and key communication differences in post-market safety advisories issued by Australia, Canada, the UK and the US for new drugs approved in Australia between 2010 and 2016.
4. To explore physicians' use of medicines safety information and their perceptions and awareness of regulatory post-market safety advisories in the US and Australia.

1.5 Presentation of the thesis and overview of methodology

This thesis makes an original contribution to the understanding of regulatory policy for post-market safety communication and its associated effects using a comparative methodology encompassing four regulators. It examines three major components of post-market safety communication: regulatory policy and authority; regulators' use of post-market safety advisories in two discrete scenarios (SGLT2 inhibitors, and new drugs approved in Australia 2010 to 2016); and the perceptions and use of medicines safety information and post-market safety advisories by prescribers.

Figure 1.1 provides an overview of the thesis and its organisation.

Figure 1.1: Thesis components



This dissertation is presented as two submitted papers and two published papers which describe the research undertaken to address the research questions and the aims of this thesis. The literature, methods, results and discussion for each piece of research are

described within each paper, each of which forms a chapter within the dissertation. An overview and introduction are provided for each chapter.

Chapter 1 provides an introduction to the literature on post-market safety advisories and the background to the remaining chapters.

Chapter 2 reports a ***comparative policy analysis*** which compares regulatory policy and authority in regard to the use of safety advisories, using an analytical framework developed by the author. EMA, FDA, Health Canada and TGA policy for post-market communications are described and compared in terms of the following: governance and public participation in decision making; legislative authority for issuing post-market safety advisories or requiring industry to do so, the role of industry, risk communication capability; and support for transparency regarding post-market data and decision making.

- Methodology: I derived an analytical framework from my review of scholarly work analysing regulatory policy in other domains. A comprehensive search for publicly available regulatory policy documents and legislation was conducted and a document analysis was carried out for each of four jurisdictions using the derived framework.

Chapter 3 is a ***case study*** comparing regulatory decision making and transparency for a specific group of safety advisories for SGLT2 inhibitors, a relatively new class of drugs for type 2 diabetes. It compares actions and transparency in the issuing of advisories, documentation of decision making, and changes to product information and timing of actions, by the EMA, FDA, Health Canada and the TGA to highlight policy differences among the four regulators.

- Methodology: an in-depth case study method derived from the social sciences[80] was used to identify and compare all regulatory documents associated with post-market safety actions and communications for SGLT2 inhibitors for the four regulators.

Chapter 4 is a ***content analysis*** of safety advisories issued by the FDA, Health Canada, the MHRA and the TGA for new drugs approved in Australia between 2010 and 2016.

- Methodology: this analysis used the database of safety advisories created for the SAFER project, which the author participated in developing, that includes regulatory safety advisories issued in Australia, Canada, the UK and the US, in the public domain, between 1 January 2007 and 31 December 2016. A content analysis was conducted on a subset of the database, consisting of safety advisories issued for the cohort of all new drugs approved in Australia between 2010 and 2016. This analysis focused on the actions of the TGA, compared with other regulators.

Chapter 5 reports a ***qualitative study*** in which prescribers in Boston US and various Australian locations were interviewed regarding their perceptions and awareness of post-market drug safety advisories, to better understand the impact of advisories on health professionals in these two countries, who are the intended recipients of safety advisories.

- Methodology: qualitative methods were used to elicit perceptions and awareness amongst generalist physicians and specialist endocrinologists in two locations. Semi-structured interviews were conducted in Boston US and various locations in Australia, and were inductively analysed by the author to identify themes which could inform hypothesis generation for future studies.

Chapter 6 is a discussion of the overall findings of the dissertation and the resulting conclusion and recommendations for future research.

1.6 References

1. Weatherby LB, Walker AM, Fife D, et al. Contraindicated medications dispensed with cisapride: Temporal trends in relation to the sending of 'Dear Doctor' letters. *Pharmacoepidemiol Drug Saf* 2001; 10: 211-218. Article. DOI: 10.1002/pds.592.

2. Reggi V, Balocco-Mattavelli R, Bonati M, et al. Prescribing information in 26 countries: A comparative study. *Eur J Clin Pharmacol* 2003; 59: 263-270. DOI: 10.1007/s00228-003-0607-1.

3. Pfistermeister B, Saß A, Criegee-Rieck M, et al. Inconsistencies and misleading information in officially approved prescribing information from three major drug markets. *Clin Pharmacol Ther* 2014; 96: 616-624. DOI: 10.1038/clpt.2014.156.

4. Kesselheim AS, Franklin JM, Avorn J, et al. Speaking the same language? International variations in the safety information accompanying top-selling prescription drugs. *BMJ Quality and Safety* 2013; 22: 727-734. Article. DOI: 10.1136/bmjqs-2012-001704.

5. Zeitoun J-D, Lefèvre JH, Downing N, et al. Inconsistencies among European Union Pharmaceutical Regulator Safety Communications: A Cross-Country Comparison. *PLOS ONE* 2014; 9: e109100. DOI: 10.1371/journal.pone.0109100.

6. Perry LT, Bhasale A, Fabbri A, et al. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med* 2019; 179: 982-984. 2019/04/30. DOI: 10.1001/jamainternmed.2019.0294.

7. Perry LT, Bhasale A, Fabbri A, et al. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiol Drug Saf* 2020; 29: 1054-1063. DOI: 10.1002/pds.5072.

8. Bjerre LM, Parlow S, De Launay D, et al. Comparative, cross-sectional study of the format, content and timing of medication safety letters issued in Canada, the USA and the UK. *BMJ Open* 2018; 8. Article. DOI: 10.1136/bmjopen-2017-020150.

9. Hooimeyer A, Bhasale A, Perry L, et al. Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. *Pharmacology Research & Perspectives* 2020; 8: e00680. DOI: https://doi.org/10.1002/prp2.680.

10. Australian Government Department of Health Therapeutic Goods Administration. Pharmacovigilance responsibilities of medicine sponsors. Australian recommendations and requirements. Version 2.0 September 2017 ed. ACT: TGA, 2017.

11. European Medicines Agency and Heads of Medicines Agencies. *Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2)*. 2013. London: EMA with HMA.

12. Kuehn BM. Frances Kelsey Honored for FDA Legacy. *JAMA* 2010; 304: 2109-2112. DOI: 10.1001/jama.2010.1652.

13. Darrow JJ, Avorn J and Kesselheim AS. FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA* 2020; 323: 164-176. DOI: 10.1001/jama.2019.20288.

14. New Drugs: Section 505(d) 21 U.S.C. § 355(d), Federal Food, Drug and Cosmetic Act. US.

15. Demortain D. The tools of globalization: ways of regulating and the structure of the international regime for pharmaceuticals. *Review of International Political Economy* 2015; 22: 1249-1275. DOI: 10.1080/09692290.2015.1066695.

16. Carpenter D. The other side of the gate: Reputation, power, and post-market regulation. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press, 2014.

17. Carpenter D. Reputation and regulatory power. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press, 2014.

18. Lexchin J. *Public profits vs private policy*. Toronto: University of Toronto Press, 2016.

19. Carpenter D. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press, 2014.

20. Krumholz HM, Ross JS, Presler AH, et al. What have we learnt from Vioxx? *BMJ* 2007; 334: 120-123. 2007/01/20. DOI: 10.1136/bmj.39024.487720.68.

21. Moynihan R. Court hears how drug giant Merck tried to "neutralise" and "discredit" doctors critical of Vioxx. *BMJ* 2009; 338: b1432. 2009/04/08. DOI: 10.1136/bmj.b1432.

22. U.S. Department of Health and Human Services Food and Drug Administration. The future of drug safety — promoting and protecting the health of the public. FDA's response to the Institute of Medicine's 2006 report. Maryland: FDA, 2007.

23. Commission of the European Communities. Commission staff working document. Accompanying document to the Proposal for a Regulation of the European Parliament and of the Council amending, as regards information to the general public on medicinal products for human use subject to medical prescription, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency and Proposal for a Directive of the European Parliament and of the Council amending, as regards information to the general public on medicinal products subject to medical prescription, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Summary of the impact assessment. Brussels: Commission of the European Communities, 2008.

24. Institute of Medicine (U.S.). Committee on the Assessment of the US Drug Safety System. The future of drug safety — promoting and protecting the health of the public. In: Baciu A, Stratton K and Burke SP, (eds.). *Committee on the Assessment of the US Drug Safety System, Board on Population Health and Public Health Practice*. Washington D.C.: The National Academies Press, 2006.

25. Sarpatwari A and Kesselheim AS. The 21st century cures act: Opportunities and challenges. *Clin Pharmacol Ther* 2015; 98: 575-577. 2015/08/13. DOI: 10.1002/cpt.208.

26. Lexchin J. New drugs and safety: What happened to new active substances approved in Canada between 1995 and 2010? *Arch Intern Med* 2012; 172: 1680-1681. DOI: 10.1001/archinternmed.2012.4444.

27. Eichler H-G, Pignatti F, Flamion B, et al. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat Rev Drug Disc* 2008; 7: 818. Perspective. DOI: 10.1038/nrd2664.

28. Califf RM and Kramer JM. The balance of benefit and safety of rosiglitazone: important lessons for our system of drug development and postmarketing assessment. *Pharmacoepidemiol Drug Saf* 2008; 17: 782-786. Comment.

29. Eichler H-G, Bloechl-Daum B, Brasseur D, et al. The risks of risk aversion in drug regulation. *Nat Rev Drug Disc* 2013; 12: 907. Perspective. DOI: 10.1038/nrd4129.

30. Herder M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. *Milbank Q* 2019; epub ahead of print.

31. Fain K and Alexander GC. Are Food and Drug Administration prescription drug safety plans working? A case study of isotretinoin. *Pharmacoepidemiol Drug Saf* 2013; 22: 1258-1262. Note. DOI: 10.1002/pds.3514.

32. U.S. Department of Health and Human Services Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). Isotretinoin iPLEDGE., https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=24 (2020, accessed 07 Feb 2021 2021).

33. Anonymous. European pharmacovigilance: increasingly outsourced to drug companies. *Prescrire International* 2014; 34: 536-544.

34. Anonymous. The reorganisation of European pharmacovigilance. Part 2. From spontaneous reports to agency reviews and decisions. *Prescrire International* 2014; 34: 692-697. Review.

35. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). *Guidance - Drug Safety Information – FDA's Communication to the Public. DRAFT GUIDANCE (withdrawn)*. Maryland: FDA, 2012.

36. Australian Government Department of Health and Ageing Therapeutic Goods Administration. Trans-Tasman early warning system. Processes in Australia and New Zealand. Version 1.0 ed. ACT: TGA, 2013.

37. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry and FDA Staff. Dear Health Care Provider Letters: improving communication of important safety information. Maryland: FDA, 2014.

38. Mazor Kathleen M, Andrade Susan E, Auger J, et al. Communicating safety information to physicians: an examination of dear doctor letters. *Pharmacoepidemiol Drug Saf* 2005; 14: 869-875. DOI: doi:10.1002/pds.1102.

39. European Medicines Agency. *2018 Annual report on EudraVigilance for the European Parliament, the Council and the Commission*. 2019. Amsterdam: EMA.

40. Mol PGM, Straus SMJM, Piening S, et al. A Decade of Safety-Related Regulatory Action in the Netherlands. *Drug Saf* 2010; 33: 463-474. DOI: 10.2165/11532840-000000000-00000.

41. Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA* 2017; 317: 1854-1863. DOI: 10.1001/jama.2017.5150.

42. Kesselheim AS, Sinha MS, Campbell EG, et al. Multimodal Analysis of FDA Drug Safety Communications: Lessons from Zolpidem. *Drug Saf* 2019; 42: 1287-1295. Article. DOI: 10.1007/s40264-019-00849-8.

43. Mol PGM, Arnardottir AH, Motola D, et al. Post-Approval Safety Issues with Innovative Drugs: A European Cohort Study. *Drug Saf* 2013; 36: 1105-1115. DOI: 10.1007/s40264-013-0094-y.

44. Piening S, Haaijer-Ruskamp FM, de Vries JT, et al. Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf* 2012; 35: 373-385. DOI: 10.2165/11599100-000000000-00000.

45. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care* 2012; 50: 466-478. DOI: 10.1097/MLR.0b013e318245a160.

46. Weatherburn CJ, Guthrie B, Dreischulte T, et al. Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: Systematic review, time series analysis and meta-analysis. *Br J Clin Pharmacol* 2019 2019/08/30. DOI: 10.1111/bcp.14104.

47. Goedecke T, Morales DR, Pacurariu A, et al. Measuring the impact of medicines regulatory interventions - Systematic review and methodological considerations. *Br J Clin Pharmacol* 2017 2017/11/07. DOI: 10.1111/bcp.13469.

48. Briesacher BA, Soumerai SB, Zhang F, et al. A critical review of methods to evaluate the impact of FDA regulatory actions. *Pharmacoepidemiol Drug Saf* 2013; 22: 986-994. Article. DOI: 10.1002/pds.3480.

49. Kesselheim AS, Donneyong M, Dal Pan GJ, et al. Changes in prescribing and healthcare resource utilization after FDA Drug Safety Communications involving zolpidem-containing medications. *Pharmacoepidemiol Drug Saf* 2017; 26: 712-721. Article. DOI: 10.1002/pds.4215.

50. Kesselheim AS, McGraw SA, Dejene SZ, et al. Patient and Physician Perceptions of Drug Safety Information for Sleep Aids: A Qualitative Study. *Drug Saf* 2017; 40: 531-542. Article. DOI: 10.1007/s40264-017-0516-3.

51. Kesselheim AS, Sinha MS, Rausch P, et al. Patients' Knowledge of Key Messaging in Drug Safety Communications for Zolpidem and Eszopiclone: A National Survey. *J Law Med Ethics* 2019; 47: 430-441. Article. DOI: 10.1177/1073110519876176.

52. Bahri P. A Multilayered Research Framework for Humanities and Epidemiology of Medicinal Product Risk Communication. In: Bahri P (ed) *Communicating about Risks and Safe Use of Medicines: Real Life and Applied Research*. Singapore: Springer Singapore, 2020, pp.1-84.

53. Campbell WH and Califf RM. Improving communication of drug risks to prevent patient injury: proceedings of a workshop. *Pharmacoepidemiol Drug Saf* 2003; 12: 183-194. DOI: doi:10.1002/pds.761.

54. Weatherby LB, Nordstrom BL, Fife D, et al. The impact of wording in "Dear doctor" letters and in black box labels. *Clin Pharmacol Ther* 2002; 72: 735-742. DOI: 10.1067/mcp.2002.129503.

55. Woloshin S, Schwartz LM, Dejene S, et al. Media Coverage of FDA Drug Safety Communications about Zolpidem: A Quantitative and Qualitative Analysis. *Journal of Health Communication* 2017; 22: 365-372. Article. DOI: 10.1080/10810730.2016.1266717.

56. Schwartz LM, Woloshin S, Andrews A, et al. Influence of medical journal press releases on the quality of associated newspaper coverage: retrospective cohort study. *BMJ* 2012; 344: d8164. DOI: 10.1136/bmj.d8164.

57. Højer M-MG, De Bruin ML, Boskovic A, et al. Are monitoring instructions provided in direct healthcare professional communications (DHPCs) of sufficient quality? A retrospective analysis of DHPCs sent out between 2007 and 2018. *BMJ Open* 2020; 10: e036498. DOI: 10.1136/bmjopen-2019-036498.

58. Richardson LP, Lewis CW, Casey-Goldstein M, et al. Pediatric Primary Care Providers and Adolescent Depression: A Qualitative Study of Barriers to Treatment and the Effect of the Black Box Warning. *Journal of Adolescent Health* 2007; 40: 433-439. DOI: 10.1016/j.jadohealth.2006.12.006.

59. DeFrank JT, McCormack L, West SL, et al. Unintended Effects of Communicating About Drug Safety Issues: A Critical Review of the Literature. *Drug Saf* 2019; 42: 1125-1134. Review. DOI: 10.1007/s40264-019-00840-3.

60. Wiktorowicz ME. Emergent patterns in the regulation of pharmaceuticals: institutions and interests in the United States, Canada, Britain, and France. *J Health Polit Policy Law* 2003; 28: 615-658. 2003/09/06.

61. Daemmrich A. *Pharmacopolitics. Drug regulation in the United States and Germany*. Chapel Hill: University of North Carolina Press, 2004.

62. Wiktorowicz M, Lexchin J and Moscou K. Pharmacovigilance in Europe and North America: divergent approaches. *Soc Sci Med* 2012; 75: 165-170. DOI: 10.1016/j.socscimed.2011.11.046.

63. Onakpoya IJ, Heneghan CJ and Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. *BMC Medicine* 2016; 14. DOI: 10.1186/s12916-016-0553-2.

64. Tong V, Raynor DK and Aslani P. Comparative User Testing of Australian and UK Over-the-Counter Labels and Leaflets for Diclofenac. *Therapeutic Innovation and Regulatory Science* 2018; 52: 38-48. Article. DOI: 10.1177/2168479017711730.

65. Pfistermeister B, Schenk C, Kornhuber J, et al. Different indications, Warnings and precautions, and contraindications for the same drug-an international comparison of prescribing information for commonly used psychiatric drugs. *Pharmacoepidemiol Drug Saf* 2013; 22: 329-333. DOI: 10.1002/pds.3389.

66. Eriksson R, Aagaard L, Jensen LJ, et al. Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. *Pharmacology Research and Perspectives* 2014; 2. DOI: 10.1002/prp2.38.

67. Sieluk J, Palasik B, dosReis S, et al. ADHD medications and cardiovascular adverse events in children and adolescents: cross-national comparison of risk communication in drug labeling. *Pharmacoepidemiol Drug Saf* 2017; 26: 274-284. DOI: 10.1002/pds.4164.

68. Cornelius VR, Liu K, Peacock J, et al. Variation in adverse drug reactions listed in product information for antidepressants and anticonvulsants, between the USA and Europe: A comparison review of paired regulatory documents. *BMJ Open* 2016; 6. Article. DOI: 10.1136/bmjopen-2015-010599.

69. Maor M. Organizational Reputations and the Observability of Public Warnings in 10 Pharmaceutical Markets. *Governance* 2011; 24: 557-582. DOI: 10.1111/j.1468-0491.2011.01536.x.

70. Australian Government Department of Health Therapeutic Goods Administration. International scientific guidelines adopted in Australia. https://www.tga.gov.au/ws-sg-index (2015).

71. Dal Pan GJ. Gauging the Effectiveness of Medicines Safety Communications From Global Regulatory Agencies. *JAMA Internal Medicine* 2019. DOI: 10.1001/jamainternmed.2019.0266.

72. Dal Pan GJ and Arlett PR. The US Food and Drug Administration-European Medicines Agency Collaboration in Pharmacovigilance: Common Objectives and Common Challenges. *Drug Saf* 2015; 38: 13-15. journal article. DOI: 10.1007/s40264-014-0259-3.

73. Carpenter D. Reputation, gatekeeping, and the politics of post-marketing drug regulation. *Virtual Mentor* 2006; 8: 403-406. DOI: 10.1001/virtualmentor.2006.8.6.pfor1-0606.

74. Davis C and Abraham J. The political dynamics of citizenship, innovation, and regulation in pharmaceutical governance. *Innovation-the European Journal of Social Science Research* 2012; 25: 478-496. DOI: 10.1080/13511610.2012.739377.

75. Davis C and Abraham J. *Unhealthy pharmaceutical regulation: innovation, politics and promissory science*. London: Palgrave MacMillan, 2013.

76. Wiktorowicz M, Moscou K and Lexchin J. Transnational pharmacogovernance: emergent patterns in the jazz of pharmaceutical policy convergence. *Globalization and Health* 2018; 14. DOI: 10.1186/s12992-018-0402-5.

77. Wiktorowicz M, Lexchin J, Moscou K, et al. *Keeping an eye on prescription drugs, keeping Canadians safe. Active monitoring systems for drug safety and effectiveness in Canada and internationally.* 2010. Toronto: Health Council of Canada.

78. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry and FDA Staff. Dear Health Care Provider Letters: improving communication of important safety information. Maryland: FDA, 2012.

79. European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module XV – Safety communication (Rev 1).* EMA/118465/2012 Rev 1 ed. 2017.

80. Van Evera S. *Guide to Methods for Students of Political Science*. Cornell University Press, 1997.

Chapter 2 Comparison of regulatory policy for post-market safety communications

2.1 Introduction

This chapter contains the following publication:

> Bhasale AL, Sarpatwari A, De Bruin ML, Lexchin J, Lopert R, Bahri P, and Mintzes BJ. Postmarket safety communication for protection of public health: A comparison of regulatory policy in Australia, Canada, the European Union, and the United States. *Clinical Pharmacology and Therapeutics* 2020. doi: 10.1002/cpt.2010

The manuscript and reference list are formatted as per the publisher's specifications, and hence do not correspond to the formatting in the rest of this thesis.

2.2 Overview

Regulation exists to protect the public by ensuring appropriate practices and standards for goods and services and by providing a legal framework for government intervention into industry activities. [1] In the case of medicines regulation, regulatory agencies are authorised to administer the rules and standards, and to monitor and assess compliance of the regulated industry. As described in Chapter 1, the historical role of medicines regulators is one of public interest protection, [2] however there is a tension between this role and another role commonly ascribed to them, which is to ensure a viable medicines industry.[3]

While Australia, the UK, the US and Canada ascribe to similar, globally recognised fundamentals of post-market surveillance and regulatory science, previous comparisons and analyses have found that jurisdictions can differ in policy details, structures and processes.[4-6] Pharmaceutical regulation may vary considerably due to political, organisational, legal and historical factors. [7,8]

Of the regulators included in this dissertation, European and US regulators have been most often compared. For example, attempts have been made to determine which is the more precautionary or permissive regulator, [9] with one factor in the debate the extent to which regulators are influenced by commercial interests. In the regulation of pharmaceuticals, a precautionary approach is one that values greater safety in the face of uncertainty, while a permissive approach is more accepting of risk. The 'flip-flop' hypothesis suggests that the US regulation of consumer products was precautionary up until the 70's and 1980's, after which it became more permissive of risk than European countries.[9] In their analysis of risk management strategies espoused by the EMA and the FDA, Davis and Abraham argue that stronger, more precautionary regulation in the US in the 1970's and 80's prevented exposure of the US population to some of the serious safety concerns occurring, for example, in the UK.[9] However, they point to three later examples (trovafloxacin, tolcapone and levomethadyl) where the EMA response was drug withdrawal, while the FDA chose to manage risk with warnings and other regulatory interventions. A similar divergence was seen comparing these regulators response to rosiglitazone, which was withdrawn in Europe by the EMA but maintained with a boxed warning in the US, leading Davis and Abraham to conclude that the European regulator had become more precautionary than the FDA.[10] In a subsequent analysis of drug safety withdrawals from 1993-2004 comparing the MHRA with the FDA, Davis and Abraham found that the two regulators had converged in their behaviour, with both regulators approving drugs with evidence of safety concerns at approval, and similar rates of drug safety withdrawals - although the US was more likely to leave unsafe drugs on the market.[11]

Health Canada has been the subject of policy analysis across many aspects of regulatory policy, [12-17] and discrepancies in regulatory authority have been identified when comparing the FDA and Health Canada. While the FDA Amendments Act of 2007 gave the FDA the authority to require safety-related changes to the product information,[18] this power was not available to Health Canada until the passing of the *Protecting Canadians from Unsafe Drugs*

Act (Vanessa's Law) in 2014. [19] Additionally in Canada, until 2006 the regulator could not make product information available to the public unless a Freedom of Information request was submitted. [20,21] While the FDA, Health Canada, and UK and EU regulators have been extensively studied, there have been fewer studies of TGA policy, and no holistic critical examination was identified.

2.3 Methods

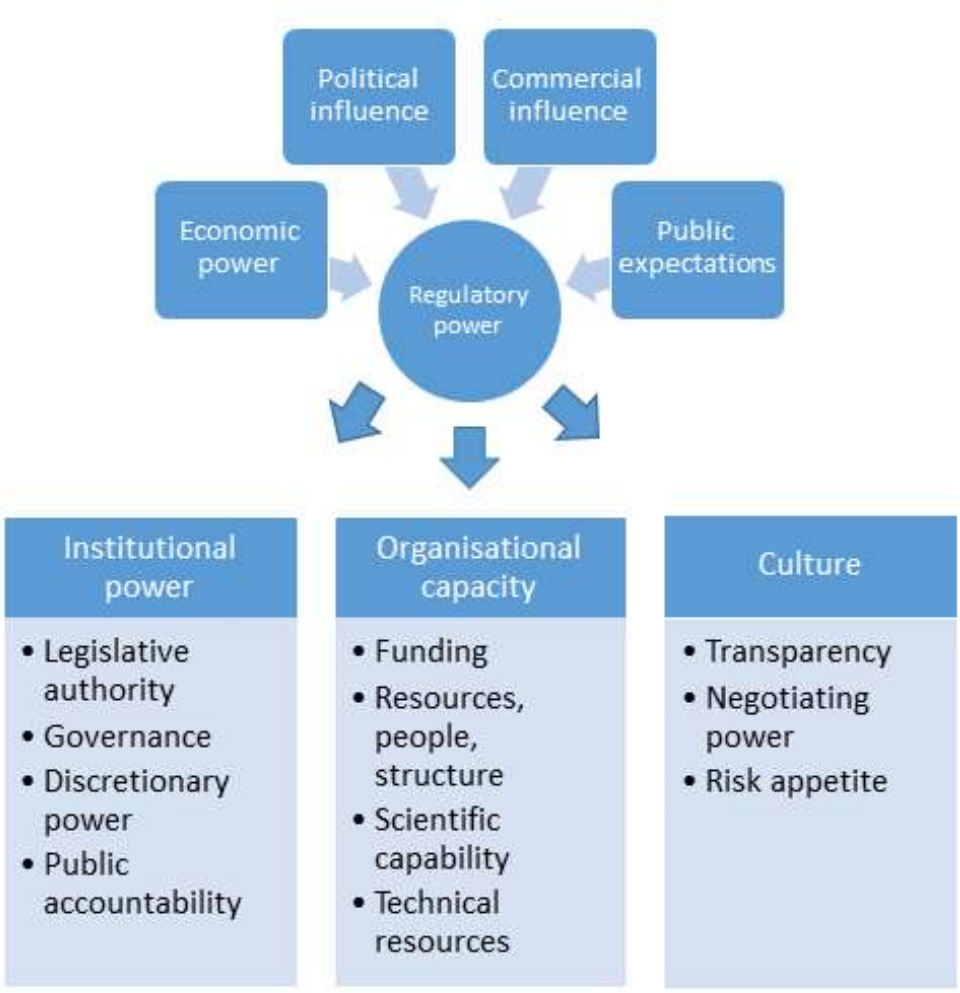
The publication described in this chapter compared the EMA, FDA, Health Canada and the TGA on several key aspects of regulatory strength for the communication of post-market safety issues, using a framework based on a documentary review of other analyses of policy and regulation, including for regulatory actions unrelated to the use of safety advisories.

The methods, presented as a supplementary appendix in the published paper, are provided here for context.

2.4 Developing the framework for regulatory comparison

The aim of this study was to compare regulators in regard to current policy for post-market safety advisories. In order to carry out this comparison I developed a framework based on key parameters used to assess regulatory strength and effectiveness in previous research. Through review of relevant literature, I identified key factors germane to the assessment of regulatory strength and effectiveness, in both policy analyses of individual regulators[13,22-28] and comparisons of different regulators[5,7,29,30] by previous regulatory analyses. [4,5,13,22,24-32] These factors were aligned into specific overarching domains as indicated in Figure 2.1. I then used this analysis to develop an analytical framework as the basis for comparing regulatory policy, as described in section 2.6.

Figure 2.1: Factors influencing regulatory strength and effectiveness



2.4.1 Inclusion of regulatory agencies

The SAFER database contains advisories issued by the FDA, TGA, Health Canada and the MHRA. However, for the purposes of the analysis of regulatory policy, I chose to examine EMA policy (at the time, the UK was part of the European Union). The reason for this was primarily the significant role of the EMA in safety-related decisions for many medicines marketed in EU countries, particularly newer drugs that are centrally authorised. While the EMA does not manage the communication channels of national regulators, it does co-ordinate some safety communications. A secondary reason was an absence of publicly available information regarding MHRA policy.

2.4.2 Data identification

I searched relevant governing legislation and regulations for policy related to use of safety advisories as follows:

- TGA: the *Therapeutic Goods Act 1989*, regulations and relevant explanatory statements.
- FDA: the *Federal Food, Drug, and Cosmetic Act* and subsequent amending statutes as codified into Title 21 Chapter 9 of the United States FDA code, and the *FDA Amendments Act* (*FDAAA 2007*).
- EMA: Directives and Regulations relating to pharmacovigilance as described on the EMA website.
    - Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance
    - Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC
    - Regulation (EU) no 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004
- Health Canada: the *Food and Drugs Act* and related regulations, and explanatory statements regarding '*Vanessa's Law*'.

I also systematically searched government and regulator websites for policies, guidelines for industry, policy information for the public, reports and evaluations. Documents were included initially if titles suggested relevance to post-market safety, pharmacovigilance or risk management. References and links in these documents were followed to identify other relevant government sources. The TGA, Health Canada, and FDA were contacted by email or in person and asked for any specific relevant policy documents relating to post-market

safety communication in the public domain. For EMA, one author (PB) identified additional specific relevant documents.

Searches were conducted between July 2018 and July 2019.

Documents were assumed to be current unless labelled as superseded, archived or removed, regardless of date of issue. Some FDA documents were included that were labelled ‘draft’ but had been updated for currency over a period of several years, suggesting they were in use but not formally adopted. Documents referring to planned amendments were not considered to reflect current policy unless I could substantiate that the change had occurred.

2.4.3 Analysis

All source documents were reviewed to inform an overall understanding of regulatory approaches. Relevant extracts of information were then compiled according to the broad categories in the framework. Further sub-groupings within the broad categories were formulated. Relevant information or text extracts were identified, grouped and tabulated within categories to allow comparison of regulatory policies.

2.5 References

1. Baldwin R, Scott C and Hood C. Introduction. *A reader on regulation*. Oxford: Oxford University Press, 1998.

2. Carpenter D. Reputation and regulatory power. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press, 2014.

3. House of Commons Health Committee. *The influence of the pharmaceutical industry. Fourth Report of Session 2004-5*. 2005. London: House of Commons.

4. Wiktorowicz ME. Emergent patterns in the regulation of pharmaceuticals: institutions and interests in the United States, Canada, Britain, and France. *J Health Polit Policy Law* 2003; 28: 615-658. 2003/09/06.

5. Wiktorowicz M, Lexchin J and Moscou K. Pharmacovigilance in Europe and North America: divergent approaches. *Soc Sci Med* 2012; 75: 165-170. DOI: 10.1016/j.socscimed.2011.11.046.

6. Carpenter D. American Pharmaceutical Regulation in International Context: Audiences, Comparisons, and Dependencies. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press, 2014.

7. Daemmrich A. *Pharmacopolitics. Drug regulation in the United States and Germany*. Chapel Hill: University of North Carolina Press, 2004.

8. Maor M. Organizational Reputations and the Observability of Public Warnings in 10 Pharmaceutical Markets. *Governance* 2011; 24: 557-582. DOI: 10.1111/j.1468-0491.2011.01536.x.

9. Davis C and Abraham J. A comparative analysis of risk management strategies in European Union and United States pharmaceutical regulation. *Health Risk & Society* 2011; 13: 413-431. DOI: 10.1080/13698575.2011.596191.

10. Abraham J and Davis C. A comparative analysis of drug safety withdrawals in the UK and the US (1971-1992): Implications for current regulatory thinking and policy. *Soc Sci Med* 2005; 61: 881-892. DOI: 10.1016/j.socscimed.2005.01.004.

11. Abraham J and Davis C. International and temporal comparative analysis of UK and US drug safety regulation in changing political contexts. *Soc Sci Med* 2020; 255: 113005. DOI: https://doi.org/10.1016/j.socscimed.2020.113005.

12. Lexchin J. Post‐market safety warnings for drugs approved in Canada under the Notice of Compliance with conditions policy. *British Journal of Clinical Pharmacology* 2015; 79: 847-859. DOI: 10.1111/bcp.12552.

13. Lexchin J. *Public profits vs private policy*. Toronto: University of Toronto Press, 2016.

14. Lexchin J. New drugs and safety: What happened to new active substances approved in Canada between 1995 and 2010? *Arch Intern Med* 2012; 172: 1680-1681. DOI: 10.1001/archinternmed.2012.4444.

15. Lexchin J. The Pharmaceutical Industry and the Canadian Government: Folie a Deux. *Politiques de sante* 2017; 13: 10-16. 2017/09/15. DOI: 10.12927/hcpol.2017.25195.

16. Mintzes B, Lexchin J, Sutherland JM, et al. Pharmaceutical Sales Representatives and Patient Safety: A Comparative Prospective Study of Information Quality in Canada, France and the United States. *J Gen Intern Med* 2013; 28: 1368-1375. DOI: 10.1007/s11606-013-2411-7.

17. Gaffney A and Lexchin J. Healing an ailing pharmaceutical system: prescription for reform for United States and Canada. *BMJ* 2018; 361: k1039. DOI: 10.1136/bmj.k1039.

18. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry. Safety labeling changes — implementation of section 505(o)(4) of the FD&C Act. Maryland: FDA, 2013.

19. Health Canada. Amendments to the Food and Drugs Act: Guide to New Authorities (power to require and disclose information, power to order a label change and power to order a recall), https://www.canada.ca/en/health-canada/services/drugs-health-products/legislation-guidelines/amendments-food-drugs-act-guide-new-authorities-power-require-disclose-information-power-order-label-change-power-order-recall.html (2017, accessed **1 Aug 2019**).

20. Health Canada. Transparency - release of product monographs directly to requesters, https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/product-monograph/transparency-release-product-monographs-directly-requesters.html (2006, accessed 27 March 2021).

21. Health Canada. Frequently asked questions: Product monographs posted to the Health Canada website [date not available], https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/monograph/pm_qa_mp_qr-eng.pdf (2006, accessed 27 March 2021).

22. Carpenter D. Detecting and Measuring Capture. In: Carpenter D and Moss DA (eds) *Preventing Regulatory Capture: Special Interest Influence and How to Limit it*. Cambridge: Cambridge University Press, 2013, pp.57-68.

23. Carpenter D. The other side of the gate: Reputation, power, and post-market regulation. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press, 2014.

24. Sharfstein JM, Miller JD, Davis AL, et al. Blueprint for Transparency at the U.S. Food and Drug Administration: Recommendations to Advance the Development of Safe and Effective Medical Products. *The Journal of Law, Medicine & Ethics* 2017; 45: 7-23. DOI: 10.1177/1073110517750615.

25. Kesselheim AS and Mello MM. Confidentiality laws and secrecy in medical research: improving public access to data on drug safety. *Health Affairs* 2007; 26: 483-491.

26. Institute of Medicine (U.S.). Committee on the Assessment of the US Drug Safety System. The future of drug safety — promoting and protecting the health of the public. In: Baciu A, Stratton K and Burke SP, (eds.). *Committee on the Assessment of the US Drug Safety System, Board on Population Health and Public Health Practice*. Washington D.C.: The National Academies Press, 2006.

27. Herder M. Denaturalizing transparency in drug regulation. *McGill Journal of Law and Health* 2015; 8: S57-S143.

28. Herder M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. *Milbank Q* 2019; epub ahead of print.

29. Davis C and Abraham J. *Unhealthy pharmaceutical regulation: innovation, politics and promissory science*. London: Palgrave MacMillan, 2013.

30. Demortain D. The tools of globalization: ways of regulating and the structure of the international regime for pharmaceuticals. *Review of International Political Economy* 2015; 22: 1249-1275. DOI: 10.1080/09692290.2015.1066695.

31. Carpenter D. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press, 2014.

32. Carpenter D. Corrosive Capture? The Dueling Forces of Autonomy and Industry Influence in FDA Pharmaceutical Regulation. In: Carpenter D and Moss DA (eds) *Preventing Regulatory Capture: Special Interest Influence and How to Limit it*. Cambridge: Cambridge University Press, 2013, pp.152-172.

2.6 Post-market safety communication for protection of public health: a comparison of regulatory policy in Australia, Canada, the European Union, and the United States.

Bhasale A.L.[1], Sarpatwari A.[2], De Bruin M.L.[3,4], Lexchin J. [5], Lopert R. [6], Bahri P. [4,7], Mintzes, B.J.[1]

[1] The University of Sydney Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, NSW 2006, Australia

[2] Program On Regulation, Therapeutics, And Law (PORTAL), Brigham and Women's Hospital and Harvard Medical School

[3] Copenhagen Centre for Regulatory Science, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

[4] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.

[5] York University, Toronto.

[6] George Washington University

[7] European Medicines Agency

SYNOPSIS

In the wake of the rofecoxib withdrawal, regulators worldwide reconsidered their approach to post-market safety. Many regulators have since adopted a life-cycle approach to regulation of medicines, facilitating faster approval of new medicines while recognising and planning for post-market safety issues. A crucial aspect of post-market safety is the effective and timely communication of emerging risk information using post-market safety advisories, commonly issued as letters to healthcare professionals, drug safety bulletins, media alerts and website announcements. Yet regulators differ in their authority to issue post-market safety advisories. We examined the capacity of regulators in the United States, Europe, Canada, and Australia to warn about post-market safety issues by examining their governance, legislative authority, risk communication capabilities, and transparency.

INTRODUCTION

A key aim of post-market regulation of medicines is to protect public health when new safety issues arise. Regulatory warnings in the form of letters to healthcare professionals, drug safety bulletins, media alerts and public website announcements, have long played a role in informing healthcare professionals and consumers of emerging adverse effects and other safety issues. These post-market safety advisories, the focus of this review, are a key component of regulators' post-market safety communication toolkits. Safety advisories may accompany other mechanisms for communicating post-market safety such as changes to the approved product information (e.g. adding new contraindications), risk minimisation activities (e.g., mandatory prescriber training), and suspension or withdrawal of marketing approval. More broadly, regulators' use of safety advisories may be indicative of their individual cultural and institutional characteristics, including their degree of risk aversion, propensity to act, and transparency.

Controversies over the adequacy of post-market safety communication have been a key driver of change in regulation. Following the withdrawal of the non-steroidal anti-

inflammatory drug rofecoxib in 2004, the United States (US) Institute of Medicine commented that the US Food and Drug Administration (FDA) and the pharmaceutical industry did not "consistently demonstrate accountability and transparency to the public by communicating safety issues in a timely and effective fashion."[1] Similar concerns about post-market safety communication were described in an independent study completed for the European Commission in 2007, which highlighted the "low levels of transparency relating to pharmacovigilance and relatively limited European Union (EU) coordination of communication about the safety of medicines, plus complex product information with poor penetration of key warnings."[2]

Since the rofecoxib controversy, post-market regulation has changed considerably in the US and the EU,[3, 4] underpinned by significant legislative amendments.[5-8] With international convergence and deliberate harmonisation in pharmaceutical policy and transnational standards,[9, 10] these changes have had a global influence on other agencies including Australian and Canadian regulators. An approach known as 'life-cycle regulation' now dominates, characterised by planning of data collection and risk minimisation measures in the pre-market period and an expanded range of capabilities post-market to identify, assess and respond to evolving risks, including enforced post-market studies and more purposeful attempts at making medicines use safer (**Box 1)**.

Part of the rationale for life-cycle regulation is that excessive risk aversion on the part of regulators could prevent patients from receiving the benefits of drug treatment. Hence uncertainties about safety should not delay access to medicines as some adverse effects can only be identified post-market.[3, 11, 12] Instead, life-cycle regulation contends that patient harm can be avoided or minimised by pro-active risk management.[1, 12] Post-market studies, monitoring and communication of emerging safety issues are key safeguards intended to ensure that unexpected harms are detected quickly and their impact is minimised.

Yet there is debate about the extent to which speed to market and post-market safety are equally balanced.[13, 14] While life-cycle regulation has resulted in faster drug approvals[15, 16] it has also been associated with lower evidentiary requirements pre-market that may increase the likelihood of previously undetected safety issues emerging post-market.[17, 18] Medicines approved using expedited approval processes such as priority reviews have been associated with higher rates of post-market safety warnings and withdrawals in North American studies,[14, 19] but not in Europe.[20] The FDA has been found to lack data demonstrating that post-market safety actions are effective in decreasing harms.[21]

Only a small proportion of post-market risks are anticipated by regulators in the pre-market phase,[22, 23] while between 15% and 30% of new drugs are associated with serious post-market safety issues or withdrawn within 10-12 years of approval.[19, 24, 25] Against this background, effective communication to healthcare professionals and the public is critical.

In previous research, our group found that medicines regulators in Australia, Canada, the United Kingdom (UK), and the US differed substantially in their use of post-market safety advisories.[26] All four regulators issued advisories for only 7% (40/573) of the risks communicated, for medicines approved in all countries.[26] These regulators were chosen for their comparable regulatory standards and diversity in size and global influence (the UK being part of the EU regulatory network coordinated by the European Medicines Agency (EMA) until March 2020). Similar discrepancies have been found in the use of direct healthcare professional communications (DHPCs) by different EU member states,[27] and in EU and US prescribing safety information.[28] Such divergence could lead to important differences in risk awareness and avoidance.

Box 1: Features of life-cycle risk management regulation

Pre-market

Risks that are not fully characterised at the time of approval, for example, because of limitations in data can be addressed through the following means:

- Further research (e.g., post-market studies)
    - For EMA and national EU regulators, known as post-authorisation safety studies or patient/disease registries (which may be voluntary or mandated)
    - For FDA, known as post-market requirements (mandated) and post-market commitments (agreed/voluntary).
- Routine or intensive monitoring of cases in ongoing trials or more detailed collection of spontaneous adverse event reports
- Labelling in the prescribing information* (e.g., contraindications, dose restrictions, limiting indications, safety information)
- Educational and other interventions
    - Programs to influence and control the use of drugs by clinicians (e.g., DHPC letters, consumer guides, educational materials and interventions, controlled distribution, programs to prevent pregnancy in women taking teratogenic drugs e.g., isotretinoin (called additional risk minimisation measures by EU regulators and Risk Evaluation and Mitigation Strategies (REMS) by FDA).

Risk Management Plans (RMPs) are used by EU regulators, Health Canada, and the Australian TGA to document risks and mitigation strategies.

Post-market

Regulatory interventions include (as above):

- Changes to use authorised by the approved product information for healthcare professionals and consumers (e.g., new contraindications, boxed warnings, adverse reactions)
- Post-market studies, active surveillance or and passive surveillance with enhanced review (e.g., additional requirements for research or risk mitigation when specific events are reported)
- New risk mitigation interventions: e.g., new FDA REMS, or new EU risk minimisation measures
- Post-market safety advisories from regulators including DHPCs demanded by regulators from industry
- Suspension (temporary), or withdrawal of marketing approval.

* product information encompasses the approved prescribing information (for healthcare professionals), consumer information and in some cases, package inserts and labelling. Prescribing information is known in Australia as 'Product information', in Canada as the Product Monograph, in the EU as the 'Summary of Product Characteristics', and in the US as 'Prescribing information'.

DHPC: Direct healthcare professional communications (EU), known in US as 'Dear Health Care Provider Letters' and in Canada as 'Dear Health Care Professional Letters'

FDA: Food and Drug Administration (US); TGA: Therapeutic Goods Administration (Australia)

BASIS FOR THIS REVIEW

Aims

Differences in regulatory policy may explain some variance in safety warnings, but major regulators' policies have not been compared in the scientific literature to date. Here we review relevant policies of EMA, US FDA, Health Canada, and the Australian Therapeutic Goods Administration (TGA). Our objective was to assess current regulatory policies for post-market safety advisories and the related regulatory contexts focusing on governance, legislated authority, capability and transparency of regulatory actions.

Approach to the review

We defined regulatory post-market safety advisories as notices issued or authorised by regulators to inform healthcare professionals or the public about medicine safety issues emerging post-market. There is no standardised regulatory terminology for such communications, which can occur via DHPCs, drug safety bulletins, media alerts and public website announcements. Communications pertaining to medication errors, manufacturing or quality issues, drug shortages or product recalls were not the focus of this review, as such issues are qualitatively different in terms of their impact on patient safety and treatment choices. However, the communication modalities discussed in this review could be used in such situations.

Excluded from the review were other mechanisms that regulators use for post-market safety communication, mainly changed wording in product information and 'risk minimisation' measures such as educational resources and restricted prescriber programs. [29, 30] Safety advisories differ from these forms of communication in their more expedited nature, attempting to actively communicate and publicise new information, sometimes before the risk is fully understood.

Our analytical framework (**Box 2**) was broadly informed by previous analyses of regulatory policy.[12, 31-34] We considered:

- governance for post-market safety communication and the extent of public participation in decision making about advisories
- legislative authority for regulators to issue post-market safety advisories or require industry to issue DHPCs
- the role of industry
- risk communication capability, including how regulators communicate post-market safety issues and their emphasis on behavioural change.[35, 36]
- policy support for transparency regarding post-market safety issues.

Information for our review was gathered from relevant governing legislation related to safety advisories and systematic searches of government and regulators' websites for policy documents, guidelines for industry, information for the public, reports, and evaluations of relevant policies.

Box 2: Analytical framework for post-market safety communication policies

Governance

- Responsibility for assessing safety issues
- Responsibility for communicating and disseminating post-market safety information
- Mechanisms and extent of public participation in decision-making about post-market safety and communications

Legislative authority

- Authority to issue warnings and post-market safety advisories
- Authority to require companies to issue DHPCs

Role of industry

- Industry involvement in post-market safety communication and related regulatory activity

Risk communication capability

- Goals of regulatory communication, in particular regarding behaviour change
- Methods of communicating post-market issues
- Monitoring and measurement of effectiveness
- Guidelines for writing and communicating risk
- Risk communication priority/strategy

Transparency

- Minutes of expert committee meetings
- Documents explaining how regulatory decisions were made
- Accessibility of post-market safety data

GOVERNANCE FOR POST-MARKET SAFETY AND RISK MINIMISATION

Responsibility for post-market safety communication can span different units within regulatory agencies, according to their function (Figure 1). Safety advisories may form part of an overall communication strategy or may accompany other risk minimisation measures as indicated in Box 1.

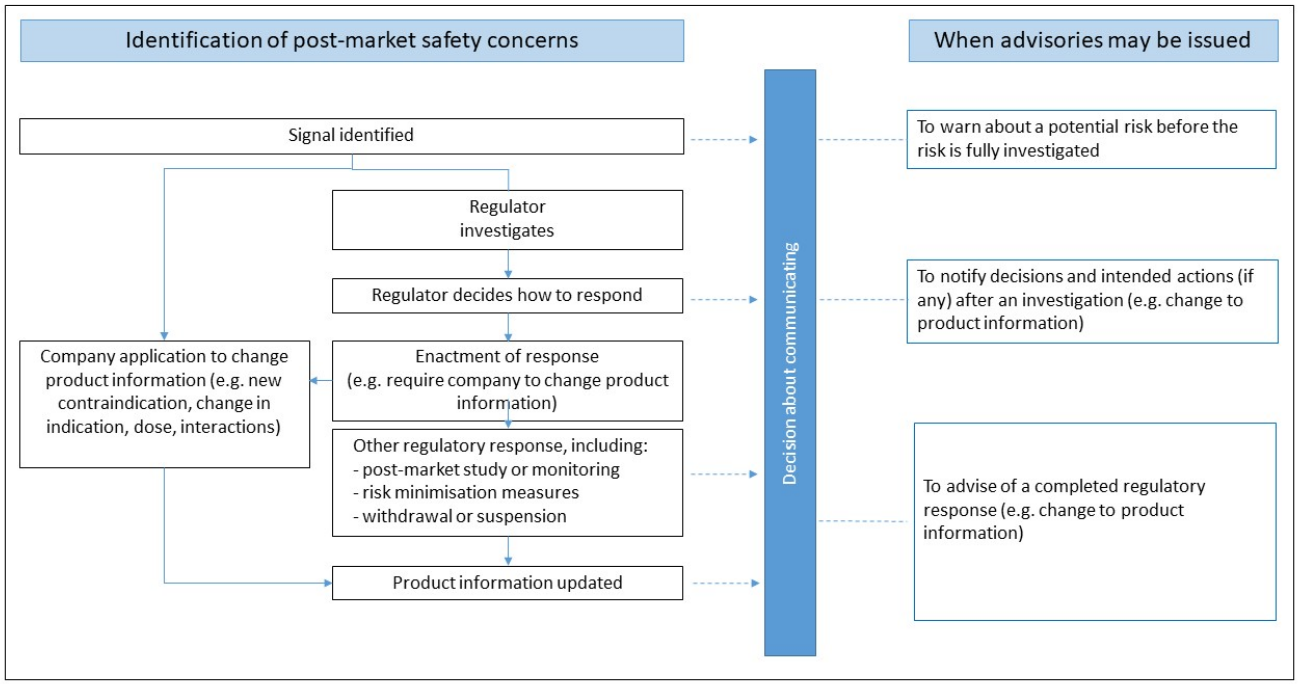
Post-market safety monitoring and medicines' life-cycle risk management are typically handled by a dedicated post-market surveillance unit within the regulatory agency. This monitoring can include adverse drug event reporting and post-market studies, typically by industry (voluntary or mandated) or active surveillance of large datasets.

Agency structure can contribute to fragmentation in awareness and decision-making. For example, to update prescribing information with new post-market safety data, companies must apply to regulators, either on their own initiative or when required to do so by regulators. In some agencies, these changes are managed by the unit that approved the drug, which is not responsible for either post-market monitoring or post-market safety advisories.

Where emerging evidence of a safety issue points to the possibility of an error or oversight in the pre-market evaluation, cognitive bias may compromise an objective review of the decision. Additionally, units responsible for surveillance or post-market safety have traditionally had less power or recognition in the institutional hierarchy than those responsible for new drug approval, and in some jurisdictions may be less well resourced.[12, 31, 34] Finally, regulatory action can be delayed by governance issues including complex decision-making structures, unclear accountability and legal hurdles.[37]

Poor clarity in roles and power imbalances have been identified as weaknesses.[1, 12] Stronger systems would allocate responsibilities clearly, and have coordinating mechanisms and oversight in place.

Figure 1: Timing of advisories and identification of post-market safety issues



Differences among regulators

FDA

At FDA, new drug assessment and post-market surveillance are managed by separate units. At new drug approval, FDA staff can mandate post-market studies and/or interventions to manage risk known as risk evaluation and mitigation strategy (REMS) programs.[38]

Post-market, safety decision-making occurs internally using a cross-team approach involving new drug assessors (Office of New Drugs), post-market surveillance staff (Office of Surveillance and Epidemiology), and communications experts (Office of Communications).[38, 39] This multi-disciplinary approach has been specifically adopted to overcome internal disagreements regarding the significance of post-market safety evidence arising from different methods of assessing harm,[40] but means that no single unit is responsible overall.[12, 41]

The Office of New Drugs is still responsible for making post-market product information changes, either before or after safety advisories are issued. Operationally, the Office of Communication prepares and disseminates drug safety messages.[42] The Office of Surveillance and Epidemiology does not therefore have full responsibility for post-market safety.

At its discretion, FDA may consult expert advisory committees on post-market issues.[31, 43] Public participation and representations are allowed as part of these committee meetings.[44]

EMA

Since the 2012 EU pharmacovigilance legislation, responsibility for post-market safety has been centralised in EMA's Pharmacovigilance Risk Assessment Committee (PRAC), replacing the Pharmacovigilance Working Party that advised the Committee for Medicinal Products for Human Use (CHMP).[45] Before the 2012 legislation, final decision-making for

pharmacovigilance was largely managed by EU countries' national regulatory agencies, with less consistency between countries.[46] The PRAC comprises representatives of EU regulatory agencies, individual scientific experts, and consumer and healthcare professional representatives. PRAC members take "rapporteur" roles for specific products, supported by their respective national regulatory agency and EMA staff. The PRAC makes recommendations to governing bodies within EMA: the CHMP for products centrally authorised across the EU (after assessment by EMA on behalf of all member states) by the European Commission, and to the Coordination Group for Mutual Recognition and Decentralised Procedures—Human for nationally authorised medicines, for which national EU regulators are the competent authorities.

This arrangement separates responsibilities for medicines approval from post-market safety assessment and allows for a co-ordinated, centralised assessment of pharmacovigilance considerations before and after approval. At the time of approval for centrally authorised products, PRAC advice on risks, surveillance requirements, and post-market studies are included in the drug's risk management plan initially proposed by the company. Post-market, for both centrally and nationally authorised products, the PRAC assesses pharmacovigilance signals and data and recommends actions, including product information changes, which are then executed following acceptance by governing bodies. Any national authority, company, or the PRAC itself can refer an issue posing a "potential serious risk to public health" to EMA for investigation. This process is called a "referral procedure" and can result in changes to or withdrawal of marketing authorisation for both centrally and nationally authorised medicines.[6] Post-market safety decisions made by EMA for centrally authorised products and referral procedures are legally binding in all member states.

For EMA, public participation in regulatory decisions includes consumer, healthcare professional and additional expert representation on the PRAC and public hearings. Public hearings are authorised by EU legislation, but only held when regulators consider them

appropriate.[5] Public hearings have been held to discuss consumer perspectives on risk management of valproate teratogenicity and serious adverse effects of fluoroquinolones.[47, 48]

Importantly, EMA differs from other regulators in that it is a supranational agency, sharing pharmacovigilance responsibilities with national regulatory agencies. EMA has primary authority for centrally authorised products and is responsible for maintaining their marketing authorisations, product information and risk management plans. For products authorised centrally or nationally, EMA supports signal management and co-ordinates other activities including maintaining EudraVigilance (a centralised repository of adverse event reports across the EU and worldwide), and a process for EU-single assessment of periodic safety update reports (PSURs) to be submitted by marketing authorisation holders according to standard or enhanced schedules. National authorities are responsible for signal detection, risk management plans, and maintaining marketing authorisations and product information for nationally authorised products.[49]

Safety communication is prepared by EMA staff and discussed and endorsed by PRAC as part of their assessments and decisions, and EMA coordinates consistent communications across the EU, while the national authorities are in charge of translations and local adaptations of PRAC-agreed materials as well as national communication strategies.[50]

Health Canada

Health Canada's governance of post-market safety is shared across different directorates within the Health Products and Food Branch. The Marketed Health Products Directorate is responsible for post-market issues including surveillance and risk communication (which is managed by the Office of Policy, Risk Advisory, and Advertising).[51, 52] Responsibility for changes to prescribing information rests elsewhere, with the directorates responsible for pre-market assessments and approval (the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate). Decisions regarding whether, for example a post-market

prescribing information change necessitates an advisory, therefore relies on consultation between different directorates.

A 2011 Auditor-General's report found that this division of responsibility, and inadequate processes for implementing recommendations were contributing to inaction and delays. Different departments were responsible for making safety-related recommendations and liaising with companies to ensure changes were made, with companies having discretion about whether or not to implement recommendations.[37]

Health Canada convenes short-term expert advisory panels for specific issues, including post-market safety issues, which include members of the public. [53] Examples include panels to consider safety risks of opioids and SSRI antidepressants.[54]

TGA

As with other regulators, responsibilities for medicine approvals and licensing are separated from post-market surveillance functions. New approvals and applications to change prescribing information post-market are assessed within one branch (Prescription Medicines Authorisation), while post-market surveillance and advisories are the responsibility of the Pharmacovigilance and Special Access Branch. The latter also evaluates and provides pre-approval advice on risk management plans decided pre-approval and monitors their implementation.

TGA staff are primarily responsible for assessing post-market safety issues and determining the appropriate response. The TGA had a dedicated expert advisory committee for post-market safety until 2017, when it was abolished, and its functions integrated into a single committee dealing with both prescription and non-prescription medicines. The current Advisory Committee on Medicines is consulted not only on pre-market matters, primarily drug approvals, but also post-market safety matters including emerging safety signals and risk management plans. The membership includes one consumer representative.[55] TGA regulations require public consultation for changes in scheduling (rules governing restrictions

on access such as classification of medicines to prescription-only or over the counter), for which a separate committee provides advice, but not for other safety-related actions.[56, 57]

LEGAL AUTHORITY FOR POST-MARKET SAFETY ADVISORIES AND THE ROLE OF INDUSTRY

Life-cycle regulation allows drugs to be approved or retained on the market despite uncertainties about safety, because of enhanced regulatory control over post-market studies and monitoring. Safety advisories play a key role in communicating post-market events; we therefore examined regulators' mandate to communicate, their authority over industry communications and the role of industry in safety communication.

Table 1: Types of post-market safety advisories used by regulators

	Primary advisory type	Additional advisory types	DHPCs used?	Dissemination
EMA/EU	DHPC	Web alerts National authorities' bulletins or alerts	Yes Company writes; EMA approves	DHPCs: Companies distribute to healthcare professionals. Some national regulators and EMA* post on their websites. National regulators may target professional societies, healthcare and consumer organisations.
FDA	*Drug Safety Communication* (online alert)	Podcasts	Only within post-approval REMS; company writes; FDA approves	REMS–DHPCs are distributed by companies to healthcare professionals; available on FDA website. Drug Safety Communication: FDA website, media and digital channels to reach specific health professionals and consumers; distributed to some US Federal authorities.[a1]
Health Canada	Multiple forms including DHPC and online alerts/notices	Health Product Infowatch (online drug bulletin) Information Update (website alert) Notice to Hospitals Public communication (must accompany any DHPC and is put on Health Canada website)	Yes, Health Canada or company may issue	DHPCs: Companies distribute to healthcare professionals, and hospitals. Health Canada posts advisories on its website and may target distribution to professional associations, health and consumer groups.[a2]
TGA	Alert	Medicine Safety Update (online drug bulletin) Direct communications to professional medical organisations and colleges (may not be publicly available)	No	DHPCs: not regulated, company distribution is not described in guidance or regulation (informal process).[a3] As well as online alerts, the TGA may selectively disseminate other information to professional societies and consumer groups [a4]

Note: Different terms are used by individual regulators for letters directly sent to health professionals as follows: **Health Canada** - 'Dear Health Care Professional Letter (DHCPL) for direct letters to health professionals; Health Professional Communication (HPC) includes letters to health professionals and Notices to Hospitals; **FDA** - Direct Health Care Professional letters; **EMA** - Direct Health Professional Communication (DHPC).* EMA web posting of DHPCs started from February 2020

Differences among regulators

Table 1 describes the types of safety advisories used by each regulator, including DHPCs issued by industry. Various dissemination methods are used as shown in Table 1, including targeting of professional societies and consumer groups, or directly to individual healthcare professionals. Regulators' authority for issuing advisories is described below.

FDA

The FDA Amendments Act of 2007 (FDAAA) required FDA to maintain a website providing "information, alerts and recalls" as well as the power to require REMS programs, strengthening FDA's role of providing information to the public.[7] Prior to FDAAA, the Food, Drug, and Cosmetic Act described how drug safety warnings letters should be formatted typographically, but had no requirements for when they should be issued or their content. FDAAA required FDA to develop robust and multi-faceted systems to communicate emerging post-market drug risks."[7]

FDA *Drug Safety Communication,* FDA's primary post-market safety communication includes information for both healthcare professionals and consumers. It is disseminated via FDA's website, email, and social media and described as "FDA's independent analysis of emerging information and FDA's scientific judgment as to the appropriate communication of this emerging drug safety information to the public." Industry's role is limited to providing factual accuracy checks where required, with companies given 24 hours' notice prior to issuing advisories.[58, 59] *Drug Safety Communications* focus on emerging safety issues, and can be issued early in regulatory investigation or after a product information change.[59]

DHPCs are regulated by FDA in a limited way. Companies may choose to issue DHPCs voluntarily but cannot be compelled to do so by FDA except as part of a REMS. REMS-related DHPCs may be imposed pre- or post-market as a component of a communication plan.[21, 30] FDA review of DHPC content is mandated when the DHPC is part of a REMS, but

can only be requested for letters issued voluntarily by companies;[60, 61] only REMS-DHPCs are available on the FDA website.

EMA

EU legislation requires regulators to provide "important information to the public on pharmacovigilance concerns…in a timely manner" (Article 102, Directive 2001/83/EU).[62] Companies must advise regulators of any planned safety communications (Article 106a) and must ensure that any safety communication is 'presented objectively and is not misleading' (Table 1).[62]

EMA issues safety announcements on its website, which are shared under embargo across the European regulatory network prior to publication so that they can be translated and disseminated by national authorities if they choose to do so. The PRAC is responsible for risk communication at EMA level. However, each member state determines how to disseminate communications, for example, via drug safety bulletins or website information. Apart from adjustments for local context (for example drug names or available doses), safety decisions made by EMA cannot be reassessed by an individual member state and core content cannot be changed.[50]

EMA guidance[50] states that only certain communications are likely to be co-ordinated centrally for practical reasons related to capacity and workload. The list of such communications is not proscriptive, but prioritises new contraindications, restrictions of indications, changes in dosing, and the outcomes of referral procedures.[50]

The outcomes of all referral procedures are communicated through the EMA website and EMA issues media releases, information for consumers and healthcare professionals as well as detailed information about the decision-making process, all of which are accessible through a single location on its website.

DHPCs are commonly used in Europe[63] and according to EMA guidance,[16] should be developed in cooperation between companies and regulators. The final text is approved by EMA's PRAC,[50] whose agreement with the wording is noted in the letter, although EMA approval is not formally required by regulation. The DHPC is then disseminated by the company directly to healthcare professionals in their national language and may additionally be posted on EU regulators' websites.

Health Canada

Post-market safety communications are not specifically described in Canada's Food and Drugs Act or the Food and Drug Regulations.[64, 65] Significant reform to drug safety regulation in Canada occurred with the *Protecting Canadians from Unsafe Drugs Act of 2013* (Vanessa's Law), requiring companies to report safety-related actions undertaken by international regulators, including those leading to regulatory risk communications or actions such as recalls or withdrawals. Further, Vanessa's Law provides Health Canada with the mandate to obtain safety data held by companies, along with powers to recall products where there is a "serious or imminent risk of injury to health," authorities previously lacking.[66] Despite this, Vanessa's Law has no additional provisions for post-market safety communication.[67]

In guidance documents, Health Canada states that companies have the "primary responsibility to monitor the continued safe use of its products and communicate new information on the safety of a product in an effective and timely manner."[68] However, the recommendations in guidance documents are not enforceable. Health Canada has several different forms of risk communication, including DHPCs and website notices.[69] (See **Table 1**) High-urgency communications, when "death or other serious adverse health effects" are "reasonably probable," are led by Health Canada. Otherwise a risk communication could be led by either a company or Health Canada.[68]

As with other regulators, Health Canada expects companies to provide DHPC content for review but does not have the force of law to require it. When a company issues the communication, Health Canada's agreement with the content is indicated in the letter. Accompanying notices may also state that Health Canada did not conduct its own review as it agreed with the actions taken by the company.[70] According to guidance, Health Canada will take the lead if "industry refuses to issue or refuses to issue in a timely manner" or if the "company disagrees with or will not discuss with Health Canada content of industry-issued communication." Healthcare professional communications should be accompanied by a consumer notice on the regulator's website.[71]

TGA

A legislative basis for post-market safety advisories in Australia was formally introduced via a 2009 amendment to a section of the Therapeutic Goods Act 1989 allowing the release of "specified information," with safety alerts newly specified as a form of regulatory information.[72] Prior to this, the regulator had issued a regular drug safety bulletin intended for healthcare professional audiences.

Companies must notify the TGA of any "significant safety issues," which include any development that in the professional judgment of the company warrants the "urgent attention of the TGA….because of the seriousness and potential major impact on the benefit-risk balance of the medicine and/or on patient or public health," including those that might require "prompt regulatory action and/or communication to patients and healthcare professionals." Any issue leading to action by a foreign regulator is considered reportable and must be notified to the TGA within 72 hours of the company becoming aware of it.[73]

There is no formal requirement in Australian regulation or guidance for the TGA to oversee post-market safety communications by industry. The TGA does not publish DHPCs issued by industry or provide them to parties requesting them, but discussions about DHPCs occur informally.[74]

The TGA formally adopts many EMA guidelines, (for example for risk management plans) and these may be adopted unchanged or with modifications. Public consultation occurs prior to adoption.

RISK COMMUNICATION CAPABILITY AND MONITORING EFFECTIVENESS

Whether regulator-authorised risk minimisation strategies actually reduce harm to patients has not been conclusively demonstrated, and the impact of post-market safety advisories and DHPCs on prescribing behaviour is uncertain.[36] Systematic reviews examining the effects of post-market warnings on prescribing have had mixed results,[75-78] with one review finding that FDA warnings had only weak or modest impacts on prescribing rates in 50% of studies.[75] Regulators responding to these studies have challenged whether changes in drug prescribing volume are an appropriate outcome measure;[79] raising questions about the goals of post-market safety communication, and how its effectiveness is assessed.

Communications may not achieve their intended effect due to inadequate dissemination or poor knowledge translation into practice. While 60-90% of healthcare professionals report receiving regulatory communications,[63, 80-82] their knowledge of specific messages may be less than 50%.[82, 83] Repeat communications or media attention have been shown to amplify the impact of warnings on both knowledge and prescribing.[76, 83, 84]

Behavioural-based theories of risk communication acknowledge that people do not make entirely rational decisions about risk information.[35, 85] Communication is not just the transmission of information but depends on context, including the beliefs, knowledge, and attitudes of the recipient.[35, 85]

Numerous examples demonstrate the variable responses to safety warnings. The rosiglitazone case saw regulators blamed for secrecy, delayed action, and delayed communication.[86] In contrast, regulatory warnings about increased suicidality with the use of antidepressants in young people were met by some physicians with disbelief and even

hostility.[87, 88] Natalizumab was reapproved after initial withdrawal because patients were willing to accept the risk of serious brain infections in return for the possible benefits in the treatment of multiple sclerosis.[89] Although these cases may also reflect disagreement with regulators' benefit-risk assessments, they indicate the importance of framing, context, and values in communication.

Perceptions of the messenger can also play a part. Poor public awareness of, or a lack of confidence in, the regulator may affect the salience of safety messages.[36, 90] Perceived commercial influence on regulators can reduce trust in messaging and cause reputational damage to regulators,[91] although healthcare professionals appear to prefer receiving safety advisories from regulatory authorities rather than pharmaceutical companies.[63, 83, 92]

In addition to providing information to support clinician and patient decision-making, some regulators specify behavioural goals for safety advisories (Table 2).

Table 2: Differences in regulatory policy for post-market safety advisories (also see Supplementary file)

	EMA	FDA	Health Canada	TGA
1.GOVERNANCE AND DECISION-MAKING				
Separation of authority for post-market decision-making	Yes. PRAC responsible for post-market assessment and recommendations.	No. Multi-team approach. [a5post]	No. Multiple departments involved.	No. Approvers assess applications to change product information.
Public involvement in post-market safety governance	Consumer and healthcare representatives on PRAC.	Not routinely.[a6]	Not routinely.	Not routinely.
2. LEGISLATIVE AUTHORITY, INDUSTRY RESPONSIBILITY AND REQUIREMENTS				
Regulators' responsibility for post-market safety communication - described in regulation/ legislation	Yes Article 102, Directive 2001/83/EC on the Community code relating to medicinal products for human use.[a7]	Yes FDA Amendments Act (FDAAA 2007)	No	Partial (allows information release) Subsection 61(5C) of the *Therapeutic Goods Act 1989* (amended 2010)
Regulatory requirements for industry post-market safety communication	**Regulation** Company must inform the regulator about safety announcements. (Article 106a) [a7] Information to the public must be presented objectively and not misleading.(Article 106a)[a7] **Guidance** Company should co-operate with regulator in preparing DHPCs.[a8]	**Regulation** Company can be required to issue a DHPC as part of REMS. (FDAAA)[a9] Format of markings (e.g. "Drug safety warning') for DHPCs and envelopes are legislated but not when to issue. (CFR 200.5)[a10] **Guidance** REMS-DHPCs must be approved by the FDA. For non-REMS DHPCs, companies are encouraged to collaborate with FDA.[a11]	**Regulation** Not described in regulation. **Guidance** Company encouraged to inform Health Canada' about DHPCs. Health Canada may request DHPCs and will issue a Health Canada alert if the company disagrees or delays.[a12]	DHPCs are not regulated by TGA and no guidance is in place.
Industry involvement in regulator-issued alerts	Companies draft DHPCs for EMA review and approval.	No role of industry stated beyond fact-checking.[a13]	Companies draft DHPCs for Health Canada review.	Company may review alerts for fact-checking.[a4]

	EMA	FDA	Health Canada	TGA
3. RISK COMMUNICATION CAPACITY				
Regulatory goals for safety advisories include to i) inform and ii) achieve behavioural outcomes	Inform and change behaviour[a8]	Inform [a14]	Inform[a2‘a15]	Inform[a16]
Risk communication criteria, guidelines and resources	Guidelines for regulators and industry[a8]; specific guidelines for vaccine risk communications and young people.[a17, 18]	Guidance for industry and FDA for DHPCs.[a11] Guidance for classifying post market safety concerns.[a13] Risk communication guidance.[a19]	Guidance for industry and template for DHPCs.[a12, 20] Process, criteria and description of all risk communication products (2008). [a2]	Process, criteria, description and template for regulatory alerts.[a4]
Risk communications strategic activity and planning	Yes [a21, 22]	Yes [a23]	Yes (2006, 2015) [a24]	Not in public domain
Activities for monitoring effectiveness of advisories	Described in regulation, guidance and strategy.[a7, 8, 25] Research undertaken.	Required by regulation for REMS only. Required by legislation to develop robust systems in partnership with academics and professionals.[a9] Research to examine effectiveness of Drug Safety Communication alert.[a26-29]	Not described in regulation. Evaluation framework published but unclear if implemented. [a24]	Not described in legislation or guidance.

Differences between regulators

FDA

FDA's goal in communicating risk information is primarily to enable informed decisions by patients and clinicians. (Table 2) The agency has sponsored research into the impact of FDA safety communications,[42, 93-95] and issued guidance regarding best practice in risk communication for industry and regulators.[61, 96] Since 2006, FDA's Risk Communication Advisory Group has provided strategic oversight but is rarely involved in individual communications.

FDA asks companies to provide assessment plans containing information about the effectiveness of REMS programs (which often include communications), yet FDA does not have any enforcement authority if companies do not submit the information requested, and the methods for evaluating effectiveness continue to evolve, according to FDA guidance.[21, 97] An independent evaluation found that reliable methods for assessing effectiveness had not been established. Of 49 REMS assessments reviewed, only 7 were considered to be meeting FDA goals.[21] The REMS communication plans reviewed were rated poorly, patient and prescriber awareness of the communicated drug risks was low or not measured.[21] FDA has conducted research to help identify appropriate methods for assessing the impact of risk communication.[75, 98]

EMA

EMA goals for safety communication include changing behaviour, attitudes and decisions of physicians and patients, and increasing public confidence in regulators (see Table 2). EMA has conducted research to understand clinicians' and other stakeholders' preferences for communication,[63, 99, 100] and systematically reviewed the impact of regulatory interventions.[77] Published guidance describes best practice in risk communication for industry (including

DHPC templates) and national EU regulators, and advice for tailoring safety communications for vaccines and to younger people.[50, 101, 102]

EU regulations require regulators "to monitor the outcome of risk minimisation measures contained in risk management plans,"[5] while guidance[50] states that the effectiveness of safety communications should be measured where possible, generally using a research-based approach, to measure outcomes "including behaviour, attitudes, and knowledge."

EMA has conducted research to help identify appropriate methods for improving risk communication[100] and assessing its impact.[77]

Health Canada

Health Canada's goals for advisories relate primarily to enabling better decisions by healthcare professionals and patients. It has developed guidance and a DHPC template for industry use and has recently established a risk communication section within the Marketed Health Products Directorate. Health Canada guidance states that it may request follow-up information after a safety communication,[71] or recommend evaluation of risk minimisation as part of a risk management plan[103] but neither appears to be an enforceable requirement. Under Vanessa's Law, Health Canada can require companies to compile information or studies about therapeutic products, but not specifically of the effectiveness of risk mitigation.

Health Canada commissioned an external review to examine how it could measure and evaluate the effectiveness of risk communications (published in 2015),[36] but whether any further steps have been taken towards implementing recommendations is not communicated on its website.

TGA

While the TGA formally adopts many EMA guidance documents, including for those for the development of risk management plans,[104] to date it has not published any guidance to industry on how it should undertake risk communication. Like EMA, the TGA requires risk

management plans to describe how the effectiveness of risk mitigation activities will be evaluated. For drugs approved in Europe earlier than in Australia, the Australian Risk Management Plan is substantively the EMA Risk Management Plan, adapted as required for the Australian context.[105] While EMA guidance suggests new risk mitigation requirements may be requested post-market, as is authorised under EU law, there is no similar authority within TGA legislation. Updates to risk management plans are not made publicly available, nor are details of any evaluations conducted by companies, if these are in fact occurring.

TRANSPARENCY

Many of the changes in the information available about post-market safety since 2005 have arisen because of public demands for transparency. For example, the 2006 Institute of Medicine Report stated that the lifecycle approach would require industry's "increased transparency toward FDA in the process of elucidating and communicating emerging information about a drug" and further that "FDA's credibility is intertwined with that of the industry".[1] Transparency refers to processes and features which allow the disclosure of information, decisions and rationales, interactions between public bodies and the regulated industry, and dissenting views.[32, 106-108] While safety advisories publicise risks in order to raise awareness or change behaviour, transparency is a matter of public accountability,[35] and may improve public participation in value-setting through better understanding of decision-making.[32]

A considerable body of literature examines the extent to which regulatory actions and regulations may be shaped more by industry needs than those of the public,[9, 33, 108-112] arising in part because of industry's role in developing and manufacturing medicines and hence its direct participation in the regulatory process. Transparency can enhance confidence that decisions are made in the public interest.[32, 106]

After the rofecoxib withdrawal, FDA undertook to provide the public with access to information on safety signals even before their significance had been determined, allowing

independent researchers to review and interpret the data.[91] However the availability of post-market safety data remains limited and has not kept pace with improvements in the transparency of pre-market data in the form of clinical study reports.[113, 114] Most regulators allow public access to spontaneous adverse report databases but other post-market data including periodic safety update reports (PSURs) and results of post-market studies undertaken as a condition of marketing approval are often unavailable.[107, 115]

Commercial confidentiality concerns can result in the suppression of information including that which is ostensibly made public (e.g., through redaction). [107] There are instances where drug safety information has been withheld to protect a company from the potential financial impact of reducing consumer and healthcare professional confidence.[31, 107, 116] Financial conflicts of interest have been shown to be associated with decisions and voting patterns of expert advisory committee members and representations of consumer viewpoints that favour industry interests, reducing the objectivity of advice.[117-119]

Differences between regulators

Table 3 describes the documents available from each regulator in relation to post-market safety. Table 4 lists documentation available for two advisories for SGLT2 inhibitors. There was more documentation for EMA decisions than for all other regulators.[120]

Table 3: Transparency of decision-making and post-market safety data

	EMA	FDA	Health Canada *	TGA
POST-MARKET SAFETY ADVISORIES				
Sources describing decision-making and background to advisory	• PRAC minutes • PRAC assessment report for Referral procedures (include descriptions of data reviewed) • Scientific conclusions: for product information changes; and for PSUR single assessments (PSUSA) • PRAC recommendations for changes to product information following signal assessment translated in all EU languages	Data summary within each *Drug Safety Communication*	Summary safety reviews published if advisory arises from data investigated by Health Canada, but not by sponsors. If a sponsor is compelled to provide safety information, it must be made publicly available.[a30] Vanessa's Law allows Health Canada disclosure of evidence and reasoning supporting decision-making on serious risks.[a31]	Meeting statements for the Australian Committee on Medicines when post-market safety issues are discussed.
Sponsors contributions to process and decision-making for advisories	The sponsor's role and views of the safety concern may be described in 'Scientific Conclusions' for PSURs or PRAC assessment reports for referral procedures. Industry DHPCs note that content has been agreed with the regulator.	No	Industry DHPCs published by regulator have a note that Health Canada agrees with the action taken. No details of discussions with industry.	No

	EMA	FDA	Health Canada *	TGA
RISK EVALUATION ACTIVITIES				
Risk minimisation activities current and historical	The summary RMP is updated with changes. Resolved issues not listed.	Databases of: • REMS goals, materials, messages, & archives • post-market requirements (PMRs), post-market commitments (PMCs) and their completion No centralised list of all requirements for a single drug.	No	Summary Risk Management Plan at approval only. Updates are not publicly available.
Post-market safety studies required by regulators described	• Descriptions in RMP • Protocols and abstracts of results published in EU post-market study registry (ENCEPP). Provision of data is voluntary	The study is briefly described in Summary Review at approval and on FDA website as "Post market commitments and completions". No details of study results are available	No	Descriptions in AUSPAR at approval only. Protocols available (via EU ENCEPP where the same protocol applies)
Description of changes to product information and other approval history	• Yes[a32] • Procedural steps taken and scientific information after the authorisation. • Descriptions of the nature of label changes provided in EPAR for individual drugs – steps after authorisation. • List of all signals assessed and discussed by the PRAC and resulting changes to product information listed by meeting. [a33] • Outcomes of PSUR assessments: for centrally authorised medicines: EPAR • for nationally authorised medicinal products and 'mixed' procedures: the Community register maintained by the European Commission [a34]	No Response letter from FDA briefly describes change required. Some FDA review memos published (e.g. canagliflozin, amputation).	Partial: Post-authorisation activity table (PAAT) for new drugs and subsequent entry biologics since 2012. States that a change has occurred and the date but not the nature of the change.	No
All revisions of product information available	Yes	Yes	No (Current version only)	No (Current version only. For drugs approved >2010 the

	EMA	FDA	Health Canada *	TGA
				original is in the AUSPAR.)
SURVEILLANCE DATA				
Signals being tracked	EMA provides a spreadsheet of all signals tracked, discussed and whether they resulted in label changes. The internal EPITT database is not public.	List of issues being tracked in FAERS, but not the internal DARTTS database.	No	No
PSURs published	No (provided on request in person to EU citizens)	No	No	No
Adverse drug event reports	Eudravigilance - yes	FAERs - yes	Canada Vigilance adverse reaction online database	DAEN - yes

* Vanessa's Law enabled the Minister to release certain confidential business information to certain people to protect or promote public health and safety. The results of any post-market safety examination undertaken by the regulator must be made publicly available on the Government of Canada website. Health Canada intends to make meeting minutes available, and to include adverse event reports with decisions and product monograph on product register. [a35]

AUSPAR: Australian Product Assessment Report. DAEN: Database of Adverse Event Notifications - database of adverse event reports submitted to the TGA. DARTTS: Document Archiving, Reporting, and Regulatory Tracking System – used to track significant safety issues related to marketed prescription and over-the-counter drugs. EMA: European Medicines Agency. EPAR: European Product Assessment Report. EPITT: European Pharmacovigilance Issues Tracking Tool - a web-based system that tracks and monitors the safety of medicinal products. FAERS: FDA Adverse Event Reporting System – FDA's database containing information on adverse event and medication error reports submitted to FDA. FDA: Food and Drug Administration. TGA: Therapeutic Goods Administration (Australia) PRAC: Pharmacovigilance Risk Assessment Committee. PSUR: Periodic Safety Update Report. PSUSA: PSUR single assessments – the PSUR is reviewed once for all EMA member states. RMP: Risk management plan. For EMA, see: https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-when

Table 4: Case study - transparency of decision making in sodium glucose co-transporter -2 (SGLT2) inhibitor advisories for diabetic ketoacidosis (DKA) and acute kidney injury

		EMA	FDA	Health Canada *	TGA
Advisories	**Acute kidney injury**	No	Alert (*Drug Safety Communication*)	Bulletin/Investigation report	No
	Diabetic ketoacidosis (DKA)	DHPC (before investigation) Alert (on identification)	Alert x 2 *(Drug Safety Communication) – before and after investigation*	Information Update (web alert) DHPC	Alert
Product information changed	**Acute kidney injury**	Yes (canagliflozin)	Yes (all SGLT2s)	Yes (canagliflozin and dapagliflozin)	Unknown
	DKA	Yes	Yes (boxed warning)	Yes (boxed warning)	Yes
	Acute kidney injury	• PRAC agendas and minutes • PRAC scientific conclusion – PSUSA <u>Individual drug information</u> • Risk Management Plan summary (updated) • EPAR Procedural steps taken after authorisation • Webpage listing full assessment history • Revised product information and date of change (in EU languages)	*Drug Safety Communication* data summary section <u>Individual drug information</u> • Letters to sponsors approving safety-related product information change (but not what was requested) • All historical product information	Summary Safety Review <u>Individual drug information</u> Post-authorisation Activity Table (Summary basis of decision) – lists changes made after approval, including when applications made by sponsors (content of request not provided)	

		EMA	FDA	Health Canada *	TGA
Information about decision making	**DKA**	• PRAC Minutes and agendas • Referral procedure documents: - rationale for starting the review - timetable for procedure - PRAC list of questions to the sponsor - PRAC Assessment Report - Scientific conclusion - Press release - Information for prescribers and the public <u>Individual drug information</u> • Risk Management Plan summary (updated) • EPAR Procedural steps taken after authorisation • Webpage listing full assessment history • Revised product information and date of change (in EU languages)	As above	As above	- -

DHPC: Direct Health Professional Communication. EMA: European Medicines Agency. EU: European Union. EPAR: European Public Assessment Report FDA: Food and Drug Administration. TGA: Therapeutic Goods Administration (Australia) PRAC: Pharmacovigilance Risk Assessment Committee. PSUR: Periodic Safety Update Report. PSUSA: PSUR single assessments – the PSUR is reviewed once for all EMA member states.
RMP: Risk management plan

FDA

FDA's Drug Safety Communication includes a data summary in each advisory, but little other information regarding data or decision-making processes is published by FDA. Summary reviews, similar to those published about new drug approvals, are not routinely available for post-market safety changes. In situations where an FDA advisory committee is consulted about a post-market safety issue, all meeting papers and transcripts are available as per usual committee processes.[44]

For individual drugs, archives of previous prescribing information and the letters from FDA to companies approving changes are published online. Since only the FDA approval letter is published, without any details of correspondence or review processes, the impact of negotiations with the company cannot usually be ascertained.

FDA documents all post-market requirements and commitments and their fulfillment dates but does not publish the final reports or data from post-market studies.

EMA

The EU pharmacovigilance legislation places requirements on regulators for transparency, as long as they do not breach personal data protection or commercial confidentiality, defined broadly as "any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information."[121]

Information is provided on many aspects of post-market safety decision-making, including PRAC meetings, summaries of PRAC assessments of post-market signals, recommendations resulting in product information changes, and actions taken on post-market safety reports (Table 3). Meeting materials, including draft documents for discussion and meeting transcripts. are not available, and items may be omitted from summaries when considered necessary for commercial confidentiality. Detailed assessment reports are

available for EMA referral procedures (specific post-market investigations undertaken by the PRAC in response to an identified signal or issue on behalf of all EU member states). For these procedures, the PRAC assessment report describes the trigger for the safety concern, data, and decision-making rationales, along with descriptions of companies' contributions to the procedure. There is no equivalent documentation in other jurisdictions.

For individual drugs, the European Public Assessment Report (EPAR) is a single collection of documents for centrally approved medicines. It includes a summary of pre-authorisation information, all changes made to a medicine's product information and regulatory status after approval, details of post-market studies and requirements introduced after marketing, including a summary of the risk management plan, assessment reports, and a medicine overview written in lay language. The EPAR Procedural Steps after Authorisation document describes changes to product information and when they occurred. Rationales for these changes, dates, and previous versions in EU languages are available (Table 3).

A register of post-market studies by companies and others is maintained by EMA, with companies required to document details of any studies required by regulators.[122] EMA guidance asks companies to provide details of voluntarily conducted studies and to include interim and final study reports on the register, but this is not mandated.[123]

Health Canada

Published Summary Safety Reviews explain some regulatory post-market safety decisions but appear to be published only for reviews undertaken by Health Canada, not by industry. Health Canada-approved risk management plans are not publicly available.[103] As part of its Regulatory Transparency and Openness Framework and Action Plan 2017-2018. Health Canada has said it will publish decisions made by Scientific Advisory Panels and Scientific Advisory Committees, as well as aggregated regulatory decision documents with product monographs and adverse event reports.[124] Vanessa's law requires the regulator to provide information about post-market safety investigations it mandates or information it requests

from companies.[125] Currently, limited information and meeting minutes are available for some post-market safety decisions.

Vanessa's Law additionally allows Health Canada (as the representative of the Minister or her/his delegate) to disclose confidential business information "if the Minister believes that the product may present a serious risk of injury to human health" (section 21.1 (2)) or if the disclosure is "related to the protection or promotion of human health" and the disclosure is to a suitably qualified person (health or research qualifications or experience).[125, 126] A guide to the legislation states that the Minister will provide reasoned decisions to companies, justifying her/his actions when making any order (e.g., changes to prescribing information) based on the new provisions.[125]

Health Canada provides a summary of changes to the product monograph in a post-authorisation activity table, modelled on EMA's EPAR Steps After Approval for new drugs and biosimilars approved since 2012. Health Canada's table provides limited detail, describing, for example, the date of a prescribing information change, but not the nature of the change.

TGA

In 2009, amendments to the Therapeutic Goods Act (the Therapeutic Goods Amendment [Medical Devices and Other Measures] Act 2009) allowed the TGA to release more information to the public, including TGA and Expert Committee evaluations of new medicines, committee minutes, and details of pharmacovigilance activities required of companies.[72] The provisions allow a broad range of information to be released to the public referring to "any decision or action taken under this Act or the regulations." Despite this, there is little post-market information in the public domain documenting safety-related decision-making, changes to prescribing information, or risk management plans. Published meeting statements very briefly summarise Advisory Committee on Medicines discussions on those post-market issues,[127] with the TGA stating that for post-market safety discussions

"the information referred to, and relied on, by the Advisory Committee on Medicines does not usually contain commercial-in-confidence material."[127]

CONSIDERATIONS

Post-Market Safety Governance and Risk Minimisation Frameworks

Governance structures and lack of clear accountability within regulatory agencies can contribute to regulatory communication failures and delays.[1, 37, 66, 128] Amongst the four regulators, EMA had the most focused governance structure for pharmacovigilance, with the PRAC responsible for post-market safety under legislation. The PRAC's sphere of activity encompasses the whole life-cycle from pre-market pharmacovigilance and risk minimisation planning to monitoring ongoing benefit-risk balance and withdrawing marketing approval. EMA's supranational role means that its structure cannot be directly compared with national regulators, and it is not possible to say whether this more holistic arrangement results in better decision making or timeliness.

The PRAC's inclusion of both regulators and public representatives in post-market safety decision making also contrasts with other regulators, who draw on non-regulatory healthcare professional expertise and consumer representation on an ad hoc basis (e.g., public consultations on opioid prescribing (Canada), fluoroquinolones and tendon rupture (FDA), valproate and birth defects (EMA), and codeine safety (TGA)). The depth of public engagement in drug safety decisions vary[129] and the most effective methods have not been determined. Techniques including consumer testing of patient communications, public consultation, public hearings, and consumer representation on advisory committees. There is growing concern about the independence of consumer voices due to evidence that industry funding may influence patient group representations to regulators.[118, 130, 131] Mechanisms for public participation must therefore provide safeguards against conflicts of interest as well as ensuring adequately informed consumer input. An alternative model could be similar to the UK's National Institute for Health and Care Excellence (NICE) Citizens

Council, an independent body of consumers consulted on a range of specific matters using a deliberative approach, to better understand community perspectives.[132]

Legal authority and the role of industry

EMA and FDA have a legislative mandate for post-market risk communication, giving them authority to issue their own safety alerts. A similar public health role in post-market risk communication is absent from TGA and Health Canada legislation. Australian advisories are legitimated in the Therapeutic Goods Act by defining them as a type of information authorised for release, while Health Canada relies on guidance documents. Calls to revise Australian legislation have criticised the Therapeutic Goods Act for not including public health as an object of the legislation.[133]

DHPCs issued by industry are a common form of advisory in Europe and Canada.[27, 63, 80, 134] EMA and, to a lesser extent, FDA are more empowered to determine the content of DHPCs than Health Canada and the TGA, with EU legislation requiring that company communications are objective and not misleading and that companies collaborate with regulators, while FDA can mandate content in REMS-related DHPCs, but not in other circumstances.[5, 61]

However no regulator has complete authority under legislation over all DHPCs issued by industry, and potential problems exist with their use as safety warnings. First, discussions over the wording of safety warnings can contribute to delays.[51] Second, companies can contest proposed wording in DHPCs. A Canadian evaluation found that “developing a risk communication involves a considerable amount of negotiation between Health Canada and the Marketing Authorisation Holder (MAH), and that drafting and posting of a risk communication may be delayed until appropriate changes have been made to the product’s labelling.[51] Such situations may lead to compromise and dilution of wording, as seen with FDA negotiations regarding canagliflozin and amputation risk.[120] Most regulatory messages include information targeted to the public, but when the chosen form of communication is an

industry DHPC, there may be no equivalent message to consumers. Finally, healthcare professionals are less likely to trust communications disseminated by industry.[63, 92, 135]

Legislation does not bind the TGA to consult or collaborate with industry for the development or dissemination of safety warnings, nor does it provide the TGA with any authority over DHPCs issued by companies. There is some evidence that TGA informally negotiates with and advises industry in a collaborative manner on preparing and disseminating DHPCs .[74] Australian DHPCs fall within a grey area, as they are neither subject to regulation nor placed in the public domain by TGA because of their commercial ownership. Further, the TGA operates in a model of "responsive regulation," which relies on co-operation and responsible compliance from industry.[136]

While risk communication is intended to support patient safety, paradoxically it also enables medicines with serious adverse effects to remain on the market. While this may be justified when the perceived benefits exceed the risks, there are situations when a warning may not be adequate to mitigate harm. Decisions about whether to warn or withdraw may be directly or indirectly influenced by industry, and depend on the strength of regulation and regulatory decisionmaking.[108, 137] In Europe, the ongoing marketing of benfluorex in France after it had been withdrawn in other EU member states led to both the company and the French regulator facing criminal charges.[138] The benfluorex case led to stronger regulation for EU-wide consideration of serious risks. In Australia, attempts to withdraw dextropropoxyphene because of cardiotoxicity were hampered by the legislated process for appealing TGA decisions, providing the company with multiple opportunities to appeal and the TGA appearing to compromise rather than prolong the appeal process in the hope of achieving a favourable decision.[139] The drug was withdrawn in the Canada, US and UK due to the same adverse effects.

Risk communication capability and monitoring effectiveness

When considering risk communication capability, we noted a continuum of policy development amongst regulators progressing from the acquisition of knowledge, skills, expertise (for example staff or expert advice), guidance, and communication standards, to mechanisms to ensure the effectiveness of risk communication.

EMA is the only regulator to explicitly state that behaviour change, rather than the provision of information alone, is a goal for risk communication,[50] and EMA is required by legislation to ensure that its strategies are effective in achieving this outcome. Regulators should consistently evaluate and continually improve regulatory and industry safety communications to ensure patient safety. This is essential when drugs are approved with an expectation that new safety issues will emerge.[11] Only FDA and EMA require industry to demonstrate the effectiveness of risk mitigation measures including communications. Despite this, standards of measurement and acceptable thresholds for effectiveness have not been established, and a 2013 Office of Audit report found that FDA lacked the ability to determine the effectiveness of REMS.[21] FDA and EMA research undertaken to date has highlighted the complexity of communicating risks of medicines to both healthcare professionals and the lay public and the appropriate methods to evaluate risk communication outcomes remains unclear.[42, 75, 77]

To educate the public on the evolving nature of safety issues, regulators should not shy away from mentioning uncertainties over safety when new drugs are approved. Such uncertainties are identified as part of the approval process, yet are rarely highlighted in public arenas or media releases about new drug approvals.[89] The media plays a key role in disseminating regulatory messages to both consumers and healthcare professionals, but often fail to provide important information[84, 87, 89], potentially leading to unintended consequences such as cessation of treatment by patients not affected by a warning.[35] Regulators could ensure that media releases accompany safety advisories and include key information such as quantified information about risk and benefit.[89]

Smaller regulatory bodies like Health Canada and the TGA do not have the same regulatory systems for post-market risk management or authorities over industry as FDA or EMA. These regulators may rely to some extent on EMA and FDA to identify emerging concerns and on companies to report foreign regulators' actions.[67, 140] This lack of capacity may put their citizens at risk of delayed action. Smaller regulators may still be effective communicators, but need adequate networks and systems in place.[141]

In addition, some regulators have begun using structured benefit-risk decision templates and tools to quantify and systematise decision making. While their initial exploration and assessment have been for the capture of regulatory approval decisions, these tools may also have an application in documenting post-market changes in benefit-risk assessments and identifying thresholds for safety advisories. [142]

Transparency

Regulators have privileged access to new safety information and are uniquely responsible amongst public health agencies for determining its importance and communicating risks to healthcare professionals and patients. Yet this important task occurs in a context of restraint imposed by the industry-focused nature of the regulatory process, particularly in regard to transparency.

Public access to data underlying post-market advisories - except for spontaneous report databases - is limited in all jurisdictions. For example, no jurisdiction provides periodic safety reports publicly, although EU citizens can obtain these on request.[121] Even the results of post-market studies required as a condition of marketing approval are generally not available directly from regulators although they may eventually be published in journals.[107, 121] To ensure that post-market studies provide benefit and value in the clarification of safety profiles, public access is essential.[143] EU legislation has enabled the establishment of a post-market study registry on which EMA-required non-interventional studies must be registered with public protocols and abstracts of results.[50, 122] While a significant step,

complete final reports of mandated studies need not be made available and registration of non-mandated studies is optional.[50]

The imperative for transparency comes from an ethical goal of public accountability and ensuring that decisions are made in the public interest. Given the commercial impacts of regulatory decisions, this remains critical. The transparency of post-market data lags that of hard-won gains in the pre-market arena. Beyond this, improved public understanding of the risks, benefits and uncertainties that inevitably surround drug safety data could support more rational drug use. When new medicines are approved, the average citizen expects this means that they are safe, and the dominant public concerns are of access and price. However, it is well known that serious safety issues often emerge in the early years of real-world use due to the limited data available at the time of approval.[19]

EMA decision making was overall the most transparent, with all decisions relevant to the market authorisation of a drug available on a single web page that is regularly updated, and contains comprehensive information on regulatory processes. A publicly available risk management plan summary is updated regularly with key risks and mitigation strategies. Both Health Canada and FDA provide comparatively less information about post-market safety decisions, while TGA transparency is far less.

Regulators' decisions to make information public may be disputed and contested by industry through legal mechanisms; hence regulatory transparency should be supported with adequate powers under legislation. At the same time, regulators' actions in themselves create precedents, and the decisions made by regulators in individual cases become the basis of future actions, guidance and rules. [106, 144] The influence of industry on these individual decisions and thus on rulemaking, may be substantial, highlighting the need for transparency.[112, 144] Even without legislation, regulators can improve transparency. A Blueprint for FDA Transparency listed actions the regulator could take to improve transparency without legislative change, including greater disclosure of its own decisions

and release of data from required post-market studies.[107] Independent bodies with a legislated role (e.g., ombudsmans offices) can play an important role in interpreting and enforcing public rights to information. Ultimately, transparency measures should be adequate to allow public confidence that conflicts of interest are being dealt with appropriately.

While not on par with EU transparency legislation, FDA, TGA and more recently Health Canada legislation[113] allows for the possibility of much greater transparency than is currently routine.[107]

CONCLUSION

All regulators recognise a need for post-market safety communication and aim to support the safe use of medicines. However, we found differences in governance, legislated authority, communication capability, transparency, and the role of industry.

European pharmacovigilance legislation appears to be most unified in its focus on safety within a life-cycle paradigm, with a supporting governance structure and greater commitment to transparency. The extent to which regulators perceive ownership of post-market communication as their public health role, or as the overseers of industry communications, requires further consideration. Regulators' authority to issue safety advice independent of industry involvement and their transparency of decision-making should be key pillars on which their policy is assessed, regardless of the speed of drug approval.

The greatest challenge may be one that only larger regulators have begun grappling with – how to assess the effectiveness of advisories and other risk mitigation strategies and more importantly, what level of effectiveness will be acceptable. Without evidence of impact, current regulatory paradigms for risk communication cannot be assured to be achieving their safety, effectiveness and accountability goals.

The gap between risk communication science, regulatory requirements and real-world health outcomes requires continued investigation by regulators and researchers alike.

Name	**Ms Alice L Bhasale**
Affiliations	University of Sydney
Conflict of Interest	None
Name	**Dr Ameet Sarpatwari**
Affiliations	Program On Regulation, Therapeutics, And Law (PORTAL), Brigham and Women's Hospital and Harvard Medical School
Conflict of Interest	None
Funding	Dr Sarpatwari's work is funded by the Arnold Ventures and the Harvard-MIT Center for Regulatory Science.
Name	**Prof. Marie L. De Bruin**
Affiliations	1. Copenhagen Centre for Regulatory Science, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. 2. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.
Conflict of Interest	Marie L. De Bruin (MLDB) is appointed as professor in Regulatory Science, for which the Chair is funded by the University of Copenhagen. In addition, she is director of the Copenhagen Centre for Regulatory Science (CORS), based at the same university. CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals and LEO pharma) as well as patient organisations (Rare Diseases Denmark). The centre is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and its research is not company-specific product or directly company related. Apart from the position at the University of Copenhagen, MLDB is employed part-time by Utrecht University as a senior researcher conducting research under the umbrella of the Utrecht-WHO Collaborating Centre for Pharmaceutical Policy and Regulation. This centre receives no direct funding or donations from private parties, including pharmaceutical industry. Research funding from public-private partnerships, e.g. IMI, The Escher Project (http://escher.lygature.org/) is accepted under the condition that no company-specific product or company related study is conducted. The Centre has received unrestricted research funding from public sources, e.g. World Health Organization (WHO), Netherlands Organisation for Health Research and Development (ZonMW), the Dutch National Health Care Institute (ZIN), EC Horizon 2020, the Dutch Medicines Evaluation Board (MEB), and the Dutch Ministry of Health.
Name	**Prof Joel Lexchin**
Affiliations	York University

Conflict of Interest	In 2017-2020, Joel Lexchin received payment for being on a panel at the American Diabetes Association, for talks at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and a second brief on the role of promotion in generating prescriptions for Goodmans LLP and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives royalties from University of Toronto Press and James Lorimer & Co. Ltd. for books he has written.
Name	**Dr Ruth Lopert**
Affiliations	George Washington University
Conflict of Interest	None
Name	**Dr Priya Bahri**
Affiliations	European Medicines Agency Utrecht University
Conflict of Interest	None
Name	**Assoc Prof Barbara Mintzes**
Affiliations	University of Sydney
Conflict of Interest	Barbara Mintzes is a member of Health Action International (HAI-Europe Association), a non-profit organization that supports public interests in pharmaceutical policy. She was a member of Health Canada's Expert Advisory Group on the Marketing of Opioids in 2018 and 2019. She has no other interests to declare and receives no funding from pharmaceutical companies.

Funding

This study is funded by Australia's National Health and Medical Research Council (grant ID#1122332) with co-financing by the Canadian Institutes of Health Research (grant ID #153275). Ms Bhasale received funding from a University of Sydney PhD Scholarship and a Harvard University Mobility Grant. Dr Sarpatwari's work is funded by the Arnold Ventures and the Harvard-MIT Center for Regulatory Science. Priya Bahri is an employee of the European Medicines Agency. However, the views expressed in this article may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or any of its committees or working parties.

Author contributions

All authors contributed to writing the manuscript.

AB, AS, BM, JL and PB developed the approach to the review.

AB, PB and JL and PB contributed to the review of regulatory documents.

References

(1) Institute of Medicine (U.S.). Committee on the Assessment of the US Drug Safety System. The future of drug safety — promoting and protecting the health of the public. In: *Committee on the Assessment of the US Drug Safety System, Board on Population Health and Public Health Practice* (eds. Baciu, A., Stratton, K. and Burke, S.P.) (The National Academies Press, Washington D.C., 2006).

(2) European Commission. Commission staff working document. Accompanying document to the Proposal for a regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency and the Proposal for a directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. (Commission of the European Communities, Brussels, 2008).

(3) 50 years of EU pharma legislation: Achievements and future perspectives. Conference Report. 2015.

(4) Avorn, J., Kesselheim, A. & Sarpatwari, A. The FDA Amendments Act of 2007 — Assessing Its Effects a Decade Later. *New England Journal of Medicine* **379**, 1097-9 (2018).

(5) European Parliament and Council of Ministers. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Vol. Directive 2010/84/EU (Official Journal of the European Union, 2010).

(6) European Parliament and Council of Ministers. Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance. (Official Journal of the European Union, 2010).

(7) Food and Drug Administration Amendments Act. (US Congress, 2007).

(8) European Commission. Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use

and establishing a European Medicines Agency. *Official Journal of the European Union*, 1-33 (2004).

(9) Wiktorowicz, M., Moscou, K. & Lexchin, J. Transnational pharmacogovernance: emergent patterns in the jazz of pharmaceutical policy convergence. *Globalization and Health* **14**, (2018).

(10) Demortain, D. The tools of globalization: ways of regulating and the structure of the international regime for pharmaceuticals. *Review of International Political Economy* **22**, 1249-75 (2015).

(11) Eichler, H.-G. *et al.* The risks of risk aversion in drug regulation. *Nature Reviews Drug Discovery* **12**, 907 (2013).

(12) Herder, M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. *Milbank Q* **epub ahead of print**, (2019).

(13) Frank, C. *et al.* Era of faster FDA drug approval has also seen increased black-box warnings and market withdrawals. *Health Aff (Millwood)* **33**, 1453-9 (2014).

(14) Lexchin, J. Post-market safety warnings for drugs approved in Canada under the Notice of Compliance with conditions policy. *British Journal of Clinical Pharmacology* **79**, 847-59 (2015).

(15) Darrow, J.J., Avorn, J. & Kesselheim, A.S. Speed, Safety, and Industry Funding — From PDUFA I to PDUFA VI. *New England Journal of Medicine* **377**, 2278-86 (2017).

(16) Davis, C. & Abraham, J. Desperately seeking cancer drugs: explaining the emergence and outcomes of accelerated pharmaceutical regulation. *Sociology of health & illness* **33**, 731-47 (2011).

(17) Pease, A.M., Krumholz, H.M., Downing, N.S., Aminawung, J.A., Shah, N.D. & Ross, J.S. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *BMJ* **357**, j1680 (2017).

(18) Hoekman, J. & Boon, W. Changing standards for drug approval: A longitudinal analysis of conditional marketing authorisation in the European Union. *Soc Sci Med* **222**, 76-83 (2019).

(19) Downing, N.S. *et al.* Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA* **317**, 1854-63 (2017).

(20) Arnardottir, A.H., Haaijer-Ruskamp, F.M., Straus, S.M.J., Eichler, H.-G., de Graeff, P.A. & Mol, P.G.M. Additional safety risk to exceptionally approved drugs in Europe? *British Journal of Clinical Pharmacology* **72**, 490-9 (2011).

(21) United States Department of Health and Human Services Office of Inspector General. (2013). *FDA lacks comprehensive data to determine whether risk evaluation and mitigation strategies improve drug safety* (US Department of Health and Human Services, Washington, 2013).

(22) Frau, S., Font Pous, M., Luppino, M.R. & Conforti, A. Risk Management Plans: are they a tool for improving drug safety? *European Journal of Clinical Pharmacology* **66**, 785-90 (2010).

(23) Zeitoun, J.D., Lefevre, J.H., Downing, N.S., Bergeron, H. & Ross, J.S. Regulatory anticipation of postmarket safety problems for novel medicines approved by the EMA between 2001 and 2010: a cross-sectional study. *Pharmacoepidemiol Drug Saf* **25**, 687-94 (2016).

(24) Mol, P.G.M. *et al.* Post-Approval Safety Issues with Innovative Drugs: A European Cohort Study. *Drug Safety* **36**, 1105-15 (2013).

(25) Lexchin, J. New Drugs and Safety: What Happened to New Active Substances Approved in Canada Between 1995 and 2010? *Archives of Internal Medicine* **172**, 1680-1 (2012).

(26) Perry, L.T. *et al.* Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med* **179**, 982-4 (2019).

(27) Zeitoun, J.-D., Lefèvre, J.H., Downing, N., Bergeron, H. & Ross, J.S. Inconsistencies among European Union Pharmaceutical Regulator Safety Communications: A Cross-Country Comparison. *PLOS ONE* **9**, e109100 (2014).

(28) Pfistermeister, B., Saß, A., Criegee-Rieck, M., Bürkle, T., Fromm, M.F. & Maas, R. Inconsistencies and misleading information in officially approved prescribing information from three major drug markets. *Clinical Pharmacology and Therapeutics* **96**, 616-24 (2014).

(29) European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)*. EMA/204715/2012 Rev 2* edn. (EMA: Amsterdam, 2017).

(30) U.S. Department of Health and Human Services Food and Drug Administration. *FDA's application of statutory factors in determining when a REMS is necessary. Guidance for industry. Draft Guidance.* (FDA: Maryland, 2016).

(31) Lexchin, J. *Public profits vs private policy* (University of Toronto Press: Toronto, 2016).

(32) Herder, M. Denaturalizing transparency in drug regulation. *McGill Journal of Law and Health* **8**, S57-S143 (2015).

(33) Davis, C. & Abraham, J. *Unhealthy pharmaceutical regulation: innovation, politics and promissory science* (Palgrave MacMillan: London, 2013).

(34) Carpenter, D. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA* (2014).

(35) Bahri, P. Public pharmacovigilance communication: A process calling for evidence-based, objective-driven strategies. *Drug Safety* **33**, 1065-79 (2010).

(36) Council of Canadian Academies. (2015). *Health product risk communication: Is the message getting through? The Expert Panel on the effectiveness of health product risk communication* (Council of Canadian Academies, Ottawa, 2015).

(37) Auditor General of Canada. Chapter 4—Regulating Pharmaceutical Drugs—Health Canada. In: *2011 Fall Report of the Auditor General of Canada* (Office of the Auditor General of Canada, Ottawa, 2011).

(38) Dal Pan, G.J. & Arlett, P.R. The US Food and Drug Administration-European Medicines Agency Collaboration in Pharmacovigilance: Common Objectives and Common Challenges. *Drug Safety* **38**, 13-5 (2015).

(39) Dal Pan, G.J. Gauging the Effectiveness of Medicines Safety Communications From Global Regulatory Agencies. *JAMA Internal Medicine*, (2019).

(40) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Advances in FDA's safety program for marketed drugs establishing premarket safety review and marketed drug safety as equal priorities at FDA's Center For Drug Evaluation And Research* (FDA: Maryland, 2012).

(41) Carpenter, D. Reputation, gatekeeping, and the politics of post-marketing drug regulation. *Virtual Mentor* **8**, 403-6 (2006).

(42) Kesselheim, A.S. *et al.* Methodological approaches to evaluate the impact of FDA drug safety communications. *Drug Safety* **38**, 565-75 (2015).

(43) Wiktorowicz, M., Lexchin, J. & Moscou, K. Pharmacovigilance in Europe and North America: divergent approaches. *Soc Sci Med* **75**, 165-70 (2012).

(44) The Federal Advisory Committee Act, 5 U.S.C. app. (as amended) (ed. Administration, U.S.G.S.) (U.S General Services Administration, Washington).

(45) European Medicines Agency. *European Medicines Agency bids farewell to CHMP Pharmacovigilance Working Party*. <https://www.ema.europa.eu/en/news/european-medicines-agency-bids-farewell-chmp-pharmacovigilance-working-party> (2012). Accessed 06 March 2020.

(46) Kaeding, M., Schmalter, J. & Klika, C. *Pharmacovigilance in the European Union. Practical Implementation across Member States* (Springer: Germany, 2017).

(47) European Medicines Agency. (2018). *Summary of the EMA public hearing on quinolone and fluoroquinolone antibiotics* (EMA, London, 2018).

(48) European Medicines Agency. (2017). *Summary of the EMA public hearing on valproate in pregnancy* (EMA, London, 2017).

(49) Santoro, A., Genov, G., Spooner, A., Raine, J. & Arlett, P. Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works. *Drug Safety* **40**, 855-69 (2017).

(50) European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module XV – Safety communication (Rev 1).* EMA/118465/2012 Rev 1 edn. (2017).

(51) Health Canada and the Public Health Agency of Canada. Evaluation of the Human Drugs Program 1999-2000 to 2011-2012. (2014).

(52) Health Canada. *An overview of the Marketed Health Products Directorate*. <http://publications.gc.ca/collections/collection_2011/sc-hc/H164-2-2008-eng.pdf> (2008). Accessed 12 Sept 2019.

(53) Health Canada. Health product vigilance framework. (Health Canada,, Ottawa, 2012).

(54) Health Canada. *Scientific/Expert Advisory Panels*. <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/scientific-expert-advisory-panels/scientific-advisory-bodies.html> (2012). Accessed 10 Jan 2020.

(55) Australian Government Department of Health Therapeutic Goods Administration. *Advisory Committee on Medicines (ACM)*.

<https://www.tga.gov.au/committee/advisory-committee-medicines-acm> (2019). Accessed Dec 2019 2019.

(56) Australian Government Department of Health Therapeutic Goods Administration. *Scheduling delegate's final decision: codeine, December 2016*. <https://www.tga.gov.au/scheduling-decision-final/scheduling-delegates-final-decision-codeine-december-2016> (2016). Accessed Dec 2019 2019.

(57) Commonwealth of Australia. Therapeutic Goods Regulations 1990. In: *F2019C00844* (Australia, 2017).

(58) U.S. Department of Health and Human Services Food and Drug Administration. *CDER's Drug Safety Communications: Ensuring postmarket safety*. <https://www.fda.gov/drugs/news-events-human-drugs/cders-drug-safety-communications-ensuring-postmarket-safety> (2015). Accessed 13 June 2020.

(59) U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) & Center for Biologics Evaluation and Research (CBER). *Guidance - Drug Safety Information – FDA's Communication to the Public. DRAFT GUIDANCE (withdrawn)* (FDA: Maryland, 2012).

(60) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry and FDA Staff. Dear Health Care Provider Letters: improving communication of important safety information. (FDA, Maryland, 2012).

(61) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry and FDA Staff. Dear Health Care Provider Letters: improving communication of important safety information. (FDA, Maryland, 2014).

(62) European Parliament and Council of Ministers. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Vol. 2001L0083 — EN — 16.11.2012 — 011.001 (2012).

(63) De Vries, S.T. *et al.* Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences. *Drug Safety* **40**, 729-42 (2017).

(64) Government of Canada. Food and Drug Act. In: *RSC, 1985, c F-27* Act current to 2017-12-05 and last amended on 2017-06-22 edn. (Government of Canada).

(65) Government of Canada. Food and Drug Regulations. In: *CRC, c 870* Last amended on June 17, 2019 edn. (Government of Canada, 2019).

(66) Risk Sciences International. (2013). *Review of Health Canada's actions in the recall of Alysena* (Health Canada, Ottawa, 2013).

(67) Health Canada. Regulations Amending the Food and Drug Regulations (Vanessa's Law). Regulatory impact analysis statement. *Canada Gazette* 2017.

(68) Health Canada. Risk Communication- protecting Canadians through information. (2011).

(69) Health Canada. *Description of current risk communication documents for marketed health products for human use. Guidance document.* (Health Canada,: Ottawa, 2008).

(70) Janssen Inc. INVOKANA® (canagliflozin) and INVOKAMET® (canagliflozin and metformin) - Risk of Lower Limb Amputation. 2017.

(71) Health Canada MedEffect Canada. Guidance document for industry - issuance of health professional communications and public communications by market authorization holders. Guide and template. (Minister of Health, Ottawa, 2010).

(72) Commonwealth of Australia. Therapeutic Goods Information Specification 2009. (ed. Federal Register of Legislation) (2009).

(73) Australian Government Department of Health Therapeutic Goods Administration. Pharmacovigilance responsibilities of medicine sponsors. Australian recommendations and requirements. Version 2.0 September 2017 edn. (TGA, ACT, 2017).

(74) Torka, M., Mintzes, B., Bhasale, A., Fabbri, A., Perry, L. & Lexchin, J. Secret safety warnings on medicines: A case study of information access requests. *Pharmacoepidemiol Drug Saf* **28**, 551-5 (2019).

(75) Briesacher, B.A. *et al.* A critical review of methods to evaluate the impact of FDA regulatory actions. *Pharmacoepidemiol Drug Saf* **22**, 986-94 (2013).

(76) Dusetzina, S.B. *et al.* Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care* **50**, 466-78 (2012).

(77) Goedecke, T., Morales, D.R., Pacurariu, A. & Kurz, X. Measuring the impact of medicines regulatory interventions - Systematic review and methodological considerations. *Br J Clin Pharmacol*, (2017).

(78) Weatherburn, C.J., Guthrie, B., Dreischulte, T. & Morales, D.R. Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: Systematic review, time series analysis and meta-analysis. *Br J Clin Pharmacol*, (2019).

(79) Dal Pan, G.J. Communicating the risks of medicines: Time to move forward. *Medical Care* **50**, 463-5 (2012).

(80) Piening, S., Haaijer-Ruskamp, F.M., de Graeff, P.A., Straus, S.M. & Mol, P.G. Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. *Drug Saf* **35**, 1061-72 (2012).

(81) Artime, E. *et al.* Are risk minimization measures for approved drugs in Europe effective? A systematic review. *Expert Opinion on Drug Safety* **18**, 443-54 (2019).

(82) Bell, S.G., Matsumoto, M., Shaw, S.J., Brandt, J. & Krauss, G.L. New antiepileptic drug safety information is not transmitted systematically and accepted by U.S. neurologists. *Epilepsy and Behavior* **29**, 36-40 (2013).

(83) Piening, S., De Graeff, P.A., Straus, S.M.J.M., Haaijer-Ruskamp, F.M. & Mol, P.G.M. The additional value of an e-mail to inform healthcare professionals of a drug safety issue: A randomized controlled trial in the Netherlands. *Drug Safety* **36**, 723-31 (2013).

(84) Woloshin, S. *et al.* Media Coverage of FDA Drug Safety Communications about Zolpidem: A Quantitative and Qualitative Analysis. *Journal of Health Communication* **22**, 365-72 (2017).

(85) Way, D., Blazsin, H., Löfstedt, R. & Bouder, F. Pharmaceutical Benefit–Risk Communication Tools: A Review of the Literature. *Drug Safety* **40**, 15-36 (2017).

(86) Cohen, D. Rosiglitazone: what went wrong? *BMJ* **341**, c4848 (2010).

(87) Hernandez, J.F., Mantel-Teeuwisse, A.K., Van Thiel, G.J.M.W., Belitser, S.V., Raaijmakers, J.A.M. & Pieters, T. Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study. **1**, e000290-e (2011).

(88) Riddle, M.A. Paroxetine and the FDA. *Journal of the American Academy of Child and Adolescent Psychiatry* **43**, 128-30 (2004).

(89) Schwartz, L. & Woloshin., S. (2015). *FDA and the media: Lessons from Tysabri about communicating uncertainty.* (National Academy of Medicine, Washington, 2015).

(90) Lofstedt, R. Risk communication: the Avandia case, a pilot study. **3**, 31-41 (2010).

(91) U.S. Department of Health and Human Services Food and Drug Administration. The future of drug safety — promoting and protecting the health of the public. FDA's response to the Institute of Medicine's 2006 report. (FDA, Maryland, 2007).

(92) Mollebaek, M., Kaae, S., De Bruin, M.L., Callreus, T., Jossan, S. & Hallgreen, C.E. The effectiveness of direct to healthcare professional communication - A systematic review of communication factor studies. *Research in Social & Administrative Pharmacy* **15**, 475-82 (2019).

(93) Kesselheim, A.S. *et al.* Changes in prescribing and healthcare resource utilization after FDA Drug Safety Communications involving zolpidem-containing medications. *Pharmacoepidemiology and Drug Safety* **26**, 712-21 (2017).

(94) Duckhorn, J., Lappin, B., Weinberg, J. & Zwanziger, L.L. The FDA's Message Testing: Putting health literacy advice into practice. *Inf Services and Use* **39**, 59-67 (2019).

(95) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Drug safety priorities. Initiatives and innovation. 2015-2016* (FDA: Maryland, 2016).

(96) U.S. Department of Health and Human Services Food and Drug Administration. *Communicating risks and benefits: An evidence-based user's guide* (FDA: Maryland, 2011).

(97) U.S. Department of Health and Human Services Food and Drug Administration. *REMS Assessment: Planning and Reporting. Guidance for industry. Draft Guidance.* (FDA: Maryland, 2019).

(98) Kesselheim, A.S. *et al.* Multimodal Analysis of FDA Drug Safety Communications: Lessons from Zolpidem. *Drug Safety* **42**, 1287-95 (2019).

(99) Alqvist-Radstad, J. *et al.* SCOPE Work package 6. Healthcare professional survey. Medicines safety communications and their effectiveness. (SCOPE, London, 2016).

(100) Bahri, P. & Castillon Melero, M. Listen to the public and fulfil their information interests - translating vaccine communication research findings into guidance for regulators. *Br J Clin Pharmacol* **84**, 1696-705 (2018).

(101) European Medicines Agency & Heads of Medicines Agencies. (2013). *Guideline on good pharmacovigilance practices – Product- or population-specific considerations I: Vaccines for prophylaxis against infectious diseases* (EMA London, 2013).

(102) European Medicines Agency & Heads of Medicines Agencies. (2018). *Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations IV: Paediatric population* (EMA London, 2018).

(103) Health Canada. Guidance document - submission of risk management plans and follow-up commitments. (Minister of Health, Ottawa, 2015).

(104) European Medicines Agency & Heads of Medicines Agencies. (2013). *Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2)* (EMA with HMA, London, 2013).

(105) Australian Government Department of Health Therapeutic Goods Administration. *Risk management plans for medicines and biologicals Australian requirements and recommendations*. Version 3.1, November 2017 edn. (Commonwealth of Australia: Woden, ACT, 2017).

(106) Herder, M. Toward a Jurisprudence of Drug Regulation. *Journal of Law Medicine & Ethics* **42**, 244-62 (2014).

(107) Sharfstein, J.M. *et al.* Blueprint for Transparency at the U.S. Food and Drug Administration: Recommendations to Advance the Development of Safe and Effective Medical Products. *The Journal of Law, Medicine & Ethics* **45**, 7-23 (2017).

(108) Light, D.W., Lexchin, J. & Darrow, J.J. Institutional corruption of pharmaceuticals and the myth of safe and effective drugs. *Journal of Law, Medicine & Ethics* **41**, 590-600 (2013).

(109) Carpenter, D. Corrosive Capture? The Dueling Forces of Autonomy and Industry Influence in FDA Pharmaceutical Regulation. In: *Preventing Regulatory Capture: Special Interest Influence and How to Limit it* (eds. Carpenter, D. and Moss, D.A.) 152-72 (Cambridge University Press, Cambridge, 2013).

(110) Carpenter, D. Reputation and regulatory power. In: *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton University Press, Princeton, 2014).

(111) Lexchin, J. The Pharmaceutical Industry and the Canadian Government: Folie a Deux. *Politiques de sante* **13**, 10-6 (2017).

(112) Hwang, T.J., Avorn, J., Carpenter, D. & Kesselheim, A.S. Quantifying the food and drug administration's rulemaking delays highlights the need for transparency. *Health Affairs* **33**, 309-15 (2014).

(113) Lexchin, J., Herder, M. & Doshi, P. Canada finally opens up data on new drugs and devices. *Bmj-British Medical Journal* **365**, (2019).

(114) U.S. Department of Health and Human Services Food and Drug Administration. *November 5, 2015: Joint Meeting of the Antimicrobial Drugs Advisory Committee (formerly known as the Anti-Infective Drugs Advisory Committee) and Drug Safety and Risk Management Advisory Committee Meeting Announcement*. <http://wayback.archive-it.org/7993/20170112100727/http:/www.fda.gov/AdvisoryCommittees/Calendar/ucm465275.htm> (2015). Accessed 11 Sept 2019.

(115) Fralick, M. & Kesselheim, A.S. Periodic benefit-risk evaluation reports have substantial promise to guide patient care and should be made publicly available. *Pharmacoepidemiology and Drug Safety* **26**, 597-9 (2017).

(116) Kesselheim, A.S. & Mello, M.M. Confidentiality laws and secrecy in medical research: improving public access to data on drug safety. *Health Affairs* **26**, 483-91 (2007).

(117) McCoy, M.S., Pagán, O., Donohoe, G., Kanter, G.P. & Litman, R.S. Conflicts of interest of public speakers at meetings of the anesthetic and analgesic drug products advisory committee. *JAMA Internal Medicine* **178**, 996-7 (2018).

(118) Abola, M.V. & Prasad, V. Characteristics and conflicts of public speakers at meetings of the Oncologic Drugs Advisory Committee to the US Food And Drug Administration. *JAMA Internal Medicine* **176**, 389-91 (2016).

(119) Pham-Kanter, G. Revisiting financial conflicts of interest in FDA advisory committees. *Milbank Q* **92**, 446-70 (2014).

(120) Bhasale, A., Mintzes, B. & Sarpatwari, A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. *BMJ* **369**, m1107 (2020).

(121) European Medicines Agency. European Medicines Agency policy on access to documents. POLICY/0043. (EMA, London, 2018).

(122) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCEPP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance,. 2019 edn. (European Medicines Agency, 2019).

(123) European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3)*. EMA/118465/2012 Rev 1 edn. (EMA: Amsterdam, 2017).

(124) Health Canada. *Regulatory Transparency and Openness - 2017-2018 Activities*. <https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/2017-2018-activities.html> (2019). Accessed 12 Aug 2019.

(125) Health Canada. *Amendments to the Food and Drugs Act: Guide to New Authorities (power to require and disclose information, power to order a label change and power to order a recall)*. <https://www.canada.ca/en/health-canada/services/drugs-health-products/legislation-guidelines/amendments-food-drugs-act-guide-new-authorities-power-require-disclose-information-power-order-label-change-power-order-recall.html> (2017). Accessed **1 Aug 2019**.

(126) Health Canada. *Guidance document - disclosure of confidential business information under paragraph 21.1(3)(c) of the Food and Drugs Act*. <https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/request-disclosure-confidential-business-information/disclosure-confidential-business-information/guidance.html#a1.1> (2019). Accessed **10 Sept 2019**.

(127) Australian Government Department of Health Therapeutic Goods Administration. *ACM meeting statements*. <https://www.tga.gov.au/acm-meeting-statements> (2019). Accessed Dec 2019 2019.

(128) Commission of the European Communities. Proposal for a Directive of the European Parliament and of the Council amending, as regards information to the general public on medicinal products subject to medical prescription, Directive 2001/83/EC on the Community code relating to medicinal products for human use. . (Commission of the European Communities, Brussels, 2008).

(129) Brown, P. & Bahri, P. 'Engagement' of patients and healthcare professionals in regulatory pharmacovigilance: establishing a conceptual and methodological framework. *European Journal of Clinical Pharmacology* **75**, 1181-92 (2019).

(130) Fabbri, A. *et al.* Industry funding of patient and health consumer organisations: systematic review with meta-analysis. *BMJ* **368**, l6925 (2020).

(131) Lexchin, J. Association between commercial funding of Canadian patient groups and their views about funding of medicines: An observational study. *PLOS ONE* **14**, e0212399 (2019).

(132) National Institute for Health and Care Excellence. *Citizens Council*. <https://www.nice.org.uk/get-involved/citizens-council> (2019). Accessed 10 Jan 2020.

(133) Sansom, L., DeLaat, W. & Horvath, J. Review of Medicines and Medical Devices Regulation. Report on the regulatory framework for medicines and medical devices. 2015.

(134) Mol, P.G.M., Straus, S.M.J.M., Piening, S., De Vries, J.T.N., De Graeff, P.A. & Haaijer-Ruskamp, F.M. A Decade of Safety-Related Regulatory Action in the Netherlands. *Drug Safety* **33**, 463-74 (2010).

(135) Thompson, C.A. 'Dear Healthcare Professional' letters may not be effective REMS communication tool. *Am J Health Syst Pharm* **71**, 177-8 (2014).

(136) Australian Government Department of Health Therapeutic Goods Administration. The Therapeutic Goods Administration's risk management approach to the regulation of therapeutic goods. Version 4.0 edn. (ed. TGA) (Commonwealth of Australia, ACT, 2011).

(137) Davis, C. & Abraham, J. A comparative analysis of risk management strategies in European Union and United States pharmaceutical regulation. *Health Risk & Society* **13**, 413-31 (2011).

(138) Dyer, O. France to prosecute its drug regulator and Servier in scandal over diabetes drug. *BMJ* **358**, j4231 (2017).

(139) Buckley, N.A. & Faunce, T.A. Trials and tribulations in the removal of dextropropoxyphene from the Australian register of therapeutic goods. *Medical Journal of Australia* **199**, 257-60 (2013).

(140) Commonwealth of Australia. Therapeutic Goods Act 1989. (Australia, 2017).

(141) Maor, M. Organizational Reputations and the Observability of Public Warnings in 10 Pharmaceutical Markets. *Governance* **24**, 557-82 (2011).

(142) Pignatti, F. *et al.* Structured Frameworks to Increase the Transparency of the Assessment of Benefits and Risks of Medicines: Current Status and Possible Future Directions. *Clinical Pharmacology & Therapeutics* **98**, 522-33 (2015).

(143) Doshi, P. & Jefferson, T. Disclose Data Publicly, without Restriction. *The Journal of Law, Medicine & Ethics* **45**, 42-5 (2017).

(144) Carpenter, D. FDA Transparency in an Inescapably Political World. *Journal of Law, Medicine & Ethics* **45**, 29-32 (2017).

References for Tables 1 to 4

(a1) U.S. Department of Health and Human Services Food and Drug Administration. *CDER's Drug Safety Communications: Ensuring postmarket safety*. <https://www.fda.gov/drugs/news-events-human-drugs/cders-drug-safety-communications-ensuring-postmarket-safety> (2015). Accessed 13 Jun 2020.

(a2) Health Canada. *Description of current risk communication documents for marketed health products for human use. Guidance document.* (Health Canada,: Ottawa, 2008).

(a3) Torka, M., Mintzes, B., Bhasale, A., Fabbri, A., Perry, L. & Lexchin, J. Secret safety warnings on medicines: A case study of information access requests. *Pharmacoepidemiol Drug Saf* **28**, 551-5 (2019).

(a4) Australian Government Department of Health and Ageing Therapeutic Goods Administration. Trans-Tasman early warning system. Processes in Australia and New Zealand. Version 1.0 edn. (TGA, ACT, 2013).

(a5) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Drug safety priorities. Initiatives and innovation. 2015-2016* (FDA: Maryland, 2016).

(a6) The Federal Advisory Committee Act, 5 U.S.C. app. (as amended) (ed. Administration, U.S.G.S.) (U.S General Services Administration, Washington).

(a7) European Parliament and Council of Ministers. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Vol. Directive 2010/84/EU (Official Journal of the European Union, 2010).

(a8) European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module XV – Safety communication (Rev 1).* EMA/118465/2012 Rev 1 edn. (2017).

(a9) Food and Drug Administration Amendments Act. (US Congress, 2007).

(a10) *CFR - Code of Federal Regulations Title 21*. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=20.61> (2019). Accessed 20 Oct 2019 20 Oct 2019.

(a11) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry and FDA Staff. Dear Health Care Provider Letters: improving communication of important safety information. (FDA, Maryland, 2014).

(a12) Health Canada MedEffect Canada. Guidance document for industry - issuance of health professional communications and public communications by market authorization holders. Guide and template. (Minister of Health, Ottawa, 2010).

(a13) U.S. Department of Health and Human Services Food and Drug Administration. Classifying significant postmarketing drug safety issues. Draft guidance. (FDA, Maryland, 2012).

(a14) U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) & Center for Biologics Evaluation and Research (CBER). *Guidance - Drug Safety Information – FDA's Communication to the Public. DRAFT GUIDANCE (withdrawn)* (FDA: Maryland, 2012).

(a15) Bahri, P. Public pharmacovigilance communication: A process calling for evidence-based, objective-driven strategies. *Drug Safety* **33**, 1065-79 (2010).

(a16) Skerrit, J. Therapeutic Goods Information (Early Warning System) Specification 2013. Instrument and Explanatory statement. (2013).

(a17) European Medicines Agency & Heads of Medicines Agencies. (2013). *Guideline on good pharmacovigilance practices – Product- or population-specific considerations I: Vaccines for prophylaxis against infectious diseases* (EMA London, 2013).

(a18) European Medicines Agency & Heads of Medicines Agencies. (2018). *Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations IV: Paediatric population* (EMA London, 2018).

(a19) U.S. Department of Health and Human Services Food and Drug Administration. *Communicating risks and benefits: An evidence-based user's guide* (FDA: Maryland, 2011).

(a20) Health Canada. Guide for using the Standardized Health Product Risk Communication Template. 2015-11-23. 2015.

(a21) Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. SCOPE Work package 6. Risk communication. National strategy for implementation of recommendations on risk communication: Key actions. (SCOPE, London, 2016).

(a22) Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. (SCOPE, London, 2016).

(a23) U.S. Department of Health and Human Services Food and Drug Administration. FDA Strategic plan for risk communication and health literacy 2017-2019. (ed. FDA) (FDA, Maryland, 2017).

(a24) Council of Canadian Academies. (2015). *Health product risk communication: Is the message getting through? The Expert Panel on the effectiveness of health product risk communication* (Council of Canadian Academies, Ottawa, 2015).

(a25) European Medicines Agency. PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Rev 1). In: *EMA/165407/2017 Pharmacovigilance Risk Assessment Committee* (EMA, London, 2017).

(a26) Kesselheim, A.S. *et al.* Changes in prescribing and healthcare resource utilization after FDA Drug Safety Communications involving zolpidem-containing medications. *Pharmacoepidemiology and Drug Safety* **26**, 712-21 (2017).

(a27) Woloshin, S. *et al.* Media Coverage of FDA Drug Safety Communications about Zolpidem: A Quantitative and Qualitative Analysis. *Journal of Health Communication* **22**, 365-72 (2017).

(a28) Kesselheim, A.S. *et al.* Methodological approaches to evaluate the impact of FDA drug safety communications. *Drug Safety* **38**, 565-75 (2015).

(a29) Kesselheim, A.S. *et al.* Patient and Physician Perceptions of Drug Safety Information for Sleep Aids: A Qualitative Study. *Drug Safety* **40**, 531-42 (2017).

(a30) Government of Canada. Food and Drug Act. In: *RSC, 1985, c F-27* Act current to 2017-12-05 and last amended on 2017-06-22 edn. (Government of Canada).

(a31) Health Canada. *Amendments to the Food and Drugs Act: Guide to New Authorities (power to require and disclose information, power to order a label change and power to order a recall)*. <https://www.canada.ca/en/health-canada/services/drugs-health-products/legislation-guidelines/amendments-food-drugs-act-guide-new-authorities-

power-require-disclose-information-power-order-label-change-power-order-recall.html> (2017). Accessed 1 Aug 2019.

(a32) European Medicines Agency. *What we publish on medicines and when*. <https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-when> (2020). Accessed 14 Mar 2020.

(a33) European Medicines Agency. *List of all signals assessed and discussed by the PRAC and resulting changes to product information listed by meeting*. <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management/prac-recommendations-safety-signals> (2020). Accessed 14 Mar 2020.

(a34) European Commission. *Public Health - Union Register of medicinal products*. <https://ec.europa.eu/health/documents/community-register/html/reg_hum_act.htm?sort=a> (2020). Accessed 26 Jun 2020.

(a35) Health Canada. *Regulatory Transparency and Openness - 2017-2018 Activities*. <https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/2017-2018-activities.html> (2019). Accessed 12 Aug 2019.

2.6.1 Supplementary materials

TABLE S1: Differences in regulatory policy for post-market safety advisories (Additional information)

	EMA	FDA	HC	TGA
1.GOVERNANCE AND DECISION-MAKING				
Separation of authority for post-market decision-making	PRAC has responsibility for assessment decisions and, depending on regulatory procedure, makes recommendations to the CHMP or CMDh who makes the final decision.	Multi-team approach to communication of risk. [a1] 'There is no single body within the FDA that reviews each and every recommendation'.[a2]	Multiple different departments might be involved including for biologics, prescription medicines, for assessing of safety-related product information changes, risk management and planning, and risk communications.	Pharmacovigilance section for risk management plans and post-market surveillance, and safety alerts but a separate division reviews applications to change product information.
Public involvement in post-market safety governance	Consumer and healthcare representatives on PRAC. By legislation, public hearings can be conducted but so far have occurred for only some safety concerns for off-patent drugs (e.g., valproate, fluoroquinolones).[a3]	Not routinely. If a standing expert committee is consulted on a decision, these can include a public hearing (e.g., public hearing for bevacizumab indication withdrawal, fluoroquinolones). Public involvement is supported by US legislation.[a4]	Issue-focussed committees may be formed for specific safety concerns but there is no ongoing committee involved.	A standing expert committee for medicines comprising clinical experts and a consumer representative may be consulted on occasion (ACM) but the TGA is not obliged to consult or follow advice.[a5]
2. LEGISLATIVE AUTHORITY, INDUSTRY RESPONSIBILITY AND REQUIREMENTS				
Regulator responsibility for post-market safety communication - described in regulation/ legislation	Yes Article 102, Directive 2001/83/EC on the Community code relating to medicinal products for human use[a6]	Yes FDA Amendments Act (FDAAA 2007)	No	Partial Subsection 61(5C) of the *Therapeutic Goods Act 1989* (amended 2010) allows the regulator to release information to the public but does not require it to communicate about post-market events.

	EMA	FDA	HC	TGA
	Article 102: 'Regulators **must** ensure 'public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-site and through other means of publicly available information as necessary.'	**FDA Amendments Act (FDAAA 2007)** 'Postmarket Drug Safety Information for Patients and Providers' ….., the Secretary shall improve the transparency of information about drugs and allow patients and health care providers better access to information about drugs by developing and maintaining an Internet Web site that—[provides]…(iv) the most recent safety information and alerts issued by the Food and Drug Administration for drugs approved by the Secretary under this section, such as product recalls, warning letters, and import alerts'[FDAAA]	Post-market communication is not specifically described in the Food and Drug Act or regulations, however it is stated that the regulator: '….may disclose confidential business information about a therapeutic product without notifying the person to whose business or affairs the information relates or obtaining their consent, if the Minister believes that the product may present a serious risk of injury to human health.' (21.1(2) Food and Drug Act to June 2019*	**Therapeutic Goods Act 1989** - Sect 61 Release of information '(5C) The Secretary may release to the public therapeutic goods information of a kind specified under subsection (5D). (5D) The Minister may, by legislative instrument, specify kinds of therapeutic goods information for the purpose of subsection (5C). Explanatory Specification Subsection 61(5D) of the Act empowers the Minister to, by legislative instrument, specify kinds of therapeutic goods information for the purposes of subsection 61(5C) of the Act. The purpose of the Specification is to support the release to the public of information relating to potential safety concerns about therapeutic goods that are supplied in Australia, by identifying, under subsection 61(5D) of the Act, the kinds of information that the Secretary may publish under subsection 61(5C) of the Act'.[a7]

	EMA	FDA	HC	TGA
Regulatory requirements for industry post-market safety communication • **Regulation**	Company is required to inform the regulator at the same time or before it intends to make a public announcement. (Directive, Article 106a) [a6] The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading. (Directive, Article 106a)[a6]	Company may be required to issue a DHPC as part of a REMS Communication plan. (FDAAA)[a8] Envelope format and presentation for mailing hard copy warning letters is mandated in legislation but not the content, or any process for electronic communications.(CFR 200.5)[a9]	Not described in regulation	Not described in regulation
• **Guidance**	**DHPC** Company should co-operate with regulator in preparing DHPC and this should occur before it is issued. (Guidance)[a10]	**FDA Drug Safety Communication** No role of industry stated beyond fact-checking. **REMS DHPCs** Approved by the FDA **Non REMS DHPCs** Collaboration on appropriateness of DHPC, content, audience and timeframe is encouraged by FDA.[a11]	**DHPC** Company 'has a responsibility' to inform Health Canada if a safety-related DHPC is intended or has been issued. The letter is drafted by the company, and reviewed by Health Canada before approval. Disagreements about content 'should not interfere' with timely communication and Health Canada will issue on its own if necessary. [a12]	**TGA Alerts** Industry may review alerts for fact-checking and may be requested to provide information;[a13] will have been involved in the investigation of the safety concern.[a13] **DHPCs** Not regulated by TGA and no guidance is in place.

	EMA	FDA	HC	TGA
Industry involvement in regulator-issued alerts	Companies draft DHPCs for EMA review and approval	No role of industry stated beyond fact-checking.[a14]	Companies draft DHPCs for Health Canada review.	Industry may review alerts for fact-checking and may be requested to provide information;[a13] will have been involved in the investigation of the safety concern.[a13]
3. RISK COMMUNICATION CAPACITY				
Regulatory goals for safety advisories refer to behavioural outcomes	'Safety communication aims at: • providing timely, evidence-based **information** on the safe and effective use of medicines; • facilitating changes to healthcare practices (including self-medication practices) where necessary; • changing **attitudes, decisions and behaviours** in relation to the use of medicines; • supporting **risk minimisation behaviour;** • facilitating informed **decisions** on the rational use of medicines. In addition to the above effective, high-quality safety communication can support public confidence in the regulatory system' [a10]	'FDA believes that timely communication of important drug safety information will give health care professionals, patients, consumers, and other interested persons access to the most current information concerning the potential risks and benefits of a marketed drug, helping them to make more **informed individual treatment choices**.'[a14]	'Within the public health field, risk communication may be defined as the development and dissemination of information concerning potential or existing health risks to enable patients and their healthcare professionals to make **better-informed decisions** about their health'.[a15] 'HPCs [i.e.healthcare professional communications] and the accompanying PC [a16] are risk management communication instruments aimed at informing health care professionals and the public of newly recognized and clinically significant safety concerns, recalls, or withdrawals affecting a health product — they are not marketing tools.'	'The establishment of the early warning system is expected to provide a number of benefits to both the TGA and Medsafe as well as for consumers, health professionals and health-related industries, including through providing consumers and health professionals with **more information** about potential safety concerns associated with medicines and medical devices (therefore assisting **consumers and health professionals to be better informed**), and is expected to lead to increased reporting of adverse events (which will assist in the investigation of potential safety concerns).'[a7]

	EMA	FDA	HC	TGA
Risk communication criteria, guidelines and resources	Guideline for regulators and industry - GVP XV – Safety communication[a10] Tailored advice for specific populations including vaccine recipients and young people[a17, 18]	Draft guidance - FDA's communication to the public – (withdrawn). Guidance for industry and FDA for DHPCs.[a11] Guidance for classifying post market safety concerns.[a19] Risk communication guidance[a20]	Guidance document for industry - issuance of health professional communications and public communications by market authorization holders.[a12]	Process, criteria, description and template for regulatory alerts.[a13] No guidance for development of DHPC communications by industry.
Risk communications strategy	Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) – Risk communication strategies [a21, 22];	Strategic plan for risk communication and health literacy 2017-2019 [a23]	Strategic risk communication framework (2006) [a24] Risk communication report and evaluation framework.[Council of Canadian Academies, #434	Not in public domain
Dissemination to target audiences	…. other organisations such as learned societies, local health authorities, patient and other healthcare organisations, as appropriate.[a10]	`FDAAA `(b) Partnerships for Risk Communication.-- 'The Secretary shall partner with professional medical societies, medical schools, academic medical centers, and other stakeholders to develop robust and multi-faceted systems for communication to health care providers about emerging postmarket drug risks.'	Dissemination methods depend on the targeted audience and may include targeted distribution to the health care community, including professional associations, health and consumer groups.[a15]	Regulator's website; directly to specialist societies. professional bodies and consumer organisations 'Dependent on the urgency and content '.[a13]

	EMA	FDA	HC	TGA
Activities and requirements for monitoring effectiveness of advisories	**Regulation** National regulators and the EMA must: 'monitor the outcome of risk minimisation measures contained in risk management plans ' [a6] **Strategy** PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities [a25] **Guidance** Require industry to disseminate DHPCs and any issues with doing so, and provide numbers disseminated. '**Where possible**, mechanisms should be introduced in order to measure the effectiveness of the communication. A research-based approach will normally be appropriate in order to establish that **safety communications have met the standard** of XV.B.2. This approach may measure different outcomes, including behaviour, attitudes, and knowledge 'The effectiveness of safety communication should be evaluated where appropriate and possible' [a10] Research undertaken	**Regulation** REMS are required to report on whether risk minimisation measures are ensuring safe use, using a research-based assessment. Required by legislation to develop robust systems in partnership with academics and professionals[a8] The FDA has undertaken research to examine effectiveness of its risk communication activities[a26-29]	**Regulation** Not described **Guidance** 'In some cases, Health Canada may request the MAH to submit additional follow-up information (for example, the most recently available PSUR or annual/interim summary report) to monitor the situation.[a12]	**Regulation** No requirement in Australian legislation for monitoring the effectiveness of safety communication. **Guidance** *TGA alerts* No guidance or description regarding monitoring of the effectiveness.

*[i] Accompanying regulations at time of writing did not describe whether this relates to the public disclosure of risk information such as in safety advisories.[a30]

References for Table S1

(a1) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Drug safety priorities. Initiatives and innovation. 2015-2016* (FDA: Maryland, 2016).

(a2) Dal Pan, G.J. & Arlett, P.R. The US Food and Drug Administration-European Medicines Agency Collaboration in Pharmacovigilance: Common Objectives and Common Challenges. *Drug Safety* **38**, 13-5 (2015).

(a3) European Medicines Agency. (2017). *Summary of the EMA public hearing on valproate in pregnancy* (EMA, London, 2017).

(a4) The Federal Advisory Committee Act, 5 U.S.C. app. (as amended) (ed. Administration, U.S.G.S.) (U.S General Services Administration, Washington).

(a5) Australian Government Department of Health Therapeutic Goods Administration. *Advisory Committee on Medicines (ACM)*. <https://www.tga.gov.au/committee/advisory-committee-medicines-acm> (2019). Accessed Dec 2019 2019.

(a6) European Parliament and Council of Ministers. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Vol. Directive 2010/84/EU (Official Journal of the European Union, 2010).

(a7) Skerrit, J. Therapeutic Goods Information (Early Warning System) Specification 2013. Instrument and Explanatory statement. (2013).

(a8) Food and Drug Administration Amendments Act. (US Congress, 2007).

(a9) *CFR - Code of Federal Regulations Title 21*. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=20.61> (2019). Accessed 20 Oct 2019 20 Oct 2019.

(a10) European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module XV – Safety communication (Rev 1).* EMA/118465/2012 Rev 1 edn. (2017).

(a11) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry and FDA Staff. Dear Health Care

Provider Letters: improving communication of important safety information. (FDA, Maryland, 2014).

(a12) Health Canada MedEffect Canada. Guidance document for industry - issuance of health professional communications and public communications by market authorization holders. Guide and template. (Minister of Health, Ottawa, 2010).

(a13) Australian Government Department of Health and Ageing Therapeutic Goods Administration. Trans-Tasman early warning system. Processes in Australia and New Zealand. Version 1.0 edn. (TGA, ACT, 2013).

(a14) U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) & Center for Biologics Evaluation and Research (CBER). *Guidance - Drug Safety Information – FDA's Communication to the Public. DRAFT GUIDANCE (withdrawn)* (FDA: Maryland, 2012).

(a15) Health Canada. *Description of current risk communication documents for marketed health products for human use. Guidance document.* (Health Canada,: Ottawa, 2008).

(a16) Bahri, P. Public pharmacovigilance communication: A process calling for evidence-based, objective-driven strategies. *Drug Safety* **33**, 1065-79 (2010).

(a17) European Medicines Agency & Heads of Medicines Agencies. (2013). *Guideline on good pharmacovigilance practices – Product- or population-specific considerations I: Vaccines for prophylaxis against infectious diseases* (EMA London, 2013).

(a18) European Medicines Agency & Heads of Medicines Agencies. (2018). *Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations IV: Paediatric population* (EMA London, 2018).

(a19) U.S. Department of Health and Human Services Food and Drug Administration. Classifying significant postmarketing drug safety issues. Draft guidance. (FDA, Maryland, 2012).

(a20) U.S. Department of Health and Human Services Food and Drug Administration. *Communicating risks and benefits: An evidence-based user's guide* (FDA: Maryland, 2011).

(a21) Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. SCOPE Work package 6. Risk communication. National strategy for implementation of recommendations on risk communication: Key actions. (SCOPE, London, 2016).

(a22) Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. (SCOPE, London, 2016).

(a23) U.S. Department of Health and Human Services Food and Drug Administration. FDA Strategic plan for risk communication and health literacy 2017-2019. (ed. FDA) (FDA, Maryland, 2017).

(a24) Health Canada. Strategic risk communications framework for health Canada and the Public Health Agency of Canada. (Minister of Health, Canada, Ottawa, 2006).

(a25) European Medicines Agency. PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Rev 1). In: *EMA/165407/2017 Pharmacovigilance Risk Assessment Committee* (EMA, London, 2017).

(a26) Kesselheim, A.S. *et al.* Changes in prescribing and healthcare resource utilization after FDA Drug Safety Communications involving zolpidem-containing medications. *Pharmacoepidemiology and Drug Safety* **26**, 712-21 (2017).

(a27) Woloshin, S. *et al.* Media Coverage of FDA Drug Safety Communications about Zolpidem: A Quantitative and Qualitative Analysis. *Journal of Health Communication* **22**, 365-72 (2017).

(a28) Kesselheim, A.S. *et al.* Methodological approaches to evaluate the impact of FDA drug safety communications. *Drug Safety* **38**, 565-75 (2015).

(a29) Kesselheim, A.S. *et al.* Patient and Physician Perceptions of Drug Safety Information for Sleep Aids: A Qualitative Study. *Drug Safety* **40**, 531-42 (2017).

(a30) Government of Canada. Food and Drug Regulations. In: *CRC, c 870* Last amended on June 17, 2019 edn. (Government of Canada, 2019).

Chapter 3 Case study – Communicating emerging risks of SGLT2 inhibitors - timeliness and transparency in Australia, Canada, the European Union, and the United States

3.1 Introduction

This chapter contains the following publication:

> Bhasale A, Mintzes B, and Sarpatwari A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. *BMJ* 369: m1107, 2020. doi: 10.1136/bmj.m1107

The manuscript and reference list are formatted as per the publisher's specifications, and hence do not correspond to the formatting in the rest of this thesis.

3.2 Overview

In the first of two studies of policy outcomes examining the use of advisories, I conducted an in-depth case study to explore differences amongst regulators in their approach to communicating safety issues for a specific new class of drugs, the SGLT2 inhibitors for diabetes.

A case study approach was chosen to allow a more thorough exploration of the surrounding context for specific drug safety issues to examine how differences in legislation and regulatory policy are applied in practice. For example, regulators responding to differing rates of advisories among jurisdictions have stated that there may be other mechanisms in place for mitigating the safety issue (for example product information or existing risk minimisation strategies) as well as differences in decision making.[1] This case study examined not only the advisories themselves but also pre-approval documentation and all

publicly available information about the decision-making process for each of the specific safety issues.

In order to identify a suitable case study, I identified all drug safety issues from the SAFER database to identify drugs for which all four regulators had issued at least one safety advisory. Selection of a case study was based on the following:

- The drug was approved after 2010 in Australia, when Australia began publishing Australian public assessment reports (AUSPARs) [2] for drug licensing decisions, and was also approved in all four jurisdictions
- If advisories were issued for a drug class, all drugs in the class were approved post-2010
- More than one safety concern/advisory was associated with the drug
- Among the safety concerns identified in advisories about the drug(s), there was at least one for which all regulators issued an advisory, and at least one other safety concern for which not all regulators issued an advisory.
- Likely to be prescribed by GPs for a relatively common condition.

There were 46 drug safety concerns which met these requirements, 5 of which related to SGLT2 inhibitors. The SGLT2 inhibitors were selected for the following reasons: they had a range of important post-market safety issues arising shortly after marketing, both concordance and discordance between regulators in issuing advisories, both class and individual drug alerts, and as a drug class with a new mechanism of action for diabetes mellitus, they were likely to be broadly prescribed. All SGLT2s drugs had received marketing approval in each jurisdiction no earlier than April 2012, allowing access to Australian regulatory decision making in the AUSPAR, as well as meaning they would have been subject to major pharmacovigilance changes in Europe in 2012/13.

Additionally, there was reason to expect increased regulatory caution, after serious post-market safety concerns for other diabetes drugs (rosiglitazone and pioglitazone) had resulted in their withdrawal in Europe, but not in the other study jurisdictions.

3.2.1 Background to the case study of SGLT2 inhibitors

SGLT2 is responsible for resorption of glucose in the kidney and SGLT2 inhibition increases urinary glucose excretion, lowering blood glucose - a different mechanism of action compared to other diabetes medicines.[3]

Canagliflozin and dapagliflozin came to market in a climate of heightened concern about cardiovascular safety - following the identification of serious post-market safety concerns with rosiglitazone and pioglitazone, the FDA had started requiring manufacturers to conduct pre-market trials to test new diabetes drugs for cardiovascular risks.[4] Although both canagliflozin and dapagliflozin were supported by a large clinical trial program, at the time of first approval worldwide only 1344 patients had been treated for more than one year with canagliflozin[5] and 1758 with dapagliflozin[6], relatively small numbers in view of the prevalence of diabetes and the long-term nature of treatment.

Interim data from large, long-term studies such as the CANVAS and EMPA-REG trials for canagliflozin and empagliflozin [7,8] formed much of the safety data at drug approval. Ultimately these studies provided evidence of cardiovascular safety and possible cardiovascular benefit but also revealed the unexpected evidence of harm leading to safety warnings.

Dapagliflozin was the first SGLT2 inhibitor to market in Europe and Australia, but was initially rejected in both the US and Canada. Canagliflozin was the first approved drug in the class in North America, despite initial rejection in Canada. Dapagliflozin was approved in Europe in April 2012 [6], and canagliflozin was approved in the US in March 2013. Safety concerns and the benefit-risk profile led to the initial rejection of dapagliflozin in the US and Canada, and of

canagliflozin in Canada.[9-11] By May 2014 canagliflozin and dapagliflozin were approved in all four jurisdictions and empagliflozin by July 2015.

All drugs remain on the market in each jurisdiction except Australia, where canagliflozin is no longer available after the company took the unusual step of requesting its removal from the public reimbursement schedule (the Pharmaceutical Benefits Scheme (PBS) shortly after listing, following a dispute over pricing.[12,13] The PBS price took into account comparative effectiveness with the dominant diabetes regimen, and included cost offsets for managing adverse effects such as genitourinary infections and monitoring of renal function.[14]. Prices for dapagliflozin and empagliflozin were also reduced but these drugs remain available in Australia. [14]

3.2.1.1 Objectives

The objectives of this study were to identify:

- differences in regulatory safety post-market communications for SGLT2 inhibitors in Australia, Canada, the UK, and the US
- factors that could explain these differences
- the transparency of information about regulatory decision making for post-market safety in each jurisdiction.

3.2.1.2 Methods and data collection

I compared differences in the issuing, timing, and content of post-market safety communications on SGLT2 inhibitors, including safety advisories and changes to product information, using process-tracing methodology.[15] I assessed whether differences in communication could be explained by differences in:

- conditions of marketing approval (prescribing restrictions, risk mitigation strategies), including those based on signals of safety concerns in pre-market data

- detection of post-market signals
- interpretation of data
- actions taken in relation to safety signals (decision making).

When new evidence emerges of a potential safety concern in the post-market period, decisions are seldom straightforward and require judgements and decision making about whether the data indicate a safety concern. I was also interested in the transparency of the decision-making process and examined transparency in terms of accessibility of data and information about how decisions were made and who was involved.

To trace the background to decisions, I reviewed publicly available FDA, TGA, Health Canada and EMA documents to identify regulatory decisions and actions in relation to the identified safety issues between first marketing approval (April 2012 in Europe) and 31 July 2018, when I began work on this analysis. For Europe, I included UK safety advisories, however as SGLT2 inhibitors were centrally authorised medicines, decisions about safety were made at the EMA level, so EMA documentation were used as the source data for regulatory decision making.

I searched regulators‘ websites for relevant documents including the safety advisories, regulatory approval documents, descriptions of steps taken after approval for each drug where available (canagliflozin, dapagliflozin and empagliflozin), current and original product information (US prescribing information, UK Summary of Product Characteristics, Canadian Product Monographs), investigation reports, minutes of advisory meetings and any regulatory information referred to within those documents relevant to the decision and publicly available.

3.3 References

1. Dal Pan GJ. Gauging the Effectiveness of Medicines Safety Communications From Global Regulatory Agencies. *JAMA Internal Medicine* 2019. DOI: 10.1001/jamainternmed.2019.0266.
2. Papathanasiou P, Brassart L, Blake P, et al. Transparency in drug regulation: public assessment reports in Europe and Australia. *Drug Discovery Today* 2016; 21: 1806-1813. DOI: https://doi.org/10.1016/j.drudis.2016.06.025.
3. Australian Government Department of Health Therapeutic Goods Administration. Australian Public Assessment Report for Dapagliflozin propanediol monohydrate. 2013.
4. U.S. Department of Health and Human Services Food and Drug Administration. *Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. 2008.
5. U.S. Department of Health and Human Services Food and Drug Administration. Canagliflozin Summary Review. 204042Orig1s000. 2013.
6. European Medicines Agency. *Assessment report. Dapagliflozin*. 2012. London: EMA.
7. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine* 2017; 377: 644-657. DOI: 10.1056/NEJMoa1611925.
8. Zinman B, Inzucchi SE, Wanner C, et al. Empagliflozin in women with type 2 diabetes and cardiovascular disease - an analysis of EMPA-REG OUTCOME(R). *Diabetologia* 2018; 61: 1522-1527. 2018/05/02. DOI: 10.1007/s00125-018-4630-2.
9. U.S. Department of Health and Human Services Food and Drug Administration. *Dapagliflozin Summary Review*. 2014.
10. Health Canada. Summary Basis of Decision - Forxiga - Health Canada, https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?lang=en&linkID=SBD00219 (2015).
11. Health Canada. Summary Basis of Decision - Invokana - Health Canada, https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00255#Brandname4 (2014, accessed 20 Feb 2019).

12. Janssen-Cilag Pty Ltd. Invokana (canagliflozin). Removal from the pharmaceutical benefits scheme on 1 August 2015 (Letter). Sydney: Janssen-Cilag Pty Ltd, 2015.

13. Pharmaceutical Benefits Advisory Committee AGDoH, . Public Summary Document Product: Canagliflozin, tablet, 100 mg and 300 mg, Invokana. (2013).

14. Pharmaceutical Benefits Advisory Committee Australian Government Department of Health. Deletion of Pharmaceutical Benefit Items. Effective 1 August 2015. Canberra, ACT: Commonwealth of Australia.

15. Van Evera S. *Guide to Methods for Students of Political Science*. Cornell University Press, 1997.

3.4 Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators

Alice Bhasale[1], Barbara Mintzes[1,2], Ameet Sarpatwari[3]

[1]The University of Sydney Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, NSW 2006, Australia

[2]School of Population and Public Health, University of British Columbia, Vancouver, Canada

[3]Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

Key messages

- Sodium glucose co-transporter-2 (SGLT2) inhibitors came to market amid heightened concern over the safety of diabetes drugs.
- The drugs have received several serious safety warnings since approval, but the number, timeliness, and strength of these safety communications have differed between American, Australian, Canadian, and European regulators
- One regulator identified the risk of lower limb amputation during routine pre-market assessment, but three years passed before any regulator issued a public warning.
- In some instances, the wording of warnings was weakened after interactions with industry.
- Greater transparency is required to assure the public of the impartiality of evidence assessment and ensure that decisions reflect public values.

INTRODUCTION

Medicines regulators have an important role in ensuring that newly uncovered risks of approved drugs ("post-market" risks) reach prescribers and patients. Such information is conveyed through safety advisories (such as online alerts, bulletin articles, letters to health professionals) and changes to official drug prescribing information (Box 1). Based on reviews of post-market safety controversies over the past two decades,[1-4] the public expects regulators to communicate post-market risks promptly and transparently, prioritising public over commercial interests.

Box 1: How regulators identify and communicate post-market risks

Post-market risks are identified through various means

- Studies designed to test for specific safety outcomes, sometimes as a requirement of licensing (such as FDA post-market requirements, EMA post-authorisation safety studies).
- Spontaneous adverse drug reaction reports collected and monitored by regulators
- Medical literature
- Notification or reporting by companies, as mandated by regulation
- Other regulators.

Post-market risks are communicated using

Safety advisories

- Website alerts, direct health professional communications (letters to health professionals), drug safety bulletins, and notices of safety investigations
- Can be initiated by regulators or industry. Direct health professional communications, commonly used in the EU and Canada, are jointly developed by the company and regulator. FDA drug safety communications are developed by the FDA.

Prescribing information*

- The approved statement of safety, efficacy, and authorised use may be updated to include new safety information.
- Companies must apply to regulators to make updates.
- Can be initiated by companies or when requested or required by a regulator. Companies can propose wording that regulators must assess and approve.

Safety advisories included were those related to drug adverse effects, not to administration errors, misuse, or manufacturing quality problems. FDA=US Food and Drug Administration; EMA=European Medicines Agency.
*Referred to as product information (Australia), product monograph (Canada), summary of product characteristics (UK), and informally as the drug label (US).

Assessing fidelity to these goals, we examined how the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), Health Canada, and the Australian Government Therapeutic Goods Administration (TGA) communicated emerging risks for a relatively new class of oral diabetes drugs—the sodium glucose co-transporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin—from first approval until June 2018. There are good reasons to expect timely communication of this information. First, given the

high prevalence of diabetes, even infrequent adverse effects from SGLT2 inhibitor use could have a large impact on the population. Second, SGLT2 inhibitors came to market amid heightened safety concerns over diabetes drugs. In 2010, accumulating evidence about the cardiovascular risks of rosiglitazone led to its loss of marketing authorisation in the EU and to strong regulatory warnings in the US.[5 6] Ensuing debate resulted in new FDA requirements for long term cardiovascular safety trials for all new diabetes drugs.[7] As trials like CANVAS have identified a cardiovascular benefit of SGLT2 inhibitors,[8 9] prescribing of this class of drugs is likely to rise.

We found that the regulators varied considerably in their propensity to communicate five serious risks of SGLT2 inhibitors—diabetic ketoacidosis, lower limb amputation, severe genitourinary infections, acute kidney injury and fracture—and in the timeliness and strength of their warnings. Although most regulators provided some information about their risk assessments, the level of detail was inadequate to alleviate concerns about industry influence. Greater transparency is required to assure the public of the impartiality of evidence assessment and to ensure that decisions reflect public values.

Differences in the use and timing of safety warnings

The FDA issued advisories about the most risks, communicating all five safety concerns, compared with four by Health Canada, and two each by the EMA and TGA. Each regulator released advisories about lower limb amputation and diabetic ketoacidosis. The FDA and Health Canada also warned about acute kidney injury and fracture; only the FDA warned about severe genitourinary infections.

Time lags between regulators issuing advisories for the same safety issue ranged from 19 days to over 13 months (Table 1), with Health Canada and the TGA usually following the EMA and FDA. The gap between the first and last regulator was shortest for diabetic ketoacidosis (FDA and TGA) and longest for bone loss and fracture (Health Canada and FDA).

Regardless of whether advisories were issued, most official drug prescribing information documents were updated to include these adverse effects, although the timing of these updates differed both between regulators and between drugs within a jurisdiction. The EMA, for example, added severe genitourinary infections to the prescribing information for canagliflozin and empagliflozin three years apart, whereas the FDA did so simultaneously. (**Table 1)**

Table 1: Time to advisories and prescribing information changes (April 2012 to June 2018).

	Time from lead advisory (days)			
	FDA	**EMA**	**Health Canada**	**TGA**
INITIAL ADVISORY				
Diabetic ketoacidosis	0	42	38	90
Amputation	19	0	216	39
Fracture risk	0	–	402	–
Severe genitourinary infections	0	–	–	–
Acute kidney injury	242	–	0	–
FOLLOW-UP ADVISORY (WITHIN JURISDICTION)				
Diabetic ketoacidosis	203	262	329	–
Amputation	367	327	279	–
P**RODUCT INFORMATION CHANGE**				
Diabetic ketoacidosis	203	348	453	Changed*
Amputation (canagliflozin)†	453	360	180‡ 558§	Changed*
Fracture risk (canagliflozin)	0	–532	469	NA
Severe genitourinary infections:				
canagliflozin	0	–102	189	NA
dapagliflozin	0	173	415	Changed*
empagliflozin	0	768	–	Changed*
Acute kidney injury:				
canagliflozin	217	63	213	NA
dapagliflozin	175	No change	117	No change

0 indicates the first advisory by any regulator; – indicates no advisory; a negative number indicates the action occurred before the first advisory; NA=not applicable. *The TGA does not provide an archive of previous prescribing information or a record of changes, so changes were identified by comparing current and initial prescribing information, dates of change unknown. †The EMA investigated across the class and added warnings to all prescribing information with more specific warnings for canagliflozin. The FDA and Health Canada added warnings for canagliflozin only. ‡Health Canada's initial response to the EMA advisory was a change in the adverse reactions section of the prescribing information. §Health Canada later added a boxed warning in line with the FDA's boxed warning.

Delayed action on amputation risk

That a new diabetes drug might increase the risk of a disease related complication such as lower limb amputation should have interested all regulators, particularly after the rosiglitazone controversy.[2 3] Yet, several years elapsed between the first identification of a signal by Health Canada and regulatory action.

In 2013, Health Canada cited the risk of lower limb amputation in its initial rejection of marketing approval for canagliflozin, seemingly based on interim results from the ongoing CANVAS trial.[10] It subsequently granted approval ten months later, referring in approval documents to a non-statistically significant increase in amputations but explaining that text about peripheral ischaemia and skin ulcers had been added to the prescribing information.[10] The word “amputation,” however, was not used (see **Supplement Table 1**).

At least four years of data from the trial had been reviewed by regulators at the time of canagliflozin’s approval.[11-14] Yet no other regulatory documents in the public domain described amputation until a 2016 EMA advisory that flagged the risk as a “new signal” after reviewing a report from the CANVAS programme’s independent data safety committee.[15] Notably, the EMA had continued to receive monitoring reports every six months as the trial progressed and later confirmed that “the imbalance [in amputations] occurred as early as the first 26 weeks of therapy,”[16] suggesting that the risk had been evident in unblinded data for some time.

After the EMA identified the signal, the EMA and FDA each issued “early warning” advisories to alert clinicians and patients that the possible risk was being investigated. The initial FDA advisory reported that “amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo” but stated that the agency had “not determined whether canagliflozin increases the risk of leg and foot amputations.”[17] The EMA said that the issue was “under investigation, and any mechanism behind the events is as yet unknown.” But 10-12 months elapsed before findings were announced (Table 1). Health

Canada's eventual boxed warning came 16 months after the first EMA advisory and four years after Health Canada first assessed the data on lower limb amputation before approval.

Differences in clarity and strength of warnings

After assessing the CANVAS lower limb amputation data, the FDA communicated the risk in stronger terms than the EMA. The risk was described by the EMA as affecting "mainly toes" and "toe amputation," but by the FDA as "leg and foot amputations." Both regulators were factually correct as 30% of amputations for both placebo and canagliflozin in CANVAS were above the foot, but the EMA focused on the less severe outcome.[18]

The FDA also ascribed causality to canagliflozin in its post-assessment advisory ("canagliflozin causes an increased risk"), whereas the EMA and Health Canada advisories were more neutral (increased risk "has been observed"). The TGA advisory implied that the risk was probably a disease related complication, stating that "it should be noted that CANVAS involves patients at high risk of problems with the heart and blood vessels and that lower limb amputations occurred in both the canagliflozin and placebo groups in the study" (see **Supplement Table 1**).

Not all key language in the FDA advisory was carried through to canagliflozin's prescribing information (Box 2). Statements regarding causality and the advice to "inform patients that canagliflozin is associated with an increased risk of amputations" were omitted. FDA documents reveal extensive negotiations between the agency and the drug's manufacturer over revisions to the prescribing information and patient medication guide. Among other changes, the FDA agreed to delete the "numbers needed to harm" calculations, which the manufacturer argued was "not a metric commonly used by providers" and "not interpretable unless put in the context of benefit." The FDA did, however, resist repeated requests to change the patient warning about multiple amputations, citing the strength of evidence and need for clear communication. For prescribers it warned that "some patients had multiple amputations, some involving both limbs" [19]

Box 2: Changes after negotiation with company: canagliflozin prescribing information.

FDA-drafted changes before company negotiation
In CANVAS, use of **INVOKANA increased the risk of lower limb amputations** from 2.8 amputations per 1000 patients per year to 5.9 amputations per 1000 patients per year (**number needed to harm: 323**). In CANVAS-R, the use of INVOKANA **increased the risk of lower limb amputations** from 4.2 amputations per 1000 patients per year to 7.5 amputations per 1000 patients per year (**number needed to harm: 270**).
FDA-approved changes after company negotiation
In CANVAS, **INVOKANA-treated patients and placebo-treated patients had** 5.9 and 2.8 amputations per 1000 patients per year, respectively. In CANVAS-R, **INVOKANA-treated patients and placebo-treated patients had** 7.5 and 4.2 amputations per 1000 patients per year, respectively.

Emphasis added to indicate changes

The EMA's prescribing information, meanwhile, emphasised the similar distribution of major, minor, and multiple amputations in both canagliflozin and placebo groups rather than the overall doubling of amputation risk with canagliflozin, stating that "multiple amputations (some involving both lower limbs) were observed infrequently and in similar proportions in both treatment groups" (see **Supplement Tables 1 and 3**).

Regarding fracture risk, the EMA was more reticent than the FDA to attribute the effect to canagliflozin and in communicating this risk to prescribers. Unlike the other regulators, the EMA did not include fracture risk in the prescribing information at approval (see **Supplement Table 2**). When it later tackled this inconsistency at the company's request, the EMA did not issue an advisory despite the risk being mentioned in the prescribing information for the first time.

At approval, the EMA, FDA, and TGA had required post-market research clarifying canagliflozin's effects on bone mineral density. The final study results spurred an FDA advisory announcing that "canagliflozin caused greater loss of bone mineral density at the hip and lower spine than a placebo" at two years, with stronger warnings on fracture risk.[20] By contrast, the prescribing information approved by the EMA reassured prescribers that canagliflozin "did not adversely affect bone mineral density after 104 weeks of treatment." Although no references are listed in the prescribing information, both regulators apparently examined the same data but reached opposing conclusions (Box 3). Additionally, the EMA prescribing information implies that the 104-week bone density data came from a pooled dataset of over 5800 people, rather than the actual 714 person trial population (Box 3). Despite the FDA's stronger warning, its advisory came nearly 18 months after the EMA prescribing information update.

Box 3: FDA and EMA—contradictory views regarding canagliflozin and possible effects on bone mineral density

FDA prescribing information—updated 10 Sep 2015
Bone mineral density (BMD) was measured by dual energy x ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years). At 2 years, patients randomised to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. *
EMA prescribing information—updated 10 Apr 2014
In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of approximately 5800 patients, no difference in fracture risk was observed relative to control. † After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.*

*A study required by regulators and undertaken by the sponsor describes two year (104 week) follow-up of 714 patients with serial bone mineral density measurement.[22]
†A study undertaken by the sponsor describes a pooled dataset of fracture risk in 5840 patients but no measurement of bone mineral density.[21]

Reasons for differences in communication and their implications

What are the reasons for these differences in safety communications? Compared with the detailed data released when drugs are approved, limited information is available about how regulators assess post-market risks. Summaries of some assessments were made publicly available by the EMA, FDA, and Health Canada but many lacked explanatory detail or the ability to link to the original data, while assessment material was not provided by the TGA. Regarding fracture, we found no information on the EMA's assessment or the reasons for the FDA's delayed response. Most lacking was transparency as to interactions between industry and regulators.

Some differences in safety communications might reflect intentional policy choices; for example, fewer safety advisories could arise from regulators' uncertainty about the strength of post-market findings or from perceived drawbacks of frequent notification, such as alert fatigue or excessive alarm. To determine whether these approaches are appropriate, better

evidence is needed on the effects of safety advisories and the degree to which prescribers recognise changes to prescribing information without additional warnings.

Relative constraints in regulatory capacity probably contributed to the differences we observed. Regulators must balance the resources they assign to post-market safety with the attention they give to new drug approvals.[23] In attempting this balance, the FDA has struggled to ensure that companies fulfil post-market study obligations.[24] Smaller regulators, meanwhile, are hampered by smaller operating budgets and population sizes for identifying adverse effects.[25 26] Unsurprisingly, the timing of Health Canada and the TGA's responses indicates some reliance on the FDA and EMA to identify and respond to safety issues.[27 28] As a supranational agency, the EMA relays safety communication decisions to 28 member states. Accordingly, for "practical" reasons, EMA policy is to centrally coordinate and translate direct health professional communications for only limited types of safety updates, such as new contraindications and EU-wide investigations.[29 30] This could explain the lack of an EMA safety advisory for fracture, despite being previously described by the agency as an "important potential risk."[31]

Finally, the relative involvement of sponsors in drafting and disseminating safety communications might have had an important role in substance and timing. Current models of post-market safety regulation in most jurisdictions rely heavily on industry capacity. Commentators have noted the intrinsic paradox of relying on industry to collect, analyse, and report data that might negatively affect business goals.[32 33] Regulators have the authority to unilaterally compel industry to make safety related changes to prescribing information, but surrounding negotiations can weaken safety messages—as seen with lower limb amputation—and delay risk communication.[34] Such discussions are largely conducted in confidence and should be more transparent. Additionally, the issuance of safety communications by sponsors might affect the trust with which they are received.[35 36] Although European doctors have indicated that they prefer to receive safety advisories from

regulators rather than industry,[35 36] a key form of safety advisory in the EU are letters from sponsors with text agreed by regulators.

Conclusions

Decisions about when to issue safety communications are largely discretionary and might depend on regulators' ability to detect post-market risks, their perception of the significance of those risks, and their propensity to communicate.[23 34 37-39] In our review of post-market safety communications for SGLT2 inhibitors, we found that the FDA issued more safety advisories but was not always the first to act. Time lags between regulators were common, suggesting limitations in capacity.

Although regulators are not required to harmonise safety decisions,[40 41] a senior FDA official, responding to evidence of differences between regulators' safety alerts,[42] acknowledged that "with the increasing global reach of communications . . . discordance can create confusion if the basis for the differing conclusions is not made clear."[41] In addition to detailed explanatory summaries, we think that regulators should provide public access to post-market safety reports submitted by industry to regulators.[43] Industry interactions with regulators regarding the interpretation of safety data should likewise be a matter of public record. Such records are currently either unavailable or extensively redacted beyond what might justifiably be considered commercially in confidence. Greater transparency in decision making would increase the accountability of both regulators and industry and allow more informed treatment choices to be made.

Contributors and sources: This paper was developed as a case study of safety advisories for AB's doctoral research on regulatory post-market safety policy and is related to an Australian government National Health and Medical Research (NHMRC)-funded research project on safety advisories. BM is the chief investigator on the NHMRC-funded project and has a longstanding interest in regulatory and pharmaceutical policy. AS is a co-investigator on the NHMRC-funded project and an epidemiologist and lawyer with research expertise in US pharmaceutical policy. AS's work is also funded by Arnold Ventures and the Harvard-MIT Center for Regulatory Science. Research and writing of the article was supported by funding provided by The University of Sydney and Harvard University Mobility Scheme.

AB conducted the documentary review and preliminary analysis. All three authors contributed to the interpretation and synthesis of the findings and the writing of the manuscript. Colleen Fuller and Ellen Reynolds provided helpful comments and perspectives on an earlier draft of this paper.

Patient involvement: Colleen Fuller, a Canadian researcher and writer with patient advocacy experience in diabetes, provided helpful comments on an earlier draft, including a perspective on the significance of diabetic ketoacidosis associated with the use of SGLT2s for type 1 diabetes.

Competing interests: We have read and understood BMJ policy on declaration of interests and have the following interests to declare: None

Provenance and peer review: Not commissioned; externally peer-reviewed.

References

1 US Institute of Medicine. Committee on the Assessment of the US Drug Safety System. The future of drug safety — promoting and protecting the health of the public. In: Baciu A, Stratton K, Burke SP, eds. Committee on the Assessment of the US Drug Safety System, Board on Population Health and Public Health Practice. The National Academies Press, 2006.

2 Moynihan R. Rosiglitazone, marketing, and medical science. BMJ 2010;340:c1848. doi:10.1136/bmj.c1848. PubMed

3 Califf RM, Kramer JM. The balance of benefit and safety of rosiglitazone: important lessons for our system of drug development and postmarketing assessment. Pharmacoepidemiol Drug Saf 2008;17:782-6. PubMed doi:10.1002/pds.1617

4 Hugman B. The Erice declaration: the critical role of communication in drug safety. Drug Saf 2006;29:91-3. doi:10.2165/00002018-200629010-00007. PubMed

5 European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. 2010. https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-suspension-avandia-avandamet-avaglim.

6 Woodcock J, Sharfstein JM, Hamburg M. Regulatory action on rosiglitazone by the U.S. Food and Drug Administration. N Engl J Med 2010;363:1489-91. doi:10.1056/NEJMp1010788. PubMed

7. US Department of Health and Human Services Food and Drug Administration. Guidance for industry. Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. 2008.

8 Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57. doi:10.1056/NEJMoa1611925. PubMed

9 Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. doi:10.1056/NEJMoa1504720. PubMed

10 Health Canada. Summary Basis of Decision. Invokana. Health Canada Ottawa: Health Canada, 2014. https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00255#Brandname4 .

11. U.S. Department of Health and Human Services Food and Drug Administration. Canagliflozin Summary Review. 204042Orig1s000. 2013. [to A: this one: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042orig1s000sumr.pdf: to ED – Correct URL]

12 US Department of Health and Human Services Food and Drug Administration. Application Number: 204042orig1s000 Medical Review(s). FDA, 2013.

13 Australian Government Department of Health Therapeutic Goods Administration. Australian Public Assessment Report for Canagliflozin (as hemihydrate). TGA, 2014.

14 European Medicines Agency. Assessment report. Canagliflozin. EMA/374133/2013 Committee for Medicinal Products for Human Use (CHMP) ed. London: EMA, 2013.

15 European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC). Minutes of the PRAC meeting on 11-14 April 2016. EMA, 2016.

16 European Medicines Agency. PRAC assessment report. Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data. SGLT2 inhibitors and lower limb amputation (canagliflozin, dapagliflozin, empagliflozin-containing medicines). EMA/PRAC/637349/2016. EMA, 2017.

17 US Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate. 18 May 2016. 2016. https://www.fda.gov/Drugs/DrugSafety/ucm500965.htm.

18. Napp Pharmaceuticals. Invokana. Summary of product characteristics. Updated 13 Sep 2018. UK.

19 US Food and Drug Administration Center for Drug Evaluation and Research. Approval Package for: Application Number: 204042Orig1s026 Trade Name: INVOKANA Generic Name: Canagliflozin. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/204042Orig1s026.pdf (accessed 02/06/2019).

20 U.S. Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. 09 October 2015. 2015. https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm.

21 Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2016;101:157-66. doi:10.1210/jc.2015-3167. PubMed

22 Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. J Clin Endocrinol Metab 2016;101:44-51. doi:10.1210/jc.2015-1860. PubMed

23 Herder M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. Milbank Q 2019;97:820-57. PubMed doi:10.1111/1468-0009.12413

24 United States Government Accountability Office. Drug safety. FDA expedites many applications, but data for postapproval oversight need improvement. GAO, 2015.

25 Jain AB, Mollet A, Szucs TD. Regulatory watch: structural and procedural characteristics of international regulatory authorities. Nat Rev Drug Discov 2017;16:594. doi:10.1038/nrd.2017.135. PubMed

26 OECD Data. Population Paris: OECD. 2019 https://data.oecd.org/pop/population.htm.

27 European Medicines Agency. Connecting the dots. Towards global knowledge of the international medicine regulatory landscape: mapping of international initiatives. EMA, 2016.

28 Health Canada. Health product vigilance framework. Health Canada, 2012.

29 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module IX Signal management (Rev 1). EMA with HMA, 2017.

30 European Medicines Agency. Questions & answers on Article 31 pharmacovigilance referral procedures. EMA, 2015.

31 European Medicines Agency. Assessment report. Dapagliflozin. EMA/689976/2012. EMA, 2012.

32 Anonymous. European pharmacovigilance: increasingly outsourced to drug companies. Prescrire Int 2014;23:302-3, 305-7. PubMed

33 Lexchin J. Public profits vs private policy. University of Toronto Press, 2016.

34. Health Canada and the Public Health Agency of Canada. Evaluation of the Human Drugs Program 1999-2000 to 2011-2012, 2014.

35 de Vries ST, van der Sar MJM, Cupelli A, et al; SCOPE Work Package 6. Communication on safety of medicines in Europe: Current practices and general practitioners' awareness and preferences. Drug Saf 2017;40:729-42. doi:10.1007/s40264-017-0535-0. PubMed

36 Piening S, Haaijer-Ruskamp FM, de Graeff PA, Straus SM, Mol PG. Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. Drug Saf 2012;35:1061-72. doi:10.1007/BF03261992. PubMed

37 Eichler H-G, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008;7:818-26. doi:10.1038/nrd2664. PubMed

38 Kesselheim AS, Franklin JM, Avorn J, Duke JD. Speaking the same language? International variations in the safety information accompanying top-selling prescription drugs. BMJ Qual Saf 2013;22:727-34. doi:10.1136/bmjqs-2012-001704. PubMed

39 Zeitoun J-D, Lefèvre JH, Downing N, Bergeron H, Ross JS. Inconsistencies among European Union pharmaceutical regulator safety communications: a cross-country comparison. PLoS One 2014;9:e109100. doi:10.1371/journal.pone.0109100. PubMed

40 Dal Pan GJ, Arlett PR. The US Food and Drug Administration-European Medicines Agency collaboration in pharmacovigilance: common objectives and common challenges. Drug Saf 2015;38:13-5. doi:10.1007/s40264-014-0259-3. PubMed

41 Dal Pan GJ. Gauging the effectiveness of medicines safety communications from global regulatory agencies. JAMA Intern Med 2019;179:984-5. doi:10.1001/jamainternmed.2019.0266. PubMed

42 Perry LT, Bhasale A, Fabbri A, et al. Comparative analysis of medicines safety advisories released by Australia, Canada, the United States, and the United Kingdom. JAMA Intern Med 2019;179:982-4. doi:10.1001/jamainternmed.2019.0294. PubMed

43. Sharfstein JM, Miller JD, Davis AL, et al. Blueprint for transparency at the US Food and Drug Administration: recommendations to advance the development of safe and effective medical products. J Law Med Ethics 2017;45 Suppl_2:7-23.

3.4.1 Supplementary files for published paper

Supplement Table 1: Content of warning statements: amputation and bone fracture

EMA [3 5]	FDA [12 17 18]	Health Canada [19 20]	TGA [21]
AMPUTATION			
Advisories			
Headline			
SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information[3] Canagliflozin-Containing Medicines INVOKANA▼ (canagliflozin), VOKANAMET▼(canagliflozin, metformin) and the risk of Lower Limb Amputation (Primarily of the Toe).[5]	FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)	INVOKANA® (canagliflozin) and INVOKAMET® (canagliflozin and metformin) - Risk of Lower Limb Amputation	Canagliflozin. Safety advisory - potential increased risk of lower limb amputation
Causality and risk descriptions			
An increase in **lower limb amputation (mostly affecting the toes) has been observed** in two long-term clinical trials, CANVAS and CANVAS-R, in patients taking canagliflozin compared with those taking placebo. The studies, which are still ongoing, involved patients at high cardiovascular risk.	Based on new data from two large clinical trials, the U.S. Food and Drug Administration (FDA) has concluded that the type 2 diabetes medicine canagliflozin (**Invokana, Invokamet, Invokamet XR) causes an increased risk of leg and foot amputations.** We are requiring new warnings, including our most prominent Boxed Warning, to be added to the canagliflozin drug labels to describe this risk.	An approximately two-fold increased risk of **surgical lower limb amputation (primarily of the toe and midfoot but also of the leg) has been observed** in two long-term clinical studies in type 2 diabetes patients with established cardiovascular disease (CVD) or at least two risk factors for CVD treated with INVOKANA.	Consumers and health professionals are advised that an ongoing clinical study involving canagliflozin has identified a **potential increased risk of requiring lower limb amputations, primarily of the toes** …. It should be noted that CANVAS involves patients at high risk of problems with the heart and blood vessels, and that lower limb amputations occurred in both the canagliflozin and placebo groups in the study. Patients with diabetes (especially those with poorly controlled diabetes and preexisting problems with the heart and blood vessels) are at increased risk of infection and

			ulceration that can lead to requiring lower limb amputations.
Product information			
Of the subjects who had an amputation, the toe and midfoot were the most frequent sites (71%) in both treatment groups (see table 2). Multiple amputations (some involving both lower limbs) were observed infrequently and in similar proportions in both treatment groups.	Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.	Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.	Not available
Consideration may also be given to stopping treatment with canagliflozin in patients that develop events preceding amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.	Monitor patients receiving INVOKANA for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue if these complications occur	Monitor patients receiving INVOKANA® for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA® if these complications occur	
Special warnings and precautions for use Lower limb amputations • In long-term clinical studies of canagliflozin in type 2 diabetes patients with established cardiovascular disease (CVD) or at least 2 risk factors for CVD, an approximately 2-fold increased risk of lower limb amputation (primarily of the toe and midfoot), has been observed in patients treated with canagliflozin (see section 4.8). As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown. • Before initiating Invokana, consider factors in the patient history that may increase the risk for amputation. As precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate	**Boxed warning** WARNING: LOWER LIMB AMPUTATION • An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD. • Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs. • Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. • Monitor patients receiving INVOKANA for infection, new pain or tenderness, sores or ulcers involving the lower limbs,	**Serious warnings and precautions** Lower Limb Amputation • An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA® use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD. • Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs. • Before initiating INVOKANA®, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. • Monitor patients receiving INVOKANA® for infection, new pain or tenderness, sores or ulcers involving the lower limbs,	Not available (Canagliflozin is no longer available in Australia)

hydration. Consideration may also be given to stopping treatment with Invokana in patients who develop events which may precede amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.	and discontinue if these complications occur Short warning (highlights section of prescribing information WARNING: LOWER LIMB AMPUTATION See full prescribing information for complete boxed warning. • In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD, INVOKANA has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg (5.1) • Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKANA for infections or ulcers of the lower limbs, and discontinue if these occur. (5.1)	and discontinue INVOKANA® if these complications occur.	

BONE LOSS AND FRACTURE			
Advisories			
N/A	The U.S. Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine canagliflozin (Invokana, Invokamet) related to the increased risk of bone fractures and added new information about decreased bone mineral density. A clinical trial that we required the manufacturer of canagliflozin to conduct evaluated changes to bone mineral density over two years in 714 elderly individuals and showed that canagliflozin caused **greater loss of bone mineral density at the hip and lower spine than a placebo**.	A safety review was carried out by Health Canada to evaluate the risk of bone-related side effects of using SGLT2 inhibitors. The review was triggered by a notice about international reports of bone-related side effects experienced in patients taking the SGLT2 inhibitor canagliflozin. Health Canada's safety review concluded that the evidence supported a link between the risks of bone fracture and loss of bone mineral density with the use of canagliflozin. With use of dapagliflozin, these risks were only identified in patients who had kidney problems.No evidence of bone-related side effects was found to date with the use of empagliflozin.	N/A
Product information			
In a cardiovascular study (CANVAS) of 4,327 treated subjects with established or at least two risk factors for cardiovascular disease, the incidence rates of all adjudicated bone fracture were 1.6, 1.8, and 1.1 per 100 patient-years of follow-up to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. ……. In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of 8,114 patients, no difference in fracture risk was observed relative to control. The incidence rates of all adjudicated bone fracture were 1.2 and 1.1 per 100 patient-years of follow-up to canagliflozin and control, respectively.**After 104 weeks of treatment,**	**Bone Fracture** An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA. Consider factors that contribute to fracture risk prior to initiating INVOKANA **Decreases in Bone Mineral Density** At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively.	**Bone fractures**: In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA® (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA® 100 mg, and INVOKANA® 300 mg, respectively, with the fracture imbalance observed within the first 26 weeks of therapy and not progressing thereafter. **Decreases in Bone Mineral Density**: Bone mineral density (BMD) was measured by dualenergy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years). At 2 years, patients randomized to INVOKANA® 100 mg and INVOKANA® 300 mg had placebo- corrected declines in BMD	

canagliflozin did not adversely affect bone mineral density.*		at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA® doses and 0.4% at the distal forearm for patients randomized to INVOKANA® 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA® 100 mg was 0%.	

*only one study measured BMD over 104 weeks [13]. This study showed decreased BMD at the hip that was statistically significant – but no significant change for all other sites combined.

Supplement Table 2: Risk history, identification and communication

Pre-market assessment	Post-market issues	Safety advisories	Product information
DIABETIC KETOACIDOSIS			
TGA noted possible risk in a pre-clinical study but no regulator identified the risk in clinical cases	FDA reported that it had identified 20 serious, sometimes life-threatening cases in the FAERS database in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014, issuing an advisory on 15 May 2015. EMA performed a search in the Eudravigilance database on 19 May 2015, identifying 102 serious and sometimes life-threatening cases of DKA suggestive of a causal association were identified in T2DM patients for the three SGLT2s. [1-3]	All countries issued advisories	All countries added new prominent warnings – FDA and Health Canada as boxed warnings.
AMPUTATION			
Health Canada rejected the initial marketing application for canagliflozin in 2013, citing "amputations occurring at a rate of 3.6 per 1,000 patient-years in Invokana treated subjects compared to 1.8 per 1,000 patient-years in the non-Invokana subjects"… "almost all of which were attributed to ischemic and/or infectious complications"[4] The subsequent approval states that "the sponsor submitted updated clinical data which addressed the safety concerns identified", and text was included in the product information about "skin ulcers and peripheral ischemia" (not 'amputation'). No other regulator described this data in its pre-market assessment report.	EMA (PRAC) raised a new signal based on an interim safety report in March 2016, routinely provided every six months. *A two-fold higher incidence of lower limb amputation (primarily of the toe) has been seen in a clinical trial with canagliflozin (CANVAS an on-going long-term cardiovascular outcomes trial).* *The risk in the canagliflozin groups was 6 per 1000 patient years, compared with 3 per 1000 patient years with placebo.*[5]	FDA, Health Canada and TGA issued advisories for canagliflozin. EMA-issued advisories also warned of a possible risk for other SGLT2s.	All countries updated labels – FDA, Health Canada boxed warnings for canagliflozin only. EMA added warnings to canagliflozin and a caution for other SGLT2s. TGA added caution to other SGLT2s (canagliflozin product information not available).
SERIOUS GENITOURINARY INFECTIONS			
Less serious genital and urinary tract infections were recognised pre-market as	Post-market ADR reports of more serious infections leading to hospitalisation were	FDA advisory warned about both serious genitourinary infection and diabetic	Changes made for all SGLT2s in Australia, Canada, and the US.

Pre-market assessment	Post-market issues	Safety advisories	Product information
common adverse effects resulting from increased urinary glucose. *"although frequent and unpleasant, are no important risk"* [6] At approval, EMA- and TGA-approved dapagliflozin labels stated that there was no increased incidence of pyelonephritis and urosepsis.[7] [8]	reported soon after marketing, with sequelae including renal failure and death in two cases. "*19 cases of urosepsis reported with the SGLT2 inhibitors (canagliflozin ((n=10)) and dapagliflozin ((n=9))). All 19 patients were hospitalized, and a few required admission to an intensive care unit or dialysis in order to treat kidney failure." – FDA Advisory 12 April 2015*[9] EMA – ""*enough evidence for a more prominent presentation to alert physicians that a common urinary tract infection might ascend and become a pyelonephritis" – EMA conclusion following review of periodic safety update report (PSUR)*[10]	ketoacidosis in the same advisory, citing the the FDA Adverse Event Reporting System (FAERS) database.	In Europe there were delays between updates: canagliflozin – 2015 dapagliflozin - 2016 empagliflozin - 2018.
BONE LOSS AND FRACTURE			
Pre-market data showed more fractures with canagliflozin than placebo, but a number were upper limb fractures occurring shortly after drug initiation. Hence there was uncertain whether the cause was drug effects on bone, or falls due to hypotension and volume depletion (a known adverse effect). EMA was the only regulator not to include fracture data in the product information at approval. Both EMA and the TGA included fracture as an 'important potential risk' in Risk Management Plans.[6] [11] Final data on bone mineral density (BMD) outcomes from an ongoing trial was made a post-market requirement by the FDA; the same study (DIA3010) was then included in EMA and TGA Risk Management Plans.	The completed post-market study (DIA3010) measuring BMD, showed a "placebo-corrected decline" in hip and lumbar spine BMD, according to the FDA.[12] The related publication states that only the decrease in hip BMD was statistically significant compared to placebo and that there was no difference at other sites.[13]	The FDA and Health Canada issued advisories strengthening warnings. "*A clinical trial that we required the manufacturer of canagliflozin to conduct evaluated changes to bone mineral density over two years in 714 elderly individuals and showed that canagliflozin caused greater loss of bone mineral density at the hip and lower spine than a placebo."*	Updates by the FDA and Health Canada indicated reduced BMD at the hip and lower spine, in addition to fracture risk. Fracture risk was added to the EMA product information, after a company application to align the product information for its single and combination products.[14] The revised EMA label describes fracture rates but says there is no effect on BMD, though apparently based on the same study as the FDA statement. "*After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density."*

Pre-market assessment	Post-market issues	Safety advisories	Product information
ACUTE KIDNEY INJURY			
Serious renal adverse events were infrequent pre-market and attributed to use in people with poor renal function. Risk was mitigated by restricting use in renal impairment and recommending monitoring of kidney function. [6 11 15] TGA and FDA evaluators expressed concerns that adverse renal effects would be seen post-market setting [11 16].Both EMA and TGA described renal injury as an 'important potential risk' in their Risk Management Plans. The TGA's Expert Advisory Committee recommendation to restrict use in renal impairment (eGFR<30ml/min) was not adopted by the regulator and the company's proposed indication based on the FDA precedent was followed.[11]	Post-market ADR reports of acute kidney injury included cases requiring dialysis and resulting in death were described by the FDA, based on events in the FAERs database. Only 10% of cases were in people with chronic kidney disease. FDA - *101 cases of acute kidney injury with sufficient detail to confirm the diagnosis and demonstrate a temporal relationship with canagliflozin (73 patients) and dapaglifozin (28 patients).* *96 were hospitalised, 22 cases admitted to an intensive care unit. Four deaths occurred during hospitalization, 2 of which were cardiac-related. In 58 cases, the time to onset of acute kidney injury occurred within one month or less of initiating the drug. A prior history of chronic kidney disease was reported in 10 of the 101 cases.*	Advisories were issued by HC and the FDA, strengthening existing warnings.	Updated for canagliflozin and dapagliflozin in the US and Canada, canagliflozin in EU. No changes by TGA to dapagliflozin product information; no record of canagliflozin which is no longer available in Australia.

Supplement Table 3: Presentations of amputation data in FDA and EMA product information

FDA product information 2017:

Table 2: CANVAS AMPUTATIONS

	Placebo N=1441	INVOKANA 100 mg N=1445	INVOKANA 300 mg N=1441	INVOKANA (Pooled) N=2886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Table 3: CANVAS-R AMPUTATIONS

	Placebo N=2903	INVOKANA 100 mg (with up-titration to 300 mg) N=2904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

EMA product information 2018

Table 2: Integrated Analysis of Amputations in CANVAS AND CANVAS-R

	Placebo N = 4344	canagliflozin N = 5790
Total number of subjects with events, n (%)	47 (1.1)	140 (2.4)
Incidence rate (per 100 subject-years)	0.34	0.63
HR (95% CI) vs. placebo		1.97 (1.41, 2.75)
Minor Amputation, n (%) *	34/47 (72.3)	99/140 (70.7)
Major Amputation, n (%) †	13/47 (27.7)	41/140 (29.3)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation. The percentage of minor and major amputations is based on the highest level amputation for each patient.

* Toe and midfoot

† Ankle, below knee and above knee

References for supplemental files to Chapter 3

1. European Medicines Agency. Annex IV Scientific conclusion (Diabetic ketoacidosis). Diabetic ketoacidosis 2017. https://www.ema.europa.eu/documents/scientific-conclusion/invokana-epar-scientific-conclusion_en.pdf.

2. European Medicines Agency. Minutes PRAC 08-11 June 2015 for publication. London: EMA, 2015.

3. European Medicines Agency. SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information 2017 [Available from: https://www.ema.europa.eu/medicines/human/referrals/sglt2-inhibitors-previously-canagliflozin.

4. Health Canada. Summary Basis of Decision - Invokana - Health Canada [cited committee approval. Available from: https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00255.

5. Janssen UK and Ireland. Canagliflozin-containing medicines (Invokana, Vokanamet): risk of lower limb amputation (primarily of the toe). 29 April 2016 London: www.gov.uk; 2016 [cited 25 Feb 2019. Available from: https://assets.publishing.service.gov.uk/media/572cb07440f0b60374000002/FINAL_DHPC-canagliflozin_metformin-lower_limb_amputations-Signed_21Apr16.pdf accessed 25 Feb 2019 25 Feb 2019.

6. European Medicines Agency. Assessment report. Canagliflozin. EMA/374133/2013 Committee for Medicinal Products for Human Use (CHMP). EMA/374133/2013 Committee for Medicinal Products for Human Use (CHMP) ed. London: EMA, 2013.

7. Australian Government Department of Health Therapeutic Goods Administration. Australian Public Assessment Report for Dapagliflozin propanediol monohydrate. 2013

8. Bristol-Myers Squibb/AstraZeneca EEIG. Forxiga 5 mg film-coated tablets. 2012. London: EMA.

9. U.S. Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. 04 December 2015. 2015. https://www.fda.gov/Drugs/DrugSafety/ucm475463.htm.

10. Agency EM. Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation. International non-proprietary name:canagliflozin, metformin Procedure No EMEA/H/C/PSUSA/00010077/201411 2015.

https://www.ema.europa.eu/documents/scientific-conclusion/invokana-h-c-2649-psusa-00010077-201411-epar-scientific-conclusions-grounds-recommending-variation_en.pdf.

11. Australian Government Department of Health Therapeutic Goods Administration. Australian Public Assessment Report for Canagliflozin (as hemihydrate). ACT: TGA, 2014.

12. U.S. Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. 09 October 2015. 2015. https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm.

13. Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin. The Journal of clinical endocrinology and metabolism 2016;101(1):44-51. doi: 10.1210/jc.2015-1860 [published Online First: 2015/11/18]

14. European medicines Agency. EPAR - steps after approval - Canagliflozin London: EMA; 2018 [accessed 20 Sept 2018.

15. Administration USDoHaHSFaD. Canagliflozin Summary Review. 204042Orig1s000. 2013 16. <FDA - approval204042Orig1s000 cana OtherRenal review.pdf>.

17. U.S. Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate. 18 May 2016. 2016. https://www.fda.gov/Drugs/DrugSafety/ucm500965.htm.

18. U.S. Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). 16 May 2017. 2017. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-confirms-increased-risk-leg-and-foot-amputations-diabetes-medicine.

19. Health Canada. Invokana (canagliflozin) and Invokamet (canagliflozin and metformin hydrochloride) Ottawa: Health Canada; 2016 [25 Sept 2018]. Advisory]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/health-product-infowatch-december-2016-1.html#invo accessed 25 Sept 2018.

20. Janssen Inc. INVOKANA® (canagliflozin) and INVOKAMET® (canagliflozin and metformin) - Risk of Lower Limb Amputation. 2017. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/64366a-eng.php.

21. Australian Government Department of Health Therapeutic Goods Administration. Canagliflozin. 07 June 2016. 2016. https://www.tga.gov.au/alert/canagliflozin (accessed 25 Feb 2019).

Chapter 4 Australian regulatory action on post-market safety issues for new drugs (2010 to 2016) - an international comparison and content analysis

4.1 Introduction

This chapter contains the following submitted publication:

> Bhasale A.L., Perry L., McEwin E. J., Mohammad A., Hooimeyer A., Huisman A., Mintzes B.J. Post-market safety communication for new drugs approved in Australia, 2010-2016. Unpublished manuscript (2021)
>
> Submitted to British Journal of Clinical Pharmacology

The manuscript and reference list are formatted as per the publisher's specifications, and hence do not correspond to the formatting in the rest of this thesis.

4.2 Overview

As noted earlier in this dissertation, there has been little research into the post-market safety actions of the TGA in relation to prescription medicines, and none specifically investigating safety advisories prior to the SAFER project. Therefore, this research is highly relevant to the Australian context in terms of policy implications.

4.2.1 Background to Australian regulation

The Australian Government established a National Medicines Policy in 2000, which recognises a number of partners in achieving the safe use of medicines, including regulators, clinicians, the medicines industry, consumers and the media.[1] The National Medicines Policy, which articulates the importance of a rational and quality use of medicines approach, states that regulators need to balance the demand of the public for effective

medicines, for which the need for a viable pharmaceutical industry is recognised, with the regulatory responsibility of protecting the public from drug adverse effects.[1] Thus while public protection is mentioned, the policy falls short of suggesting that this overrides commercial interests.

In Chapter 2, I examined regulatory authority and policy for post-market safety communication. Australian regulation differs from other regulators in several ways, that may be partly historical. Under the Therapeutic Goods Act the TGA is authorised to require company changes to product information, and to issue recalls on the basis of product quality issues. In addition, the TGA formally adopts many EMA policies and standards, including those relating to Risk Management Plans.[2] However, Australian regulation does not have the same principles built into it, in regard to pharmacovigilance as the legislation which underpins EMA activities, including provisions relating to controls over pharmaceutical company communication.

A related study in which I was involved, describes the attempts made as part of the SAFER Project to identify DHPCs for safety issues that the TGA was involved in, or held in its records.[3] The TGA was unable to provide these letters or confirm their existence despite a Freedom of Information Request, citing workload issues related to the commercial ownership of those letters. While it appears from the response of the companies contacted that the TGA informally advises on DHPCs, it does not have the authority to put these DHPCs in the public domain.[3] It is also unclear whether DHPCs are required as part of post-market changes to risk management plans, because unlike both the EMA and the FDA, these plans are not publicly available. The frequency of DHPCs in conjunction with, or instead of TGA-issued advisories cannot be determined due to a lack of publicly available information.

Nonetheless, the TGA has a long history of post-market communication, most formally commencing in 1964 with the formation of the Adverse Drug Reactions Advisory Committee (ADRAC). ADRAC disseminated information about adverse drug reactions reported in

Australia to prescribers, publishing the first ADRAC bulletin in 1974. Doctors interviewed in the study described in Chapter 5 referred to the 'ADRAC bulletin', although this has not been disseminated for several years, having been replaced in 2010 by the TGA Medicines Safety Update bulletin. A number of serious safety concerns were first identified by the ADRAC, and between 1974 and 2007, in at least 13 cases ADRAC contributed to the early recognition of a global drug safety issue, for example the relationship between cerivastatin and rhabdomyolosis which ultimately led to the drug being withdrawn worldwide.[4]

ADRAC was replaced in 2010 by the Advisory Committee on Safety of Medicines (ACSOM). While ACSOM also had an advisory function in regard to medicines safety, it was less directly involved in analysing ADR reports directly, which had been a hallmark of the ADRAC process, with members of ADRAC reviewing incident reports themselves for many years.[5] The ACSOM was abolished in 2017 and its functions combined with those of two other Committees in the new Advisory Committee on Medicines (ACM) which provides advice on safety, quality and efficacy for both pre-market and post-market settings. [6] The ADRAC bulletin was replaced in 2010 by Medicines Safety Update, a TGA bulletin. Thus, historically Australia's safety advisory mechanisms have been based on communications from the TGA, rather than from industry. Over time, the balance of responsibility for post-market safety surveillance and decision making has moved into the TGA, with a reduced reliance on the public or independent representatives who carried out more of this role with a supporting committee secretariat, and who directly reported to the Australian Drug Evaluation Committee (ADEC). Most adverse event reports now come from industry due to their legal requirement to report.[7] However, in the early days of the scheme in 1968, private doctors provided about 70% of reports, hospitals 20%, and 7% came from the pharmaceutical industry.[4]

Having examined the policy differences between the TGA and other regulators, the purpose of this study was to further investigate the characteristics, frequency and timing of Australian

safety advisories for new drugs, focusing on the cohort of new drugs approved between 2010 and 2016.

In the study described below, I identified a set of safety advisories from the SAFER database which met specified inclusion criteria - that they were issued by regulators in Australia, Canada, the UK or the US about new chemical and biological entities approved in Australia from 2010-2016. I developed a coding frame and questionnaire for extracting data from these advisories. This included coding for the characteristics of the safety concerns, regulatory actions, and advice to consumers and clinicians. I defined the extraction dataset and participated in the coding of advisories which was undertaken primarily by a team of coders. I then analysed the data using SPSS.

4.3 References

1. U.S. Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drug saxagliptin (marketed as Onglyza and Kombiglyze XR). *FDA Drug Safety Communication*, https://wayback.archive-it.org/7993/20170406043836/https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm (2014).
2. U.S. Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. 4 May 2016. *FDA Drug Safety Communication*, https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm (2016).
3. U.S. Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. 28 May 2015. *FDA Drug Safety Communication*, https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-dpp-4-inhibitors-type-2-diabetes-may-cause-severe-joint-pain (2015).

4. AstraZeneca Pty Ltd. Australian Product Information. Onglyza (saxagliptin) tablets., https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-02123-3&d=202102211016933 (2019, accessed 21 Feb 2021).

5. Australian Government Department of Health and Ageing Therapeutic Goods Administration. Attachment 1 - Onglyza - Saxagliptin Product information. *Australian Public Assessment Report for Saxagliptin Hydrochloride, Proprietary Product Name: Onglyza, Submission No: PM-2008-03469-3-5, Sponsor: Bristol-Myers Squibb Australia Pty Ltd*, https://www.tga.gov.au/sites/default/files/auspar-onglyza.pdf (2011, accessed 21 Feb 2021).

6. Hooimeyer A, Bhasale A, Perry L, et al. Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. *Pharmacology Research & Perspectives* 2020; 8: e00680. DOI: https://doi.org/10.1002/prp2.680.

7. Mollebaek M, Kaae S, De Bruin ML, et al. The effectiveness of direct to healthcare professional communication - A systematic review of communication factor studies. *Res Social Adm Pharm* 2019; 15: 475-482. Review. DOI: 10.1016/j.sapharm.2018.06.015.

8. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care* 2012; 50: 466-478. DOI: 10.1097/MLR.0b013e318245a160.

9. Bhasale A, Mintzes B and Sarpatwari A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. *BMJ* 2020; 369: m1107. DOI: 10.1136/bmj.m1107.

10. Health Canada and the Public Health Agency of Canada. Evaluation of the Human Drugs Program 1999-2000 to 2011-2012. 2014.

11. Lexchin J. *Public profits vs private policy*. Toronto: University of Toronto Press, 2016.

12. Bhasale AL, Sarpatwari A, De Bruin ML, et al. Postmarket safety communication for protection of public health: A comparison of regulatory policy in Australia, Canada, the European Union, and the United States. *Clin Pharmacol Ther* 2020 2020/08/09. DOI: 10.1002/cpt.2010.

13. Torka M, Mintzes B, Bhasale A, et al. Secret safety warnings on medicines: A case study of information access requests. *Pharmacoepidemiol Drug Saf* 2019; 28: 551-555. 2019/03/07. DOI: 10.1002/pds.4762.

4.4 Post-market safety communication for new drugs approved in Australia 2010-2016

Alice L. Bhasale[1], Lucy T. Perry[1], Eliza J McEwin[1], Annim Mohammed[1], Ashleigh Hooimeyer,[1] Atse Huisman[2], Barbara J Mintzes.[1]

1. Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney
2. Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.

Corresponding author: Alice L. Bhasale[1], abha9370@uni.sydney.edu.au, The Hub, Level 6, Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, D17, The University of Sydney, NSW 2006, Australia.

Keywords: Drug safety, pharmacovigilance, risk communication

Acknowledgements: Emily Karanges, Lorelie Flood, Ying Ti Lee, Maisah Joarder; Joel Lexchin; Lorri Puil; Marieke De Bruin

ABSTRACT

Background: Regulators communicate information about post-market safety concerns affecting new medicines using safety advisories including direct letters to health professionals and online alerts. Internationally, regulators differ in their use of post-market safety advisories. I aimed to compare the use, content and timing of advisories by the Australian regulator and others, for new drugs in Australia.

Methods: We conducted a content analysis of advisories issued by regulators in Australia, Canada, the United Kingdom and the United States, for new chemical and biological entities approved in Australia from 2010-2016. Advisories were coded for characteristics of the safety concerns, regulatory actions, and advice to consumers and clinicians.

Results: Advisories were issued for 30% (51) of new drugs, with 73 post-market safety concerns communicated by any regulator between 2010 and 2016. Australian advisories were issued for less than a quarter of the safety concerns communicated by other regulators. Most (67/73 - 91.8%) safety concerns were serious, 39/73 (53.4%) mentioned death, and 32/73 (45.2%) led to a significant product information change such as a new contraindication or warning. Australia issued advisories for 7/39 (19.6%) of safety concerns mentioning death, and 7/33 (21.1%) of significant product information changes. Australian advice appeared to be less specific compared with other regulators, although the number of comparisons was small.

Conclusion: Australia differs markedly from other regulators in its use of post-market safety advisories. The reasons appear unrelated to prioritisation of more severe harm. Differences may be discretionary or indicate a reliance on communication methods that are not public.

INTRODUCTION

Post-market safety concerns commonly emerge for newly approved drugs, most within 5 years of approval.[8,9] Given the lack of familiarity with such medicines, clinicians and their patients need timely access to information about new safety concerns which could influence their risk-benefit decisions. This is particularly important since clinicians may perceive new medicines to have fewer safety concerns than older alternatives although this could be due to limited exposure prior to approval, rather than reflecting true differences in safety profile.

Regulators have been shown to differ in their approach to safety concerns. Inconsistencies have been seen internationally in the approved prescribing information for the same medicines - numbers of adverse effects, contraindications, warnings and post-market safety information, in drug withdrawal decisions and the timing of regulatory actions.[10-14]

Similar results have been found for post-market safety advisories – communications about serious safety concerns issued or required by regulators, broadly defined to include direct healthcare professional communication letters (DHPCs), safety alerts, and drug safety bulletins.[15-19] The latter are issued by regulators, while regulators generally ask pharmaceutical companies to distribute DHPCs to individual prescribers, and may influence their content and/or publish them on their websites.

In a study comparing four European countries, almost a third of new medicines (28.6%) approved between 2001-2010 were associated with at least one post-market DHPC or withdrawal, but only 21% of DHPCs were issued by all four regulators.[18] In a related study carried out by our group, around 9% of safety concerns identified in a ten-year period by the United States (US) Food and Drug Administration (FDA), Health Canada, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) and the Australian Therapeutic Goods Administration (TGA) were communicated in safety advisories by all four regulators.[15] The TGA issued the fewest advisories, covering 11% of the total

safety concerns communicated by any of these four regulators for drugs approved at the time in Australia.[16]

The TGA does not publish DHPCs on its website, and the TGA is not required under legislation to regulate safety advisories. This may account for some differences,[3] however the low rate has not been further explained and could indicate greater judiciousness. As has been suggested with product information, it may be that warning about too many adverse effects may be counter-productive and cause 'alert fatigue'.[10,20] Other possibilities are differences in regulators' risk assessments or chosen approaches to managing risk.[21]

Medicine safety was declared an Australian Government National Health Priority Area in 2019 [22] and the quality use of medicines has been a platform within Australia's National Medicines Policy since 2000. The latter states that Australian consumers and health professionals should have "timely access to accurate information and education about medicines and their use" and there should be an effective system for post-market safety monitoring. [1] While the *Therapeutic Goods Act 1989* describes the system for ensuring the quality, efficacy and safety of medicines available in Australia, neither the Act nor the National Medicines Policy specifically articulates the regulator's mandate for post-market safety communication.[23] However, a 2013 policy document outlines criteria for alerts and states the key principles for an Australian early warning system of safety communications: that it will be 'timely, sustainable, responsive and engaging'.[24]

Systematic reviews examining the impact of safety advisories suggest that different advisory characteristics may be associated with differing effectiveness in terms of changing clinical practice.[25,26] Characteristics may include whether specific, actionable advice is given, whether advice is repeated, and/or amplified through the media, as well as whether safety concerns are communicated through a regulatory bulletin or a DHPC.[25-29]

A comparison of DHPCs in Canada, the US and the UK found differences such as in the inclusion of quantitative information and scientific justification for the concern.[19] However,

few studies have compared the content characteristics of Australian safety advisories with those of other regulators[17] and none relate specifically to new drugs, for which the need for post-market communications is likely to be highest.

Objectives

In this study, we aimed to compare the communication of post-market safety concerns in Australia with that of other regulators. We examined safety advisories for new drugs approved in Australia from 2010 to 2016 for the:

1. Frequency and timing of post-market safety advisories
2. Characteristics of the safety concerns described
3. Nature of advice provided for safety concerns
4. Actions taken by regulators and the transparency within communications.

METHODS

We obtained safety advisories from the SAFER database which contains details of advisories issued by the FDA, Health Canada, MHRA and TGA from 1 January 2007 to 31 December 2016. Development of the database is described elsewhere.[15] Briefly, an advisory is defined as a post-market communication on a safety concern or potential harm for a prescription medicine issued by a regulator and publicly available. Product withdrawals and advisories on manufacturing quality, medication errors and deliberate misuse are excluded.

Safety advisories are classified according to advisory type (e.g. DHPC, alert, bulletin article), safety concern type (coded using the Medical Dictionary for Regulatory Activities MedDRA®) and medicines group (coded using the Anatomical Therapeutic Chemical [ATC] classification system). Advisories are assigned one or more ‘drug safety concerns’ which includes the safety concern and the drug or drug grouping or class (according to the specific safety concern).

To identify new prescription medicines approved in Australia I screened Australian Public Assessment Reports (AUSPARs), published by the TGA since 2010 for all applications for licensing of medicines, including new chemical and biological entities, major changes to indications, and new fixed dose combinations, regardless of the decision. AUSPARs record a publication date, a decision date and, if approved, the date of entry to the Australia Register of Therapeutic Goods. The following screening criteria were applied:

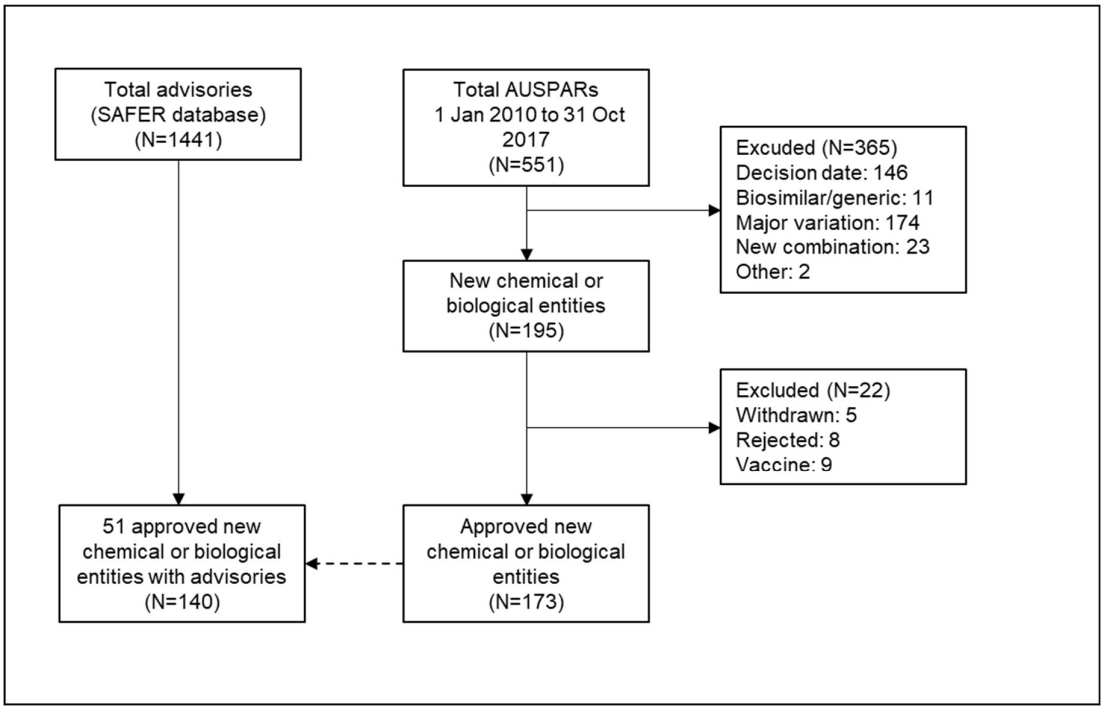
- New chemical or biological entity (as per the TGA in the AUSPAR)

- Approved for marketing in Australia

- Decision date between 1 Jan 2010 and 31 Oct 2016 (allowing at least 2 months after approval for advisories to be issued, using the SAFER database) (See Figure 1).

We excluded vaccines, generic medicines, biosimilars and new combination products for previously approved active ingredients. AUSPARs up to 31 October 2017 were screened to account for lags in publishing.

Figure 1: Inclusion of advisories and drugs



Relevant advisories from the SAFER database were matched with the AUSPAR list using drug names and ATC codes. Advisories were included if the first advisory in the UK, the US, Canada or Australia occurred after TGA approval for marketing, up till 31 December 2016. Content was coded using an instrument developed to identify the nature of the safety concern, the way harm was described, the evidence cited, advice to prescribers and consumers, and regulatory actions including product information changes. (Supplement 1) Data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Sydney.[30,31]

Severity or seriousness were assessed according to two criteria: i) whether the outcomes described in the advisory met the standard regulatory definition of serious adverse reactions[32]; ii) whether the advisory described a change to product information that involved a new contraindication, boxed or other warning, and/or loss of indication.

The coding instrument was refined based on piloting. A team initially double coded 49 advisories and calculated reliability using the intraclass correlation coefficient (ICC), with a pre-specified threshold set of ≥ 0.75.[33] As the ICC was 0.878 (95% CI 0.784 - 0.931), the remainder of the dataset was single-coded.

Data were exported to Excel and SPSS for frequencies and descriptive analyses.[34] Descriptive data from the full SAFER database of all advisories for the period 2010-2016 were also analysed for broader context.

For advisories discussing multiple safety concerns, coding was carried out for each safety concern, referred to as 'risk-specific advisory content''. Analysis was carried out at the level of the drug, the safety concern, the advisory or the risk-specific advisory content.

RESULTS

Overview of drugs, advisories and safety concerns

Of 551 AUSPARs, 365 were excluded due to timing of decisions, or not being new chemical or biological entities. Of 195 new chemical or biological entities, 173 were included after excluding vaccines and rejected or withdrawn applications. (Figure 1). As in Table 1, 51 (29.5%) of these new medicines were the subject of at least one safety advisory from any included regulator between 2010-2016. Three quarters (76.4%) of medicines had at least one advisory about the individual drug and 47% were included in a multiple drug/ class advisory. The number of safety concerns per medicine ranged from 1 to 7; 27/51 medicines (52.9%) had only one safety concern.

As shown in Table 2, there were 140 unique advisories describing 73 safety concerns for these 51 new drugs across all four countries, with coding completed for 160 risk-specific advisory content records.

Table 1: Drug and advisory characteristics

DRUG CHARACTERISTICS	N	%
Drugs meeting inclusion criteria from AUSPAR list	**173**	
Drugs with no advisory	122	70.5
Drugs with any advisory	51	29.5
Advisory focus	**51**	
Single drug only	27	52.9
Drug class or group only	12	23.5
Both single drug and class/group	12	23.5
Number of safety concerns per drug	**51**	
1	27	52.9
2-3	17	33.3
4+	7	13.7
Drugs with advisory per country[a]	**51**	
AU	20/51	39.2
CA	35/46	76.1
UK	34/47	72.3
US	27/46	58.7

a: denominators are less than 51 for Canada, the UK and US as not all 51 drugs had been approved in those countries

Table 2: Safety concerns and advisory characteristics by country

	Country									
	AU N	%	UK N	%	CA N	%	US N	%	Total N	%
ADVISORIES	**16**	11.4	**56**	**40.0**	**39**	**27.8**	**29**	**20.1**	**140**	**100.0**
Advisory type										
Alert	7	44	18	32	8	21	28	97	61	44
DHPC	-	-	37	66	22	56	-	-	59	42
Bulletin	9	56	-	0	8	21	-	-	17	12
Other[a]	-	-	1	2	1	3	1	3	3	2
SAFETY CONCERNS (N=73)[b]	**15**	**20.5**	**46**	**63.0**	**38**	**52.1**	**29[f]**	**39.7**	**73[b]**	
-with Australian (AU) advisories (n=15)	15	100.0	11	73.3	7	46.7	8	53.3	15	
-without AU advisories (n=58)	-	-	35	60.3	31	53.4	21	36.2	58	
RISK-SPECIFIC ADVISORY CONTENT[c]	**18**	**11.3**	**66**	**41.3**	**43**	**26.9**	**33**	**20.6**	**160**	**100.0**
-safety concerns with AU advisories	18	32.1	20	35.7	9	16.1	9	16.1	56	**35.0**
-safety concerns without AU advisories			46	44.2	34	32.7	24	23.1	104	**65.0**
Advisory characteristics										
Type of advice										
-Specific action for health professional	10	55.6	54	81.8	35	81.4	27	81.8	126	78.8
-Awareness only advice	5	27.8	11	16.7	8	18.6	4	12.1	28	17.5
Seriousness										
-Any significant change to product information	7	38.8	11	16.6	12	27.9	15	45.5	45	28.1
Quantitative data on adverse events	4	22.2	37	56.1	18	41.9	21	63.6	80	50.0
Consumer information in advisory[d]	7/18	38.8	0/24	0	11/19	57.9	31/33	93.9	49/94	52.1
Regulatory action	**18**		**66**		**43**		**33**		**160**	
Advisory triggered by another regulator	9	50.0		0.0	1	2.3		0.0	10	6.3
Information on regulator's decision making										
-Brief	11	61.1	36	54.5	24	55.8	5	15.1	108	67.5
-Detailed	2	11.1	16	24.2	8	18.6	25	75.8	51	31.9
Any sponsor intervention described[e]	2	11.1	41	62.1	26	60.5	11	33.3	80	50.0
Any regulatory intervention described[e]	3	16.7	10	15.2	11	25.6	9	27.3	33	20.6

a: Other advisory types included notices or results of investigations, studies, patient information and communications about risk management programs;
b: the number of safety concerns across countries do not sum to the total as each country could report the same concern **c:** An advisory could be coded more than once if it described more than one safety concern. Risk-specific advisory content refers to the coded section of the advisory related to the specific safety concern; **d**: Denominators differ as DHPCs are excluded; **e**: stating that the regulator or sponsor was sending the advisory was not included as an intervention; **f**: there were an additional 4 safety concerns with US REMS-DHPCs, 2 with AU advisories and 2 without.

Distribution of safety concerns and advisories by regulator

The UK released the most advisories (56 advisories, covering 46/73 safety concerns [63.0%]) and Australia the least (16 advisories for 15/73 safety concerns [20.5%]), with 39 Canadian advisories (38/73 safety concerns [52.1%]) and 29 US advisories (29/73 safety concerns [39.7%]). For 38 of the 73 (52.1%) safety concerns, only one regulator issued an advisory.

Regulators differed in their most frequently used types of advisories, with the FDA issuing mostly website alerts (97% of advisories), the UK and Canada DHPCs (66% and 56% respectively) and Australia bulletin articles (56%). (Table 2).

Frequency and timing of advisories

Timing

Time from approval in any included country to the first drug-specific advisory in an included country was on average 37.3 months (SD 19.8 months; median 34.4 months), ranging from 8.8 months to 8.6 years, as indicated in Table 3. The mean time from approval to the first advisory within the country were similar across countries (from 27.2 months or 2.2 years in Canada to 30.3 months or 2.5 years in the UK), but ranged considerably within countries. For most drugs, safety concerns were first communicated more than 5 years after drug approval in each country (Figure 2).

The UK and the US were most often the first country to issue an advisory for a safety concern (28/73 [38.4%] and 22/73 [30.1%]) (Table 3). For 5 of 73 safety concerns (6.8%) advisories were issued by all regulators who had approved the drug; there were a further 8 safety concerns with advisories from Canada, the UK and the US, but not Australia (Table 3). Most Australian advisories (14/15) were for safety concerns also communicated by another regulator.

The time lag between the first advisory for a safety concern and the first advisory in each other included country, after excluding first advisories issued by that country, is indicated in Table 3. The mean lag for Australian advisories was 10.1 months (SD 10.1); with shorter lags for Canada (4.9 months; SD 6.9) the US (8.8 months; SD 13.2), the UK (3.3; SD 4.8).

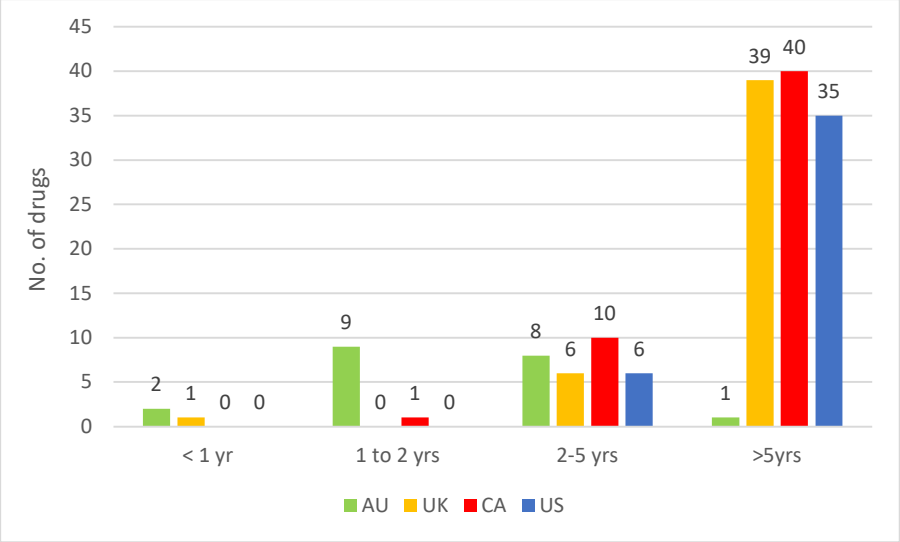
Given the small number of advisories contributing to the assessment of timing for Australia, I conducted a similar analysis of the larger SAFER dataset for all advisories issued between 1 Jan 2010 to 31 Dec 2016 for any drug or drug class. From a total of 465 safety concerns in this period there were 89 (19.1%) safety concerns with an Australian advisory, for which 49 were issued first or only by Australia. For the remaining 40 safety concerns, the mean delay from the first advisory in any included country to the first Australian advisory was 9.85 months (SD 10.13, range 0.1 to 40 months).

Table 3: Frequency of safety concerns and actions by country

SAFETY CONCERNS - TIMING AND ACTIONS										
	AU	%	**UK**	%	**CA**	%	**US**	%	**Total**	%
Country actions	**15**		**46**		**38**		**29**		**73**	**100.0**
Only country to issue (% country total)	1	6.7	16	34.8	11	28.9	10	34.5	38	52.1
Drug-specific safety concerns (% country total)	6	40.0	37	80.4	30	78.9	15	51.7	53	72.6
First country to issue for safety concern within the period (% safety concerns)[a]	5/73	6.8	28/73	38.4	18/70	25.7	22/72	30.6	73	**100.0**
All regulators with approved drug issued advisory[a]									5	6.8
UK, Canada, US all issued advisory									13	17.8
Time from approval to first advisory for safety concern (months) [b]									**Any included country**	
N	**N=20**		**N=46**		**N=51**		**N=41**		**N=94**	
Mean (SD)	28.3 (16.3)		30.3 (14.4)		27.2 (16.1)		30.3 (17.0)		37.3 (19.8)	
Median (min to max)	22.0 (9.3-70.7)		30.4 (0.2-58.8)		23.0 (3.7-65.3)		25.8 (8.8-80.9)		34.4 (8.8-103.3)	
Time from first advisory for safety concern from any included regulator to first country advisory (months) [c]										
N	**N=8**		**N=15**		**N=18**		**N=4**			
Mean (SD)	10.1 (10.1)		3.3 (4.8)		4.9 (6.9)		8.8 (13.2)		**-**	
Median (min to max)	7.1 (1.2-30.0)		2.6 (0.2-20.0)		2.1 (0.2-25.1)		3.1 (0.5 -28.4)			

a: 3 drugs were not approved in all countries at the time of the first advisory – agomelatine (not approved US and Canada), asenapine (not approved Canada), belatacept (not approved Canada). For class advisories, the advisory was counted if at least one drug in the class was approved. Denominators reflect approved drugs in each country.
b: Time calculated per drug, per safety concern (and for each drug in advisories including multiple drugs), excluding class safety concerns where the first advisory in the SAFER database was before 2010 or drug was not approved; c: Excluding safety concerns where the first advisory was issued by the regulator, counting multiple drug advisories once.

Figure 2: Time from first country approval to first advisory – by country and overall[a]



a: excluding class safety concerns where the first advisory in the SAFER database was before 2010

Characteristics of safety concerns

Drug group

Four drug classes accounted for 49/73 (67%) of the safety concerns: antineoplastic agents (other) (19 safety concerns), immunosuppressants (12), blood glucose lowering drugs (9), and direct acting antivirals (9) (Supplement 2). Only seven of these 49 safety concerns had an Australian advisory.

Seriousness of harm

In order to identify whether characteristics differed for safety concerns with Australian advisories (15/73) compared to those without (58/73), I characterised each safety concern according to whether a specific feature was communicated by at least one regulator as shown in Table 4.

Almost 80% of all safety concerns were new or emerging adverse effects (56/73); Australia issued advisories for 19.6% of these (11/56).

Most safety concerns (91.8% - 67/73) met the regulatory criteria for a serious adverse reaction (Table 4). Supplement 2 lists the specific safety concerns described in advisories. These include serious risks such as hepatoxicity, severe infections, neoplasms, hypersensitivity reactions, and cardiovascular and bone disorders.

There were Australian advisories for 7 of the 39 (17.9%) safety concerns for which death or fatal outcomes was mentioned by at least one regulator (39/73; 53.4%) (Table 4).

As a further indicator of seriousness, 33/73 safety concerns (45.2%) were associated with a significant change in the product information by any regulator (new contraindication, boxed warning, new warning, or loss of indication). Australia issued advisories for 10 of the 33 (30.3%) safety concerns with a significant product information change (Table 4); 7 of these described a significant change in the Australian product information, as shown in Table 5. Examples of the latter included agomelatine and liver injury, denosumab and osteonecrosis, and fingolimod-induced cardiac arrhythmia. Safety concerns leading to significant changes for other regulators but not in Australia included dronedarone and liver injury, DPP-4 inhibitors and arthralgia, and sitagliptin or alogliptin-related cardiac failure.

In summary, of the 58 safety concerns without Australian advisories, 55.2% mentioned death, 77.6% were about a new or emerging adverse effect, and 39.6% were associated with a significant change to product information by at least one regulator (Table 4).

Table 4: Characteristics of safety concerns with or without Australian advisories (N=73)

SAFETY CONCERNS	With Australian advisories N=15			Without Australian advisories (N=58)			TOTAL (N=73)	
	N	%	% total	N	%	% total	N	%
Characteristic according to at least one regulator								
Severity or seriousness								
Serious adverse reaction[a]	15	100%	22.4%	52	89.7%	77.6%	67	91.8%
Mentions death	7	46.7%	17.9%	32	55.2%	82.1%	39	53.4%
Novelty of safety concern								
New or emerging adverse reaction	11	73.3%	19.6%	45	77.6%	80.4%	56	76.7%
Known adverse reaction	3	20.0%	23.1%	10	17.2%	76.9%	13	17.8%
Significant product information change any included country								
New contraindication, loss of indication, new warning or boxed warning	10	66.7%	30.3%	23	39.6%	69.7%	33	45.2%

[a] Seriousness was according to an assessment by the coder against usual regulatory definitions for an adverse drug reaction such as resulting in long term outcomes or requiring ongoing treatment, hospitalisation or prolonged hospital stay, disability or permanent damage, congenital anomaly.

Table 5: Safety concerns with a significant product information change by country

	Significant product information change by regulator			
SAFETY CONCERN	**AU**	**UK**	**CA**	**US**
AUSTRALIAN ADVISORY				
agomelatine-drug-induced liver injury[a]	X	X		
BCR-ABL-tyrosine-kinase-inhibitors-hepatitis B reactivation	X			
denosumab-hypocalcaemia	X			
denosumab-osteonecrosis	X	X		
direct-acting-antivirals-hepatitis B reactivation	X			
fingolimod-cardiac arrhythmias	X			X
ibrutinib-hepatotoxicity	X			
SGLT2-inhibitors-diabetic ketoacidosis				X
SGLT2-inhibitors-genitourinary infections				X
statins-muscle disorders				X
NO AUSTRALIAN ADVISORY				
antivirals_amiodarone-cardiac arrhythmias (interaction)			X	X
apremilast-suicidal and self-injurious behaviour		X		
asenapine-hypersensitivity				X
crizotinib-cardiac failure		X		
denosumab-atypical fracture			X	
DPP-4-inhibitors-arthralgia				X
dronedarone-cardiovascular disorder		X	X	X
dronedarone-drug-induced liver injury		X		X
dronedarone-lung toxicity		X	X	
fingolimod-progressive multifocal leukoencephalopathy				X
ibrutinib-interstitial lung disease			X	
ofatumumab rituximab-hepatitis B reactivation		X		X
ofatumumab-infusion related reaction			X	
ombitasvir/paritaprevir/ritonavir/dasabuvir-hepatic and hepatobiliary disorders			X	X
pazopanib-hepatic and hepatobiliary disorders		X		
pomalidomide-hepatitis B reactivation				X
riociguat-death			X	
saxagliptin alogliptin (subset-DPP-4 inhibitors)-cardiac failure				X
SGLT2-inhibitors-osteoporotic fracture				X
telaprevir_peginterferon-alfa_ribavirin-epidermal and dermal conditions (interaction)		X	X	
tolvaptan-hepatotoxicity				X
vemurafenib-pancreatitis			X	
vismodegib-epiphyses premature fusion			X	
Total	7	10	11	13

a: Agomelatine not approved in US or Canada

Advice on safety concerns

Table 6 compares Australian and other regulators' advice and product information changes for the same safety concerns, as well as for safety concerns without Australian advisories.

Of the 156 cases where the safety concern was a potential harm and information was targeted to prescribers, most (126/156 80.8%) advice focused on specific actions, while 28/156 (17.9%) focused on raising awareness. In 24/156 cases, (15.4%) the only advice given was non-specific such as to be aware of the issue or "prescribe with caution".

Compared with other regulators addressing the same safety concerns, Australian advisories more often contained awareness advice (AU: 5/15 – 33.3% vs. Other regulators: 5/38 13.2%) and less specific advice (AU:10/15 - 66.7% vs. Other regulators: 31/38 - 81.6%) (Table 6).

Advice to test or monitor patients was the most frequent specific advice type overall, in 90/156 (57.7%) of all advisories, and 7/15 (46.7%) of AU advisories. Other common specific advice included stopping (56/156; 35.9%) or avoiding the medicine (48/156; 30.8%). Advice to follow the product information was provided in 4/15 (26.6%) of Australian advisories, 5/38 of other regulators (13.2%) for the same safety concern and 19/103 (15.5%) of other advisories. Fewer Australian advisories suggested avoiding the drug (3/15; 20.0%) than other regulators' advisories for the same safety concern (11/38; 28.9%) or advisories for safety concerns without Australian advisories (34/103; 33%).

Advice to stop in certain situations was given by other regulators in a higher proportion of cases without an Australian advisory (45/103;43.7%) than given by the TGA (3/15 [20%]). (Table 6)

Regulatory actions and transparency

Product information changes were described in 63.3% (100/158) of risk-specific advisory content overall 100/158 (excluding 2 for which product information changes were not

relevant) (Table 6). In terms of timeliness of communication, TGA advisories occurred after a product information change in 6/18 (33.3%) cases, compared with 9/37 (24.3%) for other regulators for the same issue.

No Australian advisories described a loss of indication due to the safety concern, with only one such advisory in the US regarding a loss of indication for use in cirrhosis for tolvaptan, due to hepatoxicity.

Table 2 compares individual regulators in terms of regulatory action and the transparency of information. Excluding DHPCs which are directed solely at health professionals, no UK advisories provided information for consumers, compared with 7/18 (38.8%) Australian advisories, 11/19 (57.9%) Canadian advisories and 31/33 (93.9%) of US advisories.

Australian advisories less often provided quantitative data on the frequency of events associated with safety concerns (AU 4/18[22%]; UK 37/66 [56.1%]; CA 18/43 [41.9%]; US 21/33 [63.6%]. Information about the decision making leading to the advisory was less often provided in detail in Australian advisories (2/18 [11.1%] detailed information;11/18 61.1% brief information) compared with other regulators. The US provided detailed information more often than other regulators (25/33 [75.8%] vs.11.1% to 24.2% for other regulators).

However, the TGA more often described another regulator's action as an advisory trigger (10/18 advisories), otherwise mentioned only once by Health Canada. Other actions by sponsors (pharmaceutical companies) such as undertaking additional studies, consumer communications or risk mitigation activities were described in 50% (80/160) of advisories overall, and other actions taken by regulators in 20.6% (33/160); few Australian advisories described either (2/15 and 3/15, respectively).

Table 6: Comparison of risk-specific advisory content for safety concerns with and without an Australian advisory (N=158)

	Risk-specific advisory content for safety concerns with an AU advisory				Risk-specific advisory content for safety concerns without an AU advisory		Total	
Risk-specific advisory content	**AU** **N=15**	**%**	**Other three regulators** **N=38**	**%**	**Other three regulators** **N=103**	**%**	**Total** **N=156[a]**	**%**
Advice to prescribers *Type of advice*								
Awareness raising	**5**	**33.3**	**5**	**13.2**	**18**	**17.5**	**28**	**17.9**
-General non-specific caution only	4	26.7	5	13.2	15	14.6	24	15.4
Specific action	**10**	**66.7**	**31**	**81.6**	**85**	**82.5**	**126**	**80.8**
-Testing or monitoring	7	46.7	26	68.4	57	55.3	90	57.7
- Stop in certain patients	3	20.0	8	21.1	45	43.7	56	35.9
- Avoid/do not prescribe	3	20.0	11	28.9	34	33.0	48	30.8
- Follow product information	4	26.6	5	13.2	19	15.5	28	17.9
- Discontinue and restart	3	20.0	3	7.9	20	19.4	26	16.7
- Other advice	5	33.3	13	34.2	36	35.0	48	30.8
Product information changes (n=158)	**N=18**		**N=37**		**N=103**		**N=158**	
Product information changed	9	50.0	21	56.8	71	68.9	100	63.3
Advisory issued after change	6	33.3	9	24.3	42	40.8	57	**36.1**

a: 2/158 were not targeted to health professionals so advice was not provided

DISCUSSION

The TGA issued safety advisories for less than a quarter (15/73; 20.5%) of the post-market safety concerns communicated by other regulators for new drugs approved in Australia between 2010 and 2016. Australian advisories were issued on average 10.1 months later than the first advisory by another regulator, were rarely the only advisory issued for a safety concern (1/15) and often (9/15) cited another regulator as the trigger.

I explored whether Australia more selectively communicated only the most serious safety concerns, but this did not appear to be the case. Around 90% of all safety concerns described were serious adverse reactions, and while this proportion was similar for the 15 safety concerns with Australian advisories, the same was true for safety concerns without Australian advisories, with risks including hepatoxicity, neoplasm progression and cardiovascular effects. There was no Australian advisory for 58 safety concerns, of which 55.2% mentioned death, 77.6% were about a new potential harm, and 44.8% were associated with a new contraindication, loss of indication, boxed warning, or new warning elsewhere. Hence severity of harm was not the only factor contributing to TGA advisory decisions.

Most drugs without Australian advisories were in more specialised categories of use including immunosuppressants, chemotherapy drugs, and direct acting antiviral medicines. While it is possible that the TGA reserves public communications for more commonly used medicines, Australian advisories were issued for medicines in each of these classes, just for fewer safety concerns. There were no Australian advisories for some commonly used diabetes medicines. For example, while the FDA issued both early warning and follow-up advisories for the risk of cardiac failure with alogliptin and saxagliptin,[1,2] and a single warning about severe arthralgia for the class of dipeptidyl peptidase-4 inhibitors[3] there were no Australian advisories for these issues. Comparing the current (2020) Australian saxagliptin product information with the product information at approval reveals that information on both

adverse effects have been added post-market, but without an accompanying TGA advisory.[4,5]

The small number of Australian advisories issued limits the conclusions that can be drawn about differences in content compared with other regulators. However, Australian advisories provided specific advice to prescribers less often than other regulators for the same safety concerns, (10/15 - 66.7% vs.31/38 - 81.6%), and a third of advisories were to raise awareness rather than recommend specific actions. In 4/15 (26.7%) Australian advisories, the only advice given to prescribers was a general caution to prescribe with care or be aware of the potential issue. Australia limited the advice to a general caution almost twice as often as other regulators addressing the same safety concerns 5/38 (13.2%). These results are consistent with a related study of cardiovascular harm which included 33 Australian advisories, in which 42% of Australian advisories were awareness-raising rather than specific; compared with 17-27% for the three other regulators.[6] This is of concern as surveys have found that prescribers have a strong preference for specific advice[7] which has been shown to be more likely to result in desired changes.[8]

Similarly, previous research suggests that monitoring advice may be the least often followed[8], and often lacks adequate specificity for effective implementation such as critical parameters for action,[6,7] yet this was the most common type of advice issued by all regulators.

Australian advisories performed better in providing consumer information than UK advisories, with information for consumers in almost half of advisories, compared with none in the UK. However, this probably relates to the different types of communications used by different regulators.[9] The FDA provided consumer advice in over 90% of its advisories, using a standard *Drug Safety Communication* template with sections for consumers and health professionals. Australian and UK bulletins, intended for a professional audience, do not provide consumer information, although they are publicly available.

A recent systematic review of UK advisories found that drug bulletin articles were associated with smaller changes in prescribing than DHPCs. In our research, DHPCs comprised 37/56 (66%) of MHRA advisories and 22/39 (56%) of Health Canada advisories. However, while both countries post DHPCs on their websites, the TGA does not, and the FDA does so only when they are part of a REMS. If DHPCs are more effective than bulletin articles, more direct communications should be considered rather than relying on drug bulletins alone.

Advisories were issued after an update to the product information in approximately a third of all cases. It is important that significant product information changes are communicated to prescribers. Yet deferring communication until after a change means a longer interval between detection of the concern and alerting medicine users, due to the need to negotiate and enact changes.[9,10] Whilst both FDA and TGA policies state that they will issue early warning or monitoring advisories, these seem to be far less frequent, and may be determined based on the individual risk and evidence.

Much Australian risk-specific advisory content (11/18) provided brief or no information regarding the decision-making process leading up to advisories, and few (4/18) provided information about the frequency of occurrence of harm. The latter is important for helping clinicians and consumers to assess the possible importance of the safety concern.

In conclusion, I found major differences between the approach to post-market risk communication in Australia, as compared to the three other regulators. This may be partially related to differences in statutory requirements and authority to communicate to the public, with both the EMA and the FDA subject to legislation requiring regulators to provide post-market information. However, this cannot explain all of the differences, as Health Canada's legislation on safety communications is no stronger than Australia's[11,12], yet its communication differed markedly to the TGA's. The difference may be in the regulator's public health focus, cultural factors or administrative policies. The criteria applied for TGA post-market communications remain unclear and may be discretionary.

Further examination of the strength of the evidence supporting safety concerns could explain some findings, as both seriousness and likelihood of causality are important components of risk, especially given Australia's smaller population size. Overall these findings raise important questions for investigation about how the regulator communicates new safety concerns, and whether consumers and health professionals are adequately warned.

Limitations

Advisories may have been communicated via other means that are not publicly accessible such as TGA communications to professional societies and DHPCs issued by pharmaceutical companies.[13] For at least a few drugs in our dataset, public subsidy through the Pharmaceutical Benefits Scheme (PBS) was never achieved (e.g. dronedarone, mirabegron, belatacept) which may have influenced frequency of usage, and hence advisory use. Finally, Australian advisories may have been issued, but occurred outside of the study period. US REMS letters, which are sometimes used as post-market communications, were not included in this analysis. A review of REMS identified 4 DHPCs relating to post-market events in our study.

CONCLUSION

Australia differs markedly from Canada, the UK and the US in its use of post-market safety advisories to warn professionals and the public about risks of new medicines. The difference does not appear to be due to the seriousness of the safety concerns. The responsibility for providing information about new adverse effects from a public health perspective should be clearly described in Australia's National Medicines Policy which strongly supports quality use of medicines to "improve health outcomes". Awareness of potential safety concerns for emerging medicines is an important prerequisite for quality use of medicines. Otherwise, Australians may need to rely on other regulators' safety communications for this information.

References

1. Australian Government Department of Health and Ageing. National Medicines Policy. Canberra: Commonwealth of Australia, 2000.
2. European Medicines Agency and Heads of Medicines Agencies. *Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2)*. 2013. London: EMA with HMA.
3. Torka M, Mintzes B, Bhasale A, et al. Secret safety warnings on medicines: A case study of information access requests. *Pharmacoepidemiol Drug Saf* 2019; 28: 551-555. 2019/03/07. DOI: 10.1002/pds.4762.
4. McEwen J. A history of therapeutic goods regulation in Australia. ACT: Commonwealth of Australia, 2007.
5. Australian Government Department of Health Therapeutic Goods Administration. A new era of medicines safety monitoring and communication of benefit–risk information at the TGA. *Australian Prescriber* 2010; 33.
6. Australian Government Department of Health Therapeutic Goods Administration. Advisory Committee on Medicines (ACM), https://www.tga.gov.au/committee/advisory-committee-medicines-acm (2019, accessed Dec 2019 2019).
7. Australian Government Department of Health Therapeutic Goods Administration. Medicines and vaccines postmarket vigilance. Statistics for 2016. Woden ACT: TGA, 2016.
8. Lasser KE, Allen PD, Woolhandler SJ, et al. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002; 287: 2215-2220. DOI: 10.1001/jama.287.17.2215.
9. Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA* 2017; 317: 1854-1863. DOI: 10.1001/jama.2017.5150.
10. Kesselheim AS, Franklin JM, Avorn J, et al. Speaking the same language? International variations in the safety information accompanying top-selling prescription drugs. *BMJ Quality and Safety* 2013; 22: 727-734. Article. DOI: 10.1136/bmjqs-2012-001704.

11. Onakpoya IJ, Heneghan CJ and Aronson JK. Delays in the post-marketing withdrawal of drugs to which deaths have been attributed: a systematic investigation and analysis. *BMC Medicine* 2015; 13: 26. DOI: 10.1186/s12916-014-0262-7.

12. Reggi V, Balocco-Mattavelli R, Bonati M, et al. Prescribing information in 26 countries: A comparative study. *Eur J Clin Pharmacol* 2003; 59: 263-270. DOI: 10.1007/s00228-003-0607-1.

13. Pfistermeister B, Saß A, Criegee-Rieck M, et al. Inconsistencies and misleading information in officially approved prescribing information from three major drug markets. *Clin Pharmacol Ther* 2014; 96: 616-624. DOI: 10.1038/clpt.2014.156.

14. Bhasale A, Mintzes B and Sarpatwari A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. *BMJ* 2020; 369: m1107. DOI: 10.1136/bmj.m1107.

15. Perry LT, Bhasale A, Fabbri A, et al. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiol Drug Saf* 2020; 29: 1054-1063. DOI: 10.1002/pds.5072.

16. Perry LT, Bhasale A, Fabbri A, et al. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med* 2019; 179: 982-984. 2019/04/30. DOI: 10.1001/jamainternmed.2019.0294.

17. Hooimeyer A, Bhasale A, Perry L, et al. Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. *Pharmacology Research & Perspectives* 2020; 8: e00680. DOI: https://doi.org/10.1002/prp2.680.

18. Zeitoun J-D, Lefèvre JH, Downing N, et al. Inconsistencies among European Union Pharmaceutical Regulator Safety Communications: A Cross-Country Comparison. *PLOS ONE* 2014; 9: e109100. DOI: 10.1371/journal.pone.0109100.

19. Bjerre LM, Parlow S, De Launay D, et al. Comparative, cross-sectional study of the format, content and timing of medication safety letters issued in Canada, the USA and the UK. *BMJ Open* 2018; 8. Article. DOI: 10.1136/bmjopen-2017-020150.

20. Buckley NA and Rossi S. Bringing greater transparency to "black box" warnings. *Clin Toxicol (Phila)* 2011; 49: 448-451.

21. Dal Pan GJ. Gauging the Effectiveness of Medicines Safety Communications From Global Regulatory Agencies. *JAMA Internal Medicine* 2019. DOI: 10.1001/jamainternmed.2019.0266.

22. Cooke J and Chalmers J. Medicine safety announced as a National Health Priority Area. *Australian Pharmacist, July 26 2019.* ACT: Pharmaceutical Society of Australia Ltd., 2019.

23. Bhasale AL, Sarpatwari A, De Bruin ML, et al. Postmarket safety communication for protection of public health: A comparison of regulatory policy in Australia, Canada, the European Union, and the United States. *Clin Pharmacol Ther* 2020 2020/08/09. DOI: 10.1002/cpt.2010.

24. Australian Government Department of Health and Ageing Therapeutic Goods Administration. Trans-Tasman early warning system. Processes in Australia and New Zealand. Version 1.0 ed. ACT: TGA, 2013.

25. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care* 2012; 50: 466-478. DOI: 10.1097/MLR.0b013e318245a160.

26. Weatherburn CJ, Guthrie B, Dreischulte T, et al. Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: Systematic review, time series analysis and meta-analysis. *Br J Clin Pharmacol* 2019 2019/08/30. DOI: 10.1111/bcp.14104.

27. Mazor Kathleen M, Andrade Susan E, Auger J, et al. Communicating safety information to physicians: an examination of dear doctor letters. *Pharmacoepidemiol Drug Saf* 2005; 14: 869-875. DOI: doi:10.1002/pds.1102.

28. Briesacher BA, Soumerai SB, Zhang F, et al. A critical review of methods to evaluate the impact of FDA regulatory actions. *Pharmacoepidemiol Drug Saf* 2013; 22: 986-994. Article. DOI: 10.1002/pds.3480.

29. Woloshin S, Schwartz LM, Dejene S, et al. Media Coverage of FDA Drug Safety Communications about Zolpidem: A Quantitative and Qualitative Analysis. *Journal of Health Communication* 2017; 22: 365-372. Article. DOI: 10.1080/10810730.2016.1266717.

30. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics* 2009; 42: 377-381. DOI: https://doi.org/10.1016/j.jbi.2008.08.010.

31. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics* 2019; 95: 103208. DOI: https://doi.org/10.1016/j.jbi.2019.103208.

32. Australian Government Department of Health Therapeutic Goods Administration. Pharmacovigilance responsibilities of medicine sponsors. Australian recommendations and requirements. Version 2.0 September 2017 ed. ACT: TGA, 2017.

33. Koo TK and Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of chiropractic medicine* 2016; 15: 155-163. 2016/06/23. DOI: 10.1016/j.jcm.2016.02.012.

34. IBM Corp. IBM SPSS Statistics Version 24.0. Released 2016. 24.0 ed. Armonk, NY: IBM Corp, 2020.

Funding and support: This study is funded by the Australian Government National Health and Medical Research Council (grant ID#1122332) with co-financing by the Canadian Institutes of Health Research (grant ID #153275). Ms Bhasale received funding from a University of Sydney PhD Scholarship.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval statement: This study relied entirely on publicly available data and did not fall within the scope of the Australian National Statement on Ethical Conduct in Human Research; therefore ethics approval was not required**.**

Conflicts of interest

Dr Mintzes was an expert witness for Health Canada in a legal case concerning marketing of an unapproved product in Canada**.**

4.4.1 Supplementary files for submitted paper

Supplement 1: Coding instrument (See Appendix 3)

Supplement 2: Safety concerns by ATC level 3 - with and without Australian advisories (N=73)

Drug group ATC classification - drug	Safety concern
DRUGS WITH AT LEAST ONE ADVISORY AT CLASS LEVEL	
ANTINEOPLASTIC AGENTS OTHER L01X	N=19
With AU advisories	
BCR-ABL-tyrosine-kinase-inhibitors	hepatitis B reactivation
ibrutinib	hepatotoxicity
Without AU advisories	
aflibercept	osteonecrosis of jaw
blinatumomab	pancreatitis
crizotinib	cardiac failure
ibrutinib	interstitial lung disease
idelalisib	infections
ipilimumab	posterior reversible encephalopathy syndrome
ofatumumab	hepatitis B reactivation infusion related reaction
pazopanib	hepatic and hepatobiliary disorders
trametinib	gastrointestinal disorder
vemurafenib	drug reaction with eosinophilia and systemic symptoms hepatotoxicity neoplasm progression pancreatitis radiation toxicity
vismodegib	epiphyses premature fusion teratogenicity
BLOOD GLUCOSE LOWERING DRUGS, EXCLUDING INSULINS A10B	**N=9**
With AU advisories	
canagliflozin	amputation
SGLT2 inhibitors	diabetic ketoacidosis
SGLT2 inhibitors	genitourinary infections
Without AU advisories	
DPP4 inhibitors	arthralgia
incretin mimetics	pancreatic carcinoma
Saxagliptin and alogliptin	cardiac failure
saxagliptin	hypersensitivity
sodium glucose cotransporter-2 inhibitors	acute kidney injury
sodium glucose cotransporter-2 inhibitors	osteoporotic fracture

DIRECT ACTING ANTIVIRALS J05A	**N=9**
With AU advisories	
direct-acting-antivirals	hepatitis B reactivation
Without AU advisories	
antivirals	cardiac arrhythmias (interaction with amiodarone)
boceprevir and telaprevir	hepatic and hepatobiliary disorders sepsis
boceprevir with ritonavir	lack of effect (interaction)
ombitasvir/paritaprevir/ritonavir/dasabuvir	hepatic and hepatobiliary disorders hepatobiliary neoplasms malignant
statins protease inhibitors	muscle injury
telaprevir with peginterferon alfa and ribavirin	epidermal and dermal conditions (interaction)
Lipid modifying agents C10A	N=3
With AU advisories	
statins (pitavastatin)	glucose metabolism disorders muscle disorders neuropsychiatric disorders
Antithrombotic agents B01A	N=2
With AU advisories	
novel oral anticoagulants (apixaban)	haemorrhage
Without AU advisories	
ticagrelor	haemorrhage
HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE G03A	N=1
With AU advisories	
combined-hormonal-contraceptives	embolism and thrombosis
DRUGS WITH SINGLE DRUG ADVISORIES ONLY	
IMMUNOSUPPRESSANTS L04A	N=12
With AU advisories	
fingolimod	cardiac arrhythmias
Without AU advisories	
apremilast	suicidal and self-injurious behaviour
belatacept	graft rejection
dimethyl-fumarate	progressive multifocal leukoencephalopathy
fingolimod	haematological disorders infections neoplasm malignant progressive multifocal leukoencephalopathy
pomalidomide	cardiac failure hepatitis B reactivation hepatotoxicity interstitial lung disease
ANTIARRHYTHMICS, CLASS I AND III C01B	N=3
Without AU advisories	
dronedarone	cardiovascular disorder drug-induced liver injury lung toxicity

DRUGS FOR TREATMENT OF BONE DISEASES M05B	N=3
With AU advisories	
denosumab	hypocalcaemia osteonecrosis
Without AU advisories	
denosumab	atypical fracture
CHEMOTHERAPEUTICS FOR TOPICAL USE D06B	N=2
Without AU advisories	
ingenol mebutate	herpes zoster severe eye and skin allergic reactions
ANTIHEMORRHAGICS B02B	N=2
Without AU advisories	
eltrombopag	drug-induced liver injury haematological disorders
ANTIHYPERTENSIVES OTHER C02K	N=1
Without AU advisories	
riociguat	death
DIURETICS OTHER C03X	N=1
Without AU advisories	
tolvaptan	hepatotoxicity
UROLOGICALS G04B	N=1
Without AU advisories	
mirabegron	cardiovascular disorder
ANTIGOUT PREPARATIONS M04A	N=1
Without AU advisories	
febuxostat	agranulocytosis
ANTIPSYCHOTICS N05A	N=1
Without AU advisories	
asenapine	hypersensitivity
ANTIDEPRESSANTS N06A	N=1
With AU advisories	
agomelatine	drug-induced liver injury
NERVOUS SYSTEM DRUGS, OTHER N07X	N=1
Without AU advisories	
fampridine	seizure
ALL OTHER THERAPEUTIC PRODUCTS V03A	N=1
Without AU advisories	
cobicistat	adrenal suppression

Chapter 5 Physicians' perceptions, awareness and attitudes to post-market safety communication

5.1 Introduction

This chapter contains the following publication:

> Bhasale A.L., Sarpatwari A, Lipworth W, Mollebaek M, McEwin E. J., Gautam N, Santiago O.A., Mintzes B.J. Regulatory authority and clinical acceptability: Physicians' responses to regulatory drug safety warnings. (2021)
>
> Accepted by the British Journal of Clinical Pharmacology

The manuscript and reference list are formatted as per the publisher's specifications, and hence mayo not correspond to the formatting in the rest of this thesis.

5.2 Overview

There is considerable evidence that uptake of prescribing recommendations from safety advisories is suboptimal[1,2] yet limited evidence about the factors that may be affecting prescriber behaviour. The aim of this study was to explore how prescribers identify and respond to emerging safety concerns of medicines and how they incorporate this information into their clinical practice. This is important because current regulatory policy assumes that providing prescribers with information about risks and benefits of medicines will allow them to evaluate risks, provide information to consumers and make appropriate and safe medicines decisions in discussion with patients.[3] Greater understanding of the factors affecting end-users of medicines safety advisories could improve understanding of how communications can best protect public health. Qualitative methods were chosen as the study method since these are well suited for eliciting underlying beliefs, attitudes and values that may mediate behavioural responses.

5.2.1 Background

Most studies of safety advisories have used quantitative methods. In a systematic review of the methods used to evaluate the public health impact of regulatory interventions, 55% investigated changes in drug utilisation, 27% investigated health outcomes and 18% measured knowledge, behaviour or reported changes in clinical practice. The latter category included some surveys but no qualitative studies.[4] A further two studies using qualitative methods were identified during the planning of the study described in this chapter, including a multi-modal study of FDA safety advisories for zolpidem and zopiclone, commissioned by the FDA.[5,6] Subsequently, an additional systematic review examining communication factors contributing to effectiveness of DHPCs [7] and a study of Danish GPs responses' to DHPCs for risks of direct acting oral anticoagulants were published after the completion of the research described below in section **Error! Reference source not found.** [8]

The underlying assumption of safety advisories, in simplistic terms, is that information will increase awareness of the risks and benefits of a medicine, and by adding to existing knowledge, ultimately reduce risks to patients through more appropriate prescribing. There are several reasons why safety advisories might not lead to changes in practice and these can be broadly conceptualised as barriers relating to knowledge (awareness), attitudes and behaviours of prescribers.

Research has demonstrated varying levels of prescriber awareness and knowledge of important adverse effects including black box warnings (the most serious grade of safety concern in US product information)[9] and harmful effects of NSAIDs in late pregnancy [10]. Kesselheim et al evaluated physician (and patient) awareness and understanding of FDA advisories for two sleep medicines (zolpidem and zopiclone) and their preferences for receiving emerging safety information. Physicians cited medical literature, the FDA and point of care references for safety information as their usual sources of safety information, but most had heard about safety problems of these medicines through lay media. [6] This may

suggest that a degree of social desirability in responses; an earlier study examining where physicians got their information about safety issues, found that clinicians rely on convenient sources for drug information, primarily pharmaceutical company representatives[11]

Other attributes of the communication that may influence behaviour include: [7,12-17]

- the source of the communication (e.g., from regulators, professional colleges, or pharmaceutical industry)
- the method of receiving the information (email, in medical record alerts)
- the ability to filter out non-relevant information
- the clarity of the information and the advice provided.

Prescribers may not comply with safety recommendations for several reasons. They may disagree with recommendations, preferring to rely on their own experience, those of key opinion leaders or other sources.[12,18,19] However, neither do prescribers consistently follow precautions where the safety concern is not in dispute, - such as pre-treatment pregnancy testing, dosing or testing[20]- or informing patients about well-known side effects.[12,21-24]

Richardson et al investigated primary care physicians' responses to black box warnings about SSRI antidepressants and suicidality in young people which suggested limiting use and increasing follow-up monitoring. Although aware of the warnings, some prescribers were sceptical about their significance. Prescribers were also concerned about their capacity to increase monitoring, as well as patients' tolerance for more frequent health care visits, costs and insurance issues, and a lack of non-drug alternatives. This study also found that prescribers were influenced by patient preferences for drug treatment rather than non-drug interventions. [5]

If safety information is to have its intended effect, it is important to understand the factors that make information actionable. Social, cognitive and behavioural factors may influence the effectiveness of regulatory communications and have implications for their effective design and implementation. Qualitative methods are ideally suited to elucidate such factors.

5.3 Regulatory authority and clinical acceptability: Physicians' responses to regulatory drug safety warnings

Authors

Alice L. Bhasale,[1] Ameet Sarpatwari,[2] Wendy Lipworth, [3] Mathias Møllebæk,[4]

Eliza J. McEwin[1], Nileesa Gautam,[2,] Ortiz A. Santiago,[2] Barbara J. Mintzes,[1]

[1.] Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney

[2.] Program On Regulation, Therapeutics, And Law (PORTAL), Brigham and Women's Hospital and Harvard Medical School.

[3.] Sydney Health Ethics, Faculty of Medicine and Health, The University of Sydney

[4.] Centre for Regulatory Science, Department of Pharmacy, University of Copenhagen, Denmark

Corresponding author: Alice L. Bhasale[1], abha9370@uni.sydney.edu.au, The Hub, Level 6, Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, D17, The University of Sydney, NSW 2006, Australia.

Keywords: Drug safety, pharmacovigilance, qualitative methods, prescriber attitudes, risk communication

What is already known about this subject

- Safety advisories are intended to mitigate emerging post-market safety risks, but evidence of effectiveness is mixed
- Regulators in the United States (US) and Australia differ in their use of safety advisories which may affect prescribers' perceptions

What this study adds

- Regulators are trusted but their information is less accessible and they may lack clinical authority
- Reasons that prescribers do not pass on safety warnings to patients include uncertainty about messaging, time constraints, and concerns about compliance
- Perceptions of the national regulator's role in post-market safety communication may be higher in the US than in Australia

Aim

Medicines regulators issue post-market safety warnings to advise of newly uncovered risks, but with mixed impacts. We aimed to identify factors influencing the use of regulatory warnings by primary care and specialist physicians in the US and Australia.

Methods

Semi-structured qualitative interviews with 40 primary care physicians, endocrinologists, and other generalist specialists in Boston USA and Australia. Coding and analysis were carried out inductively and iteratively to identify and examine key factors. Analysis centred around four areas; physicians' awareness of drug safety information, preferred information sources, opinion-forming, and sharing of information with patients.

Results

Uncertainty, trust, and clinical authority emerged as factors influencing use of advisories. Although regulators were trusted as authoritative institutions, they appeared to lack clinical authority, and physicians validated regulatory information against other trusted sources including evidence, expert opinion, and experience. Specialists became aware of drug safety issues through specialised literature, using evidence and clinical consensus to form opinions. Primary care physicians, fielding high volumes of information, relied on convenient, accessible information sources including the media and the 'clinical grapevine' for awareness, and on clinical colleagues, specialists, and experience for interpretation. Communicating risk to patients was complicated by uncertainty; physicians tailored information to patients' health literacy and information needs. US physicians were more aware of their national regulator's post-market safety role than Australian physicians of theirs.

Conclusion

Drug safety warnings may not be optimally received or used. Regulators should consider strategies that increase trust, clinical relevance, and accessibility, and address physicians' needs in communicating risk to patients.

Introduction

"Who do you trust? What do you trust? … it starts to make you really think about how knowledge is produced, and the interface between knowledge production and clinical practice...- on what knowledge do we base our decisions?" John, Primary Care Physician, AU

Physicians prescribe medicines with an expectation of net therapeutic benefit based on their knowledge of efficacy and safety. One source of such knowledge is information authorized by regulators such as the United States Food and Drug Administration (FDA) and the Australian Government Therapeutic Goods Administration (TGA). After a drug is marketed, regulators may warn physicians and consumers about new safety concerns using safety advisories in the form of website notices, letters to health professionals, and media releases. Warnings are also incorporated into official prescribing information, including FDA 'boxed warnings' which highlight serious risks.

Rates of medication-related harm remain a significant safety issue.[1,2] However, quantitative studies show that the impact of safety warnings on prescribing rates and patient monitoring is inconsistent, suggesting that advisories may not have their intended effects.[3,4] Although regulators expect that risk information will be passed on to patients by physicians, many patients do not report receiving them.[5,6]

Previous studies focusing on physician awareness of specific safety messages, suggest that low awareness may partly explain the limited impact of advisories.[7] However, effective risk communication is more complex than providing information to correct a 'knowledge deficit'.[8] Uptake of warnings can also be influenced by communication factors such as the clarity and 'useability' of information for clinical practice, and the strength of cited evidence.[9]

Additionally, individual beliefs, information needs, and the identity of the sender may affect how safety information is perceived.[10] Interviews with physicians about FDA warnings for sedative medicines found that in addition to awareness of advisories, the credibility of the source was an important factor in the use of information.[6] Physicians report that they prefer to receive safety information from clinical societies and regulators rather than the pharmaceutical industry.[6,9,11,12] Yet in some instances, the opposite has been found, with physicians actively disagreeing with FDA warnings.[13,14] In the case of warnings about antidepressants and suicidality in young people, prescribers cited a lack of alternatives and consumer pressure when continuing to prescribe drug treatment.[15]

International comparisons have found that regulator-approved safety information differs substantially between countries.[16-19] In Australia, the TGA has been found to issue advisories for only a small proportion of safety concerns communicated by the FDA.[16,20,21] This raises questions about physicians' awareness of potential harms in different locations and the influence of regulatory actions on their understanding.

Prescribers in Australia and Boston USA were interviewed about their use of information on serious and emerging drug safety issues to explore factors influencing their uptake of safety information.

Ethics approval

This project was reviewed and approved by the Human Research Ethics Committee at The University of Sydney (project number 2018/607) and exempted from review in the US by the Partners Human Research Institutional Review Board.

Methods

Participants and Sampling

Interviews were conducted in Boston, USA, and various locations in Australia with primary care physicians and specialists (mostly endocrinologists).[ii] We sampled purposively with regard to sex, clinical experience, and specialty to capture diversity in attitudes towards safety information, aiming to recruit up to 25 participants per site, depending on when saturation was reached.

Participants were recruited by approaching physicians in researchers' existing networks, authors of diabetes guidelines and similar publications, and by disseminating requests through professional groups. Snowball recruitment was also used, whereby respondents were asked to suggest suitable participants. Eligible participants received a participant information statement, provided written consent, and were offered an honorarium in the form of a gift certificate for $AUD100/$USD100. Interviewees were given the option to receive the final paper, but not to comment on interview transcripts.

Data Collection

Interviews were chosen as an appropriate method for examining attitudes and social perceptions. Semi-structured interviews were conducted between December 2018 and July 2019 using an interview guide designed to evoke participants' attitudes and experiences in using and responding to information about safety concerns of medicines (see **Appendix 1**). The interview guide was tested in two pilot interviews and refined accordingly. Questions could be adapted by the interviewers according to context. For example, we used a common

[ii] We chose to recruit endocrinologists to allow a focus on diabetes drug warnings as diabetes is commonly managed in both primary care and endocrinology.

drug safety case involving sodium glucose co-transporter-2 (SGLT2) inhibitors to elicit perspectives. This class of drugs is indicated for the treatment of diabetes, can be prescribed by primary care and specialist doctors, and was the subject of differing regulatory warnings by the FDA and TGA between 2012 and 2016.[22] However questions were adapted when participants had less experience with these medicines in order to elicit general behaviours. Australian interviews were conducted by one researcher (AB) in person, by telephone, or via a videoconferencing platform. Boston interviews were conducted by one of three researchers (MM, NG, ASO) in person. Interviews ranged from 20-60 minutes, were recorded, and professionally transcribed verbatim. After 40 interviews, saturation was considered reached and recruitment ceased.

Data analysis and methodological orientation

A thematic analysis was conducted.[23,24] This study was part of a broader multi-centre study using multiple methods to examine regulatory safety warnings and their impact. The research team thus had an interest in the use of regulatory advice, regulatory policy, and in research and knowledge translation in primary care practice.

As data collection was conducted simultaneously in the two sites, and the team met regularly via videoconference to reflect on the interview process, questions, and to discuss the transcripts and emerging themes. These discussions informed the subsequent analysis.

Data analysis commenced after completing data collection and included the following phases; familiarisation; initial coding; recoding; searching for themes; reviewing and finalising themes. AB read all the transcripts and coded five cases line by line as the basis for an initial coding framework with high level categories developed in discussion with team members and duplicate coding of one case. The code categories were revised several times. Regular meetings were held with members of the team to discuss the summarised coded findings; these discussions informed the final thematic categories. All relevant coded data were then re-examined by AB to assess the congruence of the themes to the data;

recoding when necessary.[25] The findings were organised into a conceptual typology that described the data across themes and was supported by exemplary quotes. Any disagreements were resolved through discussion. Transcripts were coded using NVivo v.11.[26,27]

All interviews were deidentified and a pseudonym assigned for the purpose of presentation, with participant details stored separately to interview transcripts.

Results

Participants

Forty interviews were conducted; 21 interviews in Australia and 19 interviews in Boston. Of the 40 participants, 27 were primary care physicians and 13 were specialists, including 10 endocrinologists and 3 generalist physicians in clinical practice (**Table 1**). Twenty-one participants were female and 19 were males. The participants varied widely in their clinical experience, from the first year of specialist training to near retirement. In Australia, participants came from urban and rural settings in five states. Specialists worked in public hospitals and private clinics, while primary care physicians practised in private solo or group practices. Participants differed in extent of contact and involvement with the pharmaceutical industry. In Boston, all participants worked within a single major integrated health care system spanning several city hospitals and community practices that did not allow pharmaceutical sales representative visits.

Table 1: Participant characteristics

	Australia (N=21)	Boston* (N=19)	Total
Primary care physicians	14	13	27
- Junior/in training	-- *5*	- *2*	7
Specialists	7	6	13
- Endocrinologist	- *4*	- 6	10
- Clinical pharmacologist	- *2*		2
- Geriatrician	- *1*		1
Gender			
- Female	6	15	21
- Male	15	4	19
Practice setting			
- Community health service†	2	1	3
- Primary care practice	13	11	24
- Hospital	7	7	14
Academic or policy role outside clinical practice	8	16	24

* All Boston participants worked in the same integrated health care system

†Including one Aboriginal health service; one physician worked in more than one setting

Thematic analysis

Data were initially organised into four categories of physician interactions with safety information:

1. Awareness of drug safety issues in clinical practice
2. Preferred information sources, accessibility, and useability
3. Forming opinions
4. Sharing information about risks with patients.

Three more abstract themes—uncertainty, trust, and clinical authority—were woven through all four categories.

1. Awareness of drug safety issues in clinical practice

Drug safety knowledge was acquired both purposefully and opportunistically. To keep up with new safety information, specialists kept abreast of the literature in their field, attending journal clubs and/or scientific meetings. This approach was less common with primary care participants due to time pressure and the breadth of clinical practice, with the pace of new medicines approvals exacerbating the problem of information overload.

> *'Specialists need to know 20 drugs, not 300'. (Jenson, Primary Care Physician, AU)*
>
> *'there's so many new drugs that are coming out… So forget about the side effects. It's just the volume'. (Barney, primary care physician, US)*

Emerging safety information

The term 'post-market safety warnings' was unrecognisable to physicians and most were unaware of any systematic way of receiving this information. Both specialists and primary care physicians believed they would hear about new safety issues through third party 'filters', such as emails compiling key studies and news, mainstream and medical media, and the 'clinical grapevine' - a conglomerate of information channels, professional connections, and workplace communications.

> *I think it's actually through lots of different channels that make up one sort of go-to. But I think I am in touch with a number of different resources. If there is something prominent, I will hear about it. (Bill – Clinical Pharmacologist, AU)*

There was an expectation that important messages would be repeated or duplicated, but some participants were concerned that they might miss one-off communications, such as letters describing changes in prescribing information.

2. Preferred information sources, accessibility, and useability

Drug safety information sources were described in terms of their usefulness, accessibility, and trustworthiness. 'Useful' information was germane to the task at hand (such as

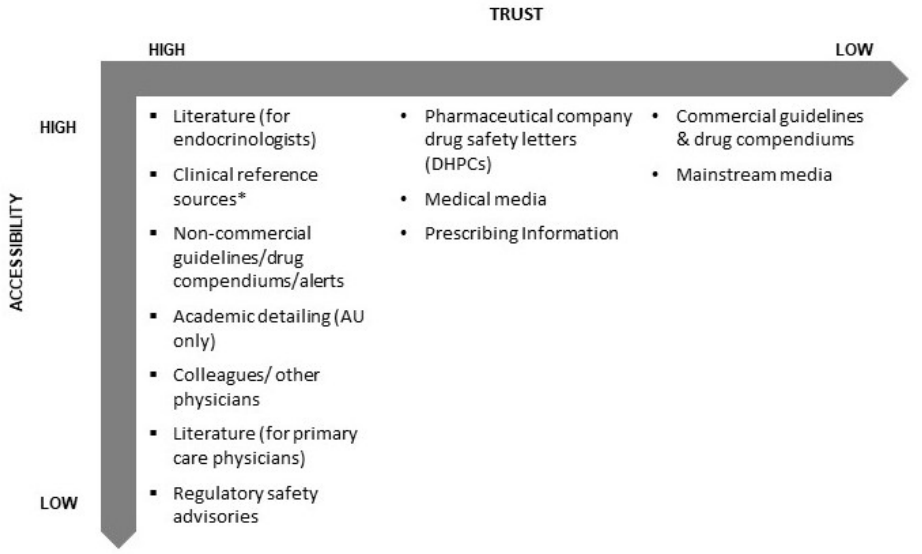
interaction-checking), concise, and clinically relevant. Highly trusted sources tended to be those that were independent, or from a clinical source, including individual physicians. These dimensions were not always aligned, as indicated in **Figure 1 (and Appendix 2)**. Drug information within clinical software was readily accessible and thus used for its convenience rather than its usefulness. Regulatory safety advisories were trusted but less accessible, while official prescribing information was widely considered to list too many adverse effects to be useful (See **Appendix 2**). Letters from pharmaceutical companies (also known as 'direct healthcare professional communications' - DHPCs) were more accessible, 'turning up' in pigeonholes for example, but were used with some reservation because of their commercial origin. Primary care physicians cited the general and medical media as a highly accessible source for important new safety issues.

There was some difference between Australian and Boston interviewees in terms of their awareness of the regulator as a source of post-market safety warnings. Australians were more aware of the TGA's drug approval activities than its post-market safety warnings, and examples provided of TGA warnings tended to be very old, such as the withdrawal of rofecoxib. US physicians cited a number of more contemporary examples including fluoroquinolones and aortic aneurysms, and the recent issues with a product recall widely publicised by the FDA.

Although awareness of FDA black-box warnings was high, even in Australia, physicians in both countries were unsure how regulators would communicate post-market issues to them.

> *I mean the idea of getting information to GPs sounds so straightforward - we'll just write them a letter or we'll put it on our website … They obviously want to do it cost-effectively and quickly but I think they need to review whether their messages are getting to the doctors at all. (Sean, Primary Care Physician, AU)*

Figure 1: Sources of drug safety information – trust and accessibility



Note: accessibility varied with clinical software used and the embedded resources.
*Most frequently mentioned clinical reference sources: in Boston, UpToDate; in Australia, Therapeutic Guidelines, the Australian Medicines Handbook and MIMS.
See Supplementary file (Appendix 2) for further information

Trust in regulators

For both Australian and Boston interviewees, there were those expressing trust in the regulator and others with lower confidence. Participants' trust in regulators was primarily due to their institutional authority as official overseers of licensing of medicines.

> *if someone [has] the oversight for safety in your country and you're licensed to practice medicine under that government, then you should probably take messages from that government seriously (Doris, Endocrinologist, US)*

Factors undermining confidence in regulators' public safety roles included perceived poor drug approval decisions, including their increasing speed and diminishing evidence standards. In addition, physicians sometimes expressed concerns about flaws in post-market safety oversight and resulting uncertainty.

> *I think of the FDA as sort of necessary but not sufficient for safety stuff. …Like if I thought it was perfect, there are a lot of medicines that I don't really prescribe that I would prescribe. (Fred, Primary Care Physician, US)*

Physicians with previous experience of post-market safety problems (for example with rosiglitazone and rofecoxib) tended to distrust new drugs generally, and in some cases this led them to distrust the regulatory process. Such prescribers tended to avoid new drugs altogether, believing that older drugs were more trustworthy than new drugs, and therefore that post-market safety issues were less likely to arise.

> *I'm not always the fastest adopter because I am always thinking about all the history we've had with all these safety warnings of your Vioxx [rofecoxib] and your Benecol [sic] and all this sort of historic record of drugs that have looked good and then had problems. (George, Primary Care Physician, US)*

Less trusted sources - commercial and pharmaceutical company information

There was low trust overall of pharmaceutical company material and even the presence of drug advertising in drug compendiums and other drug safety materials tended to reduce trust. Nonetheless these sources were often readily accessible (**Figure 1, Supplement 2**).

Attitudes to drug safety letters from companies varied. A number of participants said they always looked briefly at letters labelled as a ‘drug safety warning’. One doctor filed such letters for future reference. Others discarded or habitually deleted industry communications, as a routine approach to all unsolicited mail.

> *I don't open mail from drug companies or the FDA…(Albert, Primary Care Physician, US)*

Even participants who were skeptical of industry sources were less so of warning letters, believing that companies would only send such letters if required to do so by

regulators. As with prescribing information however, the information was not always considered clinically useful, and thought to be largely defensive.

3. Process of forming opinions and navigating uncertainty

Physicians generally took steps to validate safety information in order to assess its meaning in clinical practice, regardless of the source, and in response to the uncertainty raised by such information. Three main reference points were relied on in this validation process: evidence of harm (including biological plausibility); other physicians' opinions about the evidence or relevance of the safety issue, and individual or others' clinical experience, as shown in **Table 2.**

Most primary care physicians wanted to know the size of the risk but in general deferred to specialists for more detailed interpretations of evidence. Endocrinologists described developing their own interpretations and forming opinions as a profession. Informal and formal advice from colleagues, supervisors (such as preceptors) and specialist physicians was highly valued when deciding the significance of a risk, particularly for serious potential harms such as cancer. Personal experience of a patient with a severe adverse effect was highly salient.

Decision-making about risk information was tempered by the desirability of the benefit and differences in how individuals weighed benefits against potential harms (risk aversion).

> *Some people say it's fantastic, people lose weight, their diabetes improves, and that's all true. Other people say, yeah, but if you've got a several percent rate of ketoacidosis, which is potentially life-threatening, that outweighs it. So it's all a philosophical view of what you take and how you deal with it. (Reginald Endocrinologist, AU)*

The interplay between these factors varied between risks. Comparing responses to SGLT2 inhibitor warnings, physicians did not doubt the risk of diabetic ketoacidosis, which was

initially detected in case reports, partly as they had directly observed cases. Lower limb amputation for canagliflozin (a boxed warning at the time) was the subject of greater uncertainty. Doubters described the unclear physiological mechanism, the small absolute risk, and a lack of replication with other drugs in the class. Others, generally primary care physicians, were disturbed enough by this risk to avoid or question use of the drug. For both risks, the potential cardiovascular benefit was a key moderating factor in decisions, particularly for endocrinologists.

Table 2: Validating and assimilating safety information

Evidence	Reading original research paper before deciding Looking for quantitative information about risk (effect size, numbers effected) Seeking biological plausibility or explanation of mechanism of action as an aid to remembering (e.g. amputation risk of canagliflozin had no apparent plausible mechanism of action, while genitourinary infections can be explained by increased concentration of glucose increasing the risk of infection)
Clinical consensus	Informal conversations with colleagues Deliberative formal consensus at clinical meetings/conferences Opinions of respected clinicians
Clinical experience	Personal experience of an adverse event causing heightened concern about prescribing Lack of personal experience or that of others reducing concern about prescribing Reliance on specialist experience for significance of the safety concern Reliance on specialist experience for how to advise patients (e.g. of cancer risk) Previous experience of safety issues with new drugs causing generalised caution in prescribing

4. Sharing information about risks with patients

Interviewees were consistently alert to the expectation that they should describe risks to patients. Most said they described common adverse effects. Beyond this, we identified several barriers to communicating serious risks.

In practical terms, time pressures worked against complex discussions about risks and in some cases, drugs were not prescribed because of the additional monitoring or mitigation strategies required.

> *In some medications you have to check QT intervals. That's why I never prescribe Celexa [citalopram] anymore because it interacts with Metrazol [metronidazole]. I'm like "Forget it. I can't be checking EKGs on my patients in 15-minute time slots. (Louise, Primary Care Physician, US)*

Other barriers related to the patient's level of interest and literacy, physicians' difficulties conveying risk, and conflict between doctors' and patients' perceptions of harm (Table 3).

Many physicians were conscious of their position of trust with the patient and the implicit or explicit authority provided to them, while others had a more paternalistic approach. Those who aimed to share decisions with patients sometimes struggled to do so with less health-literate patients:

> *I think arguably the hardest part of my job is conveying risk… And it's really hard to describe risk-benefit, again, to somebody who potentially has a first-grade education in the Dominican Republic, so I try to assess whether I can be paternalistic about it and just say "I think you need this,"…whether that's enough buy-in or whether they trust me enough (Wilma, Primary Care Physician, US).*

Fear of reducing compliance could inhibit risk communication, yet explaining the potential risks was used by some as a deliberate strategy to encourage adherence. Some worried about the extent of their responsibility to share information with patients, particularly for rare

events - or potentially difficult conversations. Dilemmas included how to credibly describe serious potential harms like cancer or amputation yet justify patient exposure, and how to quantify an individual's actual risk or persuade patients that it was low. (**Table 3**)

Some prescribers avoided discussing risks for these reasons, others routinely listed risks, and a few described a very open and shared decision-making approach in which risks, benefits, and patient preferences were discussed and factored into decisions.

Table 3: Barriers and enablers to discussing risk information with patients

BARRIERS	INDICATIVE QUOTE
Patient factors	
Patient interest or health literacy	They never really ask [about side effects] …I say “It's a pill.” They go “Okay.” (Shirley, Endocrinologist US)
Fear of poor adherence	I like to be as transparent as I can, but sometimes I’m a little bit reluctant to provide too much information because I feel that it can affect compliance. (Cordelia, Primary Care Physician, AU)
Risk communication issues	
Uncertainty about responsibility	I have an internal battle over like “Do I tell every patient who's on lisinopril about this?” [lung-cancer risk] You don't know what the best practice is. (Thelma, Primary Care Physician, US)
Time involved	Like I'm gonna take, I don't know, over 15 minutes probably to like explain that risk - which I'm not. (Wilma, Primary Care Physician, US)
Difficulty in credibly explaining risk	Oh, yeah, this is the other one, “risk of lower-limb amputation.” People are like “BAAAA!” and I don't know how to explain that… And if I don't have a very convincing story for why that happens, I wouldn't take it… I mean this is the biggest, the biggest obstacle to prescribing some of these medicines. (Louise, Primary Care Physician, US)
Conflicting perceptions of risk	I prescribe a lot of bisphosphonates. There's a lot of information out there about side effects, including atypical femoral fractures and osteonecrosis of the jaw, which are exceedingly rare, but very publicized. I spend a lot of my time trying to convince people that the risks are dramatically outweighed by the benefits, but sometimes they don't listen. (Virginia, Endocrinologist, US)
ENABLERS	**INDICATIVE QUOTE**
Disclosure to increase trust and adherence	Metformin will give lots of people an upset stomach and many will stop taking it. So I'll say “This is likely to happen. Here's what you can do. Give me a call. (George, Primary Care Physician, US)
Medicolegal responsibility	I mean if you're the one prescribing a patient the medication, then you're responsible if they have an adverse effect. They should be aware of it. Yeah, I mean if you haven't done your due diligence, then you're doing your patient a disservice. (Doris, Endocrinologist US)
Orientation towards shared decision making	Again, that's an honest conversation with the patients. But often, I don't know, I've found it very helpful just to share whatever information that I have, sort of lay it on the table and then we make a decision together based on whatever is in the best interest of the patient…..It becomes shared decision-making. (Marcia, Endocrinologist US)

Note: All names are pseudonyms

Discussion

Due to the volume of unsolicited information received, primary care physicians seemed to rely on repetition of messages and medical and mainstream media to find out about new

safety information. However, as regulatory warnings may receive little media coverage,[28,29] more concerted dissemination strategies may be needed using multiple channels, trusted clinical sources, and professional networks. Commonly used and trusted information sources could include this information to reduce reliance on one-off disseminations such as letters and emails.

Physicians in this study appeared to trust regulators and believed they should act on emerging safety issues. However, regulatory warnings may be ignored due to time pressures or inaccessibility. While trusted for their institutional authority, regulators may lack clinical authority, causing physicians to determine the significance of safety information through a process of validation against clinical experience, opinion, and evidence.

Greater alignment between regulators' institutional authority and their clinical authority may help improve the uptake of safety warnings. However, this disconnect may arise because regulators generally cannot provide advice about relative safety, place in therapy or make recommendations about appropriate use, which is the kind of information physicians need. Neither are pharmaceutical companies an appropriate source, with our results supporting previous findings that such information is either less trusted or less useable.[9]

An important consequence of the uncertainty physicians have about safety messages may be that they do not inform patients about risks when they are unsure of their clinical relevance. A lack of communication may also arise from concerns about the impact of discussions on patient adherence or the length of the consultation. These findings have important implications for regulators when determining how to communicate post-market safety issues. Such warnings may fulfill a regulatory function but not meet the needs of physicians and their patients. In addition to issues of time and impact on physicians' workloads, there are clearly communication challenges. Messages asking physicians to advise patients about risk could be better targeted to real-world clinical concerns about adherence and complexity in risk communication.

When assessing risk, prescribers may rely on personal experience as much as other evidence, despite the low likelihood of seeing rare adverse events. While prescriber experiences of serious or fatal events were particularly salient, they could lead to exaggerated perceptions of the probability of harm. Similarly, prescribers may discount rare serious adverse events that they have not encountered. The extent to which the presence or absence of such experiences skews prescribing decisions could not be determined and would require further study.

Finally, it is unlikely that regulators alone can fill the needs of physicians and patients identified here, pointing to a need to consider these gaps both in national medicines policy and clinical training. Better use of trusted clinical intermediaries, or funding of independent advisors may also help. For example, in Australia a national, independent, government-funded organization, NPS MedicineWise, provides independent quality use of medicines information using an academic detailing model.

Limitations

Our study was subject to limitations, primarily related to sampling and recruitment, and should be regarded as hypothesis-generating. The findings may not be generalisable to other settings, as might be expected from qualitative research. Although there were similarities in themes between both settings there were contextual differences relating to location. For example, the Boston health care system did not allow pharmaceutical sales representative visits; and insurance limitations were cited as influencing prescribing decisions for SGLT2 inhibitors, unlike in Australia, where access was publicly subsidised. Boston primary care physicians were well connected to specialists; in Australia, this varied geographically. Boston physicians used the same clinical software, which determined their access to some information sources. Additionally, a large proportion of Boston physicians were involved in policy or academia. While we aimed to capture diversity of attitudes in the two settings, greater variation in participants would strengthen the results. Self-reported

actions—the basis of our study—may also be less reliable than direct observation. Future studies using representative sampling methods are needed.[iii]

Conclusion

To ensure the effective dissemination and uptake of safety warnings, greater consideration is required about how physicians find out about safety issues, evaluate them, and decide how and when to share them with their patients. Regulators play a key role but their actions alone may not be sufficient to ensure adequate communication of risk. Future studies could assess how to make regulatory messages more clinically authoritative and assess whether the inclusion of specific patient counselling advice influences the uptake of regulatory advice by clinicians.

References

1. Pharmaceutical Society of Australia. *Medicine Safety: Take Care.* Canberra2019.
2. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *Jama.* 2016;316(20):2115-2125.
3. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care.* 2012;50(6):466-478.
4. Piening S, Haaijer-Ruskamp FM, de Vries JT, et al. Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf.* 2012;35(5):373-385.

[iii] While the recruitment of participants from within the researchers' own networks may have resulted in a particular set of views being identified, similar data emerged in interviewees unknown to the researchers.

5. Kesselheim AS, Sinha MS, Rausch P, et al. Patients' Knowledge of Key Messaging in Drug Safety Communications for Zolpidem and Eszopiclone: A National Survey. *Journal of Law, Medicine and Ethics.* 2019;47(3):430-441.

6. Kesselheim AS, McGraw SA, Dejene SZ, et al. Patient and Physician Perceptions of Drug Safety Information for Sleep Aids: A Qualitative Study. *Drug Safety.* 2017;40(6):531-542.

7. Kesselheim AS, Sinha MS, Campbell EG, et al. Multimodal Analysis of FDA Drug Safety Communications: Lessons from Zolpidem. *Drug Safety.* 2019;42(11):1287-1295.

8. Simis MJ, Madden H, Cacciatore MA, Yeo SK. The lure of rationality: Why does the deficit model persist in science communication? *Public Understanding of Science.* 2016;25(4):400-414.

9. Mollebaek M, Kaae S, De Bruin ML, Callreus T, Jossan S, Hallgreen CE. The effectiveness of direct to healthcare professional communication - A systematic review of communication factor studies. *Research in Social & Administrative Pharmacy.* 2019;15(5):475-482.

10. Habib AS, Gan TJ. The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia. *Journal of Clinical Anesthesia.* 2008;20(1):35-39.

11. Singh T, Prakash A, Rais T, Kumari N. Decreased use of antidepressants in youth after US Food and Drug Administration black box warning. *Psychiatry.* 2009;6(10):30-34.

12. Richardson LP, Lewis CW, Casey-Goldstein M, McCauley E, Katon W. Pediatric Primary Care Providers and Adolescent Depression: A Qualitative Study of Barriers to Treatment and the Effect of the Black Box Warning. *Journal of Adolescent Health.* 2007;40(5):433-439.

13. Bahri P. Public pharmacovigilance communication: A process calling for evidence-based, objective-driven strategies. *Drug Safety.* 2010;33(12):1065-1079.

14. De Vries ST, Van Der Sar MJM, Cupelli A, et al. Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences. *Drug Safety.* 2017;40(8):729-742.

15. Piening S, Haaijer-Ruskamp FM, de Graeff PA, Straus SM, Mol PG. Healthcare professionals' self-reported experiences and preferences related to direct healthcare

professional communications: a survey conducted in the Netherlands. *Drug Saf.* 2012;35(11):1061-1072.

16. Perry LT, Bhasale A, Fabbri A, et al. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med.* 2019;179(7):982-984.

17. Kesselheim AS, Franklin JM, Avorn J, Duke JD. Speaking the same language? International variations in the safety information accompanying top-selling prescription drugs. *BMJ Quality and Safety.* 2013;22(9):727-734.

18. Shimazawa R, Ikeda M. Safety information in drug labeling: A comparison of the USA, The UK, And Japan. *Pharmacoepidemiology and Drug Safety.* 2013;22(3):306-318.

19. Bjerre LM, Parlow S, De Launay D, et al. Comparative, cross-sectional study of the format, content and timing of medication safety letters issued in Canada, the USA and the UK. *BMJ Open.* 2018;8(10).

20. Perry LT, Bhasale A, Fabbri A, et al. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiology and Drug Safety.* 2020;29(9):1054-1063.

21. Hooimeyer A, Bhasale A, Perry L, et al. Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. *Pharmacology Research & Perspectives.* 2020;8(6):e00680.

22. Bhasale A, Mintzes B, Sarpatwari A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. *BMJ.* 2020;369:m1107.

23. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology.* 2006;3(2):77-101.

24. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology.* 2013;13(1):117.

25. Ritchie J, Lewis J, McNaughton Nicholls C, Ormston R, eds. *Qualitative research practice : a guide for social science students and researchers.* Second edition. ed. Los Angeles, California: SAGE; 2014.

26. Bazeley P, Jackson K, eds. *Qualitative data analysis with NVivo.* 2nd ed. ed. London: SAGE; 2013.

27. *NVivo* [computer program]. 2020.

28. Fabbri A, O'Keeffe M, Moynihan R, et al. Media coverage of drug regulatory agencies' safety advisories: A case study of citalopram and denosumab. *Br J Clin Pharmacol.* 2020.

29. de Vries E, Denig P, de Vries ST, Monster TBM, Hugtenburg JG, Mol PGM. Drug Safety Issues Covered by Lay Media: A Cohort Study of Direct Healthcare Provider Communications Sent between 2001 and 2015 in The Netherlands. Drug Saf. 2020.

Funding and support: This study is funded by the Australian Government National Health and Medical Research Council (grant ID#1122332) with co-financing by the Canadian Institutes of Health Research (grant ID #153275). Ms Bhasale received funding from a University of Sydney PhD Scholarship.

Data availability statement: Research data are not shared due to ethical restrictions; consent for data sharing was not provided by participants.

Conflicts of interest

Dr Mintzes was an expert witness for Health Canada in a legal case concerning marketing of an unapproved product in Canada**.** Dr. Sarpatwari reports funding from the Harvard-MIT Center for Regulatory Science and Arnold Ventures during the conduct of the study and grants from United States Food and Drug Administration outside the submitted work. Dr Lipworth, Ms Bhasale, Ms McEwin, Ms Gautam, Mr Møllebæk, and Mr Santiago have no disclosures to declare.

5.3.1 Supplementary files for submitted paper

Supplement 1 to submitted paper

Interview guide – summary of questions

1. Could you tell me a bit about your medical practice and the types of patients you usually see?
2. Apart from seeing patients, what other medical activities do you spend time on (e.g. research, conferences, sitting on committees, educational events, CPD) [Not admin/governance activities]?
3. How often do you have contact with pharmaceutical industry reps?

Finding drug information

4. How do you usually get to know about side effects and other risks of medicines?
5. Do you look at the product information? If so, when?

Experience with post-market safety concerns

6. Can you recall a situation where there was information circulating about possible new risks or safety issues of medicines? (e.g. media, patients, colleagues)?
   a. What was the situation? Who did the information came from?
   b. How did you respond to that information?
   c. What makes it important, or makes you take notice?
7. What are your needs in terms of post-market safety information- new information for drugs on the market?
   a. How would you expect to be informed? Who should be responsible?
8. Do you recall receiving letters from pharmaceutical companies about safety issues?

SGLT2 example

9. How familiar are you with the SGLT2 inhibitor class of drugs (canagliflozin, dapagliflozin, empagliflozin [brand names])? Or rosiglitazone/pioglitazone?
   a. Example of prescribing to a patient?
   b. what information did you discuss with the patient, if any?
10. What side effects are top of mind for the SGLT2s?
    a. How did you found out about these risk?
    b. Do you think that safety concern has made much difference to the way doctors prescribe the drug?

Closing

11. Based on what we have discussed today, what do you think needs to be changed or improved when it comes to information and communication about medicines risks?
12. Is there anything else that you think is important that we haven't talked about?

5.3.2 Supplement 2 to submitted paper (5.4)

Additional information for Figure 1: Sources of drug safety information – trust, accessibility and useability

Type of source	Quote about Trust	Trust level	Quote about accessibility and useability	Accessibility and useability
Literature, journal articles	So, if you like the increased pool of information from RCTs, even though the RCTs are calculated on a primary end point of efficacy, they still if they systematically plan to report adverse events, major adverse events, et cetera, that's very helpful in terms of producing an understanding, and confidence in the class. (Lawrence, Endocrinologist AU) I don't think I would ever change what I would do in my practice unless I read the actual article and decided if it was worth it or not. (Thelma, Primary Care Physician, US)	High	I first heard about that issue when I saw the results of the large studies of the SGLT2 inhibitors being presented, by reading; either/or of those. So just really from the journal article, the main paper. (Tom, Endocrinologist AU So I try and read the various journals. Physician's Watch allows me to be lazy about that. So I get a really nice summary, but it is better to actually go to the article to be like "Was this a good study? Was it not? Is it going to change?" (Thelma, Primary Care Physician, US)	High for specialists Lower for Primary Care Physicians

Regulatory safety advisories	I see them as somebody who should be then responsible in part for the safety of medication, but I trust their information, (Mary Primary Care Physician, AU) Anytime I see something that says “FDA removed a black-box warning” or “Added a black-box warning, or “The FDA says this,” I pay attention. (Wilma, Primary Care Physician, US)	High	So I suppose we get emails and things from people, but I don’t have a really regular way of looking these things up. I think, perhaps, if there was this, as a sort of safety advisory alert, I don’t get that as a regular thing– (Mary, Primary Care Physician) I don't open mail from drug companies or the FDA….I used to get emails from the FDA They stopped sending me emails. (Albert, Primary Care Physician, US) The TGA might publish something on their website, but it just sits there. There is not a connection to the audience which is the meaningful process that needs to occur. (Gordon, Primary Care Physician, AU) Well, I think they are important. … It's a question of how people get information, and I don't know that they always pick up on TGA things (Reginald, Endocrinologist, AU)	Low (TGA) Moderate (FDA)

Non-commercial guidelines/ drug compendiums/ bulletins[a]	Well, just it takes a very non-commercial and non-drug company slant on things. An attitude like let's not be duped and sold on drugs that are either dangerous or don't work. [Prescrire] (Bill Clinical Pharmacologist, AU) Because I learned about it in med school, a sort of trusted, trustworthy and in-depth resource for safety and other prescribing stuff [The Medical Letter]. (Fred, Primary Care Physician, US) You're going to have to separate the guidelines that were born for the pharmaceutical companies and [other guidelines]. (Albert Primary Care Physician, US)	High	AMH [Australian Medicines Handbook] is broken down by the generic name which is just a bit easier to look through the whole – well, I'm pretty happy with it for the most part.	Moderate – depends on subscriptions
Academic detailing (AU only)	I always make a point of being around for the NPS [National Prescribing Service] visits which I think are really, really valuable, really well done (James, Primary Care Physician, AU)	High	it's very useful when discussing management of the condition with a pharmacist who really does understand the medication side of things and brings best practice and evidence to your table and usually some good resources. But I think the more remote I go the less people have heard of it. (Sean, Primary Care Physician, AU)	Moderate (Primary Care Physicians only)

Colleagues/ other clinicians	I trust the opinion. It's so easy for me to get an opinion from someone who prescribes it a lot, so I'd probably do an endocrine eConsult. (Sylvia, Primary Care Physician, US) When endocrinologists present these you ask them "Hey, how do you tell people that this might give them thyroid cancer?" Or "Who do you not give it to?" (Fred, Primary Care Physician, US) …particularly in training, you have someone you can ask and then often you look it up and then you talk to someone and just see whether there's anything else they would be concerned about or vice versa, (Sushil, Endocrinologist, AU)	High	One of the reasons that I like Journal Watch or even the New England Journal, if you read the letters from people, there's this editorializing from people that are smarter than me that I appreciate. (Wilma, Primary Care Physician US I mean if I have a question about something, I'll go ask somebody in the next room, "What do you think about this?" Or "Do you know about this?" (Nancy, Primary Care Physician, US)	Varies according to location and type of practice
Commercial drug compendiums[b]	I also get these monthly prescribing references that also show up spontaneously.…They do look like Reader's Digest. They're like thick with glossy Jardiance ads so I just throw them out. (Fred, Primary Care Physician, US) I used to look at MIMS because that seemed quicker, but I understand MIMS is actually - I think it's a drug company who put this information there. (Rani, Geriatrician, AU)	Varies	Generally it's MIMS because it's inbuilt into our medical software, ….to be honest I don't always just find it incredibly useful…–like MIMS lists everything under the sun, it's maybe a little bit hard to navigate what's the most common thing, what do I really need to watch out for. (Cleo, Primary Care Physician -Junior, AU)	High – often embedded in clinical software
Mainstream media	I think it's often one-sided and it seems to be done so it's a good story to read, more so than offering a balanced view. (Mary, Primary Care Physician, AU)	Low	The stuff that I use usually ends up in the news if there's a problem. (Nancy, Primary Care Physician, US)	High

DHPCs from pharmaceutical company	Well, I think the drug company doesn't have any ulterior motive for telling you bad things about their drugs. Why would they? …. they probably have to. (John, Primary Care Physician, AU) I don't trust pharmaceutical stuff very much. But I wouldn't expect them to hide or sort of downplay serious risks. ...I might worry "Is there something being left out?" But I wouldn't be like "Why would they tell me about osteonecrosis?" because they would have no incentive to tell me about bad things. (Fred, Primary Care Physician, US)	Moderate	…it does turn up in my pigeon-hole, (Mary, Primary Care Physician, AU) Yeah. They mail these to me - I throw them away….Because they're not useful. (George, Primary Care Physician, US)	High
Medical media	I do get a lot of emails from Medscape, many of which are very interesting, although I believe that a lot of their revenue comes from advertising and that they can't be totally trusted. (Fred, Primary Care Physician, US) The problem with the journalistic approach as well is that some of the content is sponsored and some isn't. So it is hard sometimes to define where this information is being developed from. (Gordon, Primary Care Physician, AU)	Moderate	6 Minutes and Medical Director and things like that, quite good at flagging important things, and they are reporting what's published, and so they're kind of filtering the published literature for you. (James, Primary Care Physician, AU)	High
Prescribing information [c]	…it's hard to get a gauge of how concerned one should be because they're required to list everything. (Shirley, Endocrinologist, US)	Moderate	Yeah, I know it will come in the product information but you will not have the time to go through all the information. (Juanita, Primary Care Physician, AU)	Low useability High accessibility

Clinical reference source - UpToDate[d]	I think this is why UpToDate …. it's like so helpful to people. It's because there is some component of editorializing to it and collating of information and then there's some voice in it. It's not like it's just info. (Wilma, Primary Care Physician, US) But if I need something reliable where I trust the information, then I'll go to UpToDate (Barney, Primary Care Physician, US)	High	So the quickest and easiest thing for me to do is to go to UpToDate. I know exactly where to find and to click on to get drug information. (Barney, Primary Care Physician, US) I don't use it as my sole source of information. But if I'm pressed for time, then I will use it. (Penelope, Endocrinologist US	High (for subscribers

*Boston interviewees all used EPIC; Australian Primary Care Physician interviewees varied in clinical software; Australian specialists used hospital based medical record systems according to their location.
a Non-commercial guidelines/drug compendiums/alerts = Australian Medicines Handbook (AU), Therapeutic Guidelines (AU), Physicians' Watch, Medical Letter, individual doctors' blogs
b Commercial drug compendiums = MIMs, Micromedex
c Prescribing information is the regulator-approved documentation also known as 'product information' in Australia
d Clinical reference source mentioned consistently by US interviewees was UpToDate.

Chapter 6 Discussion: implications for policy, practice and future research

6.1 Overview

The aim of this dissertation was to examine differences in regulatory policy governing post-market safety advisories and in the implementation of those policies, amongst regulators in Australia, Canada, the EU (UK) and the US. Using four different methods and research questions, I examined legislation, regulation and policy, compared the frequency and characteristics of advisories for a cohort of new drugs approved in Australia, used a process tracing case study to examine decision making and transparency in depth for SGLT2 inhibitors advisories, and explored physicians' use of medicines safety information and perceptions of regulatory safety advisories in the Boston, US and Australia.

The four studies described in Chapters 2-5 provide a range of insights into the current state of policy for regulatory safety advisories, both in terms of formal policy - as articulated in regulations, legislation and guidelines - and policy implementation. The research findings, policy implications and directions for future research are described below using the analytical framework described in Chapter 2 (reproduced here in Box 6.1) which encompasses the following aspects:

- Legislated authority
- Governance (including public participation)
- The role of industry
- Risk communication capacity and capability
- Transparency.

Two caveats should be considered when comparing regulators. Firstly, the larger population size and resources available to the FDA and EMA cannot be forgotten. This greater capacity may mean that these regulators carry much of the effort globally for surveillance and

investigation of safety issues, allowing smaller regulators to reap the rewards. However, differences in communications were seen not only between smaller and larger regulators, but between the TGA and Health Canada, which are broadly comparable in terms of capacity and population. Secondly, while I examined EMA policy, the use of safety advisories was investigated for the MHRA. While most (77%) of the MHRA advisories in the new drugs study (Chapter 4) referred to EMA actions, MHRA implementation of EMA policy may differ to that of other countries in the EU at the time of this study. In addition, towards the end of this research, the UK left the EU and after 1 January 2021, EU pharmaceutical law no longer applies in the UK except in Northern Ireland.[48] Hence these findings may not be generalisable to future UK policy.

Box 6.1: Framework for analysing regulatory policy for safety communications and components of implementation examined

Domain	Aspects of formal policy and regulation examined (Chapter 2)	Aspects of policy implementation examined (Chapters 3-5)
Governance **Legislated authority** **Role of industry**	• Responsibility for assessing safety issues • Responsibility for communicating and disseminating post-market safety information • Mechanisms and extent of public participation in decision making about post-market safety and communications • Authority to issue warnings and post-market safety advisories • Authority to require companies to issue DHPCs • Industry involvement in post-market safety communication and related regulatory activity	• Extent of public participation in decision making about post-market safety and communications • Regulatory vs.industry communications (DHPCs vs.other) • Extent of industry involvement in reporting and assessing post-market safety concerns • Industry negotiation over safety warnings and product information changes
Risk communication capability	• Goals of regulatory communication, in particular regarding behaviour change • Methods of communicating post-market issues • Monitoring and measurement of effectiveness • Guidelines for writing and communicating risk • Risk communication priority/strategy	• Number, timing and characteristics of advisories • Differences in communication content and decisions to issue advisories • Communication to consumers • Engagement of prescribers in regulatory safety communications: trust, accessibility and usefulness
Transparency	• Minutes of expert committee meetings • Documents explaining how regulatory decisions were made • Accessibility of post-market safety data	• Documentary transparency of decision making • Transparency within advisories • Availability of data about specific cases

6.2 Key findings

Despite similar regulatory goals for risk communication, and similar principles of risk identification and management, regulators differed in their communication of emerging post-market safety concerns including in the specific safety concerns communicated, how they were communicated and the timing of communication. There was the most transparency for EMA decision making, although some aspects of transparency were uniformly absent such as public access to post-market safety data. In addition, US prescribers interviewed had greater awareness of their national regulator's role in risk communication than their Australian counterparts, although for both groups regulatory safety advisories were less accessible, and less clinically authoritative than other commonly used and trusted sources. The analytical framework developed for this research helps to explain and interpret these findings, specifically the interrelated factors of governance, legislated authority, the role of industry, and risk communication capacity. However, other aspects of regulatory difference remain unexplained by the research conducted here, for which further research including specific case studies and qualitative methods may be required.

The following key findings were identified.

Countries with stronger legislated authority tended to be stronger communicators of post-market safety concerns. Both the EMA and the FDA have more explicit legislative mandates for risk communication than the TGA and Health Canada. Overall the strength of EMA and FDA risk communication was greater, when the following are taken into account: the frequency of advisories, the type of information provided, and the propensity to be the first to issue a warning for a specific safety concern. However, Australia lags behind Canada in the frequency and timing of safety advisories, despite both having smaller populations with less regulatory capacity. (Table 6.1 provides crude rankings on these variables). Regulatory culture, historical events and societal expectations of the regulator may play a role.

This research also highlights the extent to which regulators' risk communication capacity is reliant on, and augmented by, industry. This is a complex issue which might not be soluble through regulatory policy alone, but requires a broader strategic and policy approach, for example through national medicines policies.

All included regulators have amended their legislation and policy to at least some extent since 2004 after the rofecoxib (Vioxx) withdrawal and similar controversies, imposing greater obligations on industry for post-market safety activities and reporting. It may be appropriate for industry to be held accountable for post-market safety, yet some significant disadvantages to the current approach were identified. Firstly, regulators may rely primarily on industry to conduct post-market safety studies, monitor, report and interpret post-market data, which raises questions about both the independence and transparency of these activities. Secondly, some regulators may rely on industry to prepare and disseminate safety advisories, which may be problematic in terms of trust and acceptance by health professionals and the clarity of communications as well as the transparency of influences on the tone and content of safety messages. However, direct communications appear to be more effective than online notices[49] suggesting that multiple methods may be required by regulators. Thirdly, in the SGLT2 case study, the company was at considerable lengths to influence safety messages, despite the regulator's clear mandate to determine the content. Thus the finding that some regulators do not have authority over safety messages by industry may mean that these advisories are not readily available, or that safety messages may be weakened due to negotiation that may be more likely if industry is sending the advisory. The regulator's position regarding industry DHPCs is most ambiguous in Australia, as the TGA has neither authority over industry communications nor does it publish DHPCs on its website even when they have been agreed to, reviewed or requested by the TGA.

Safety advisories may fulfill a regulatory function yet not be optimally targeted to achieve the desired behavioural outcomes. Prescribers' limited awareness of safety advisories and their uncertainty about implementing some advice, suggests a disjunct between regulators' goals

and their ability to influence clinical decision-making. Different approaches and choices made by regulators when communicating specific safety issues for SGLT2 inhibitors - such as through product information or safety advisory - may further impact on prescriber awareness and clinical decision making. The extent to which regulators develop their risk communication capacity and capability may be crucial. There is some hope that improvements may be brought about by the responsibilities imposed by legislation - both the EMA and FDA are required not only to communicate safety issues, but also to monitor the effectiveness of risk mitigation, including communication.

The findings regarding Australian post-market safety communication merit particular attention. All four studies conducted as part of this dissertation suggest that the TGA performs its role in post-market safety communication very differently to other regulators, issuing advisories on fewer safety concerns than any other regulator, and ranking lower than other regulators on timeliness and transparency (See Table 6.1 and Figure 6.1). Table 6.1 summarises findings from all included studies into a set of overall rankings among the included regulators for each of the key functions. Overall position ranking for each domain is displayed graphically in Figure 6.2. Comparing regulators broadly, the EMA and FDA ranked higher than Health Canada and the TGA. However, the TGA consistently performed lowest in almost all domains. (Figure 6.2)

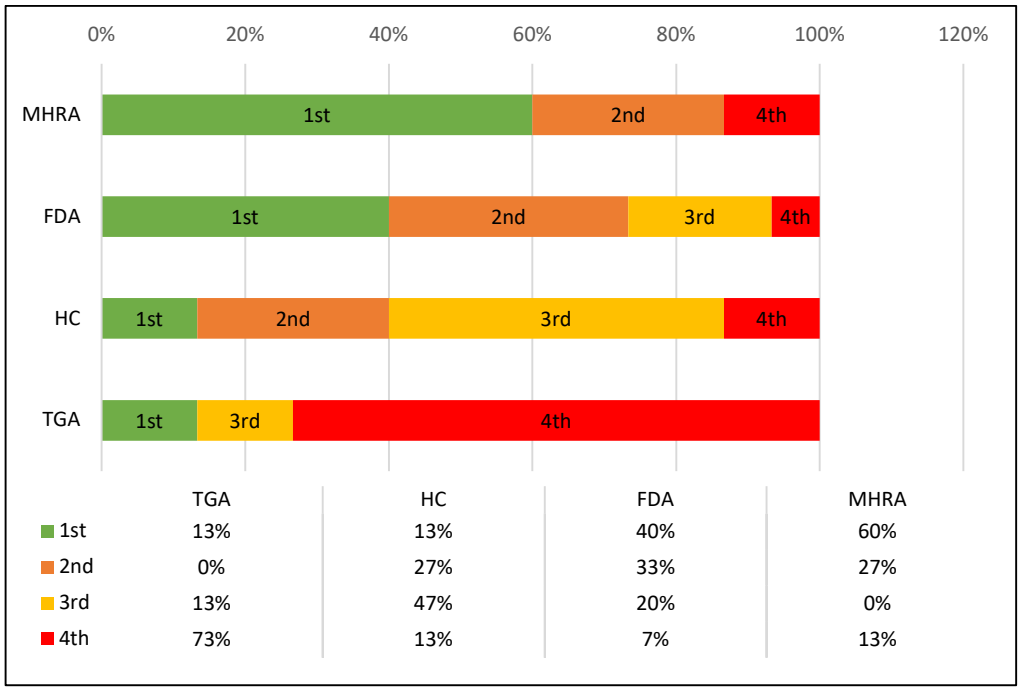
A lack of transparency made it difficult to fully compare regulators in the research conducted as part of this thesis. Access to Australian DHPCs was not available through the TGA, and records of regulatory decision making were limited in most jurisdictions except notably, the EMA. The major advance for most regulators has been to make adverse drug event databases publicly accessible. However, in general, information for post-market decision making and data is low when compared to some other forms of regulatory information, such as for new drug approval. In particular there is limited transparency regarding the interactions between regulators and industry regarding post-market decisions.

Table 6.1: Summary of regulatory comparison key findings; data and crude ranking (1= highest/best; 4 = lowest/worst)

		EMA/MHRA		Rank	FDA		Rank	Health Canada		Rank	TGA		Rank
RISK COMMUNICATION													
Issued advisory for safety concern (% safety concerns)	Content analysis	63.0%	(46/73) [a]	1	39.7%	(29/73)	3	52.1%	(38/73)	2	20.5%	(15/73)	4
	SAFER database[1]	52.4%	(344/657) [a]		41.0%	(265/647)		49.9%	(317/635)		29.6%	(183/619)	
Advisory includes numeric data on risk (% advisory specific content)	Content analysis	56.1%	(37/66) [a]	2	63.6%	(21/33)	1	41.9%	(18/43)	3	22.2%	(4/18)	4
Consumer info in advisory (% advisory specific content)	Content analysis	0%	(0/24) [a]	4	93.9%	(31/33)	1	57.9%	(11/19)	2	38.8%	(7/18)	3
Specific advice to prescriber (% advisory specific content)	Content analysis	81.8%	(54/66) [a]	1	81.8%	(27/33)	1	81.4%	(35/43)	2	55.6%	(10/18)	3
Average rank				**2**			**1.5**			**2.25**			**3.5**
TIMELINESS													
First regulator to issue (% safety concerns)	Content analysis	38.4%	(28/73) [a]	1	30.1%	(22/73)	2	24.7%	(18/73)	3	4.1%	(3/73)	4
	SAFER database[1b]	37.2%	(121/325)	2	37.3%	(118/316)	1	19.5%	(61/313)	3	10.7%	(33/308)	4
Delay after first advisory from other regulator (median; mths)	Content analysis	2.6	(n=15) [a]	2	3.1	(n=4)	3	2.1	(n=18)	1	7.1	(n=8)	4
Average rank				**1.7**			**2**			**2.3**			**4**
INDUSTRY INVOLVEMENT													
Regulation of DHPC	Policy analysis	Yes		1	Partial – for REMS		2	No		3	No		4
Use of DHPC for communication [c] - (% advisories)	Content analysis	66%	(37/56) [a]	4	0	(0/29) [d]	2	56%	(22/39)	3	0%	(0/16)	1
- (% all communications)	SAFER database[2]	39.3%	(227/577) [a]		4 REMS-DHPCs 9.7%	(49/508)		28.5%	(145/509)		0%	(0/231)	
Average rank				**2.5**			**2**			**3.0**			**2.5**
TRANSPARENCY													
Decision making transparency	Policy analysis, Case study	High		1	Moderate		2	Low		4	Low		4
Transparency of industry role in process and decision-making	Policy analysis	Moderate		1	Low		3	Moderate		2	None		4
	Case study	High		1	Moderate		2	Low		3	None		4
Information on regulator's decision making in advisory	Content analysis	24.2%	(16/66) [a]	2	75.8%	(25/33)	1	18.6%	(8/43)	3	11.1%	(2/18)	4
PSURs available	Policy analysis	Partial [c]		1	No		4	No		4	No		4
ADR database available	Policy analysis	Yes		1	Yes		1	Yes		1	Yes		1
Average rank				**1.2**			**2.2**			**2.8**			**3.5**

a – MHRA; **b** - >1 regulator issued advisory; **c** – ranking is reversed so that countries who use DHPCs more are ranked as worse, regardless of other communications used for the same issue; **d** – In Chapter 4 reported on 29 US advisories; **e** - provided on request in person to EU citizens. In addition, 4 REMS DHPCs for the safety concerns were identified. While out of scope for that analysis they are included here for completeness. REMS - Risk Evaluation and Mitigation Strategy; DHPC – direct healthcare professional communication; PSUR - periodic safety update report; ADR - Adverse drug report. Content analysis – Chapter 4; Policy analysis – Chapter 2; Case study – Chapter 3. 1: Perry et al 2019[8]; 2: Perry et al 2020[5]

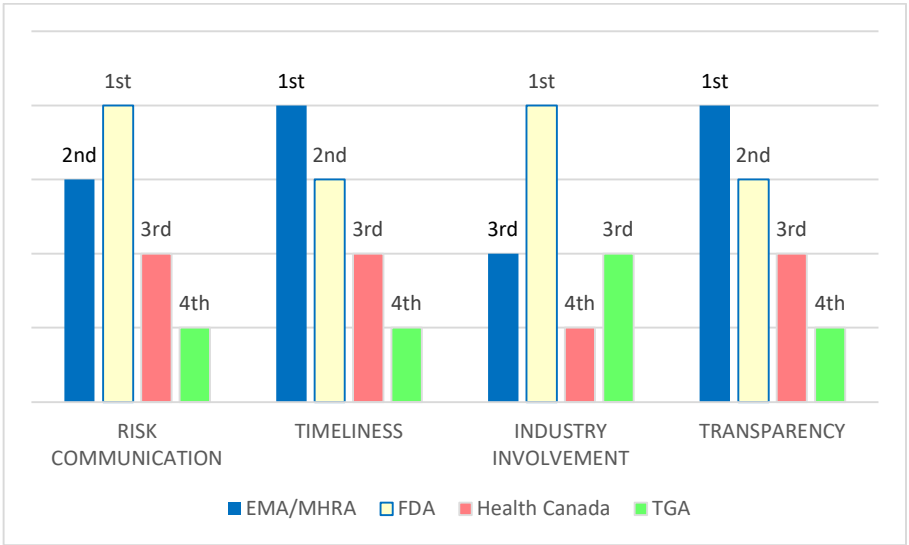
Figure 6.1: Ranking on regulatory comparison key findings by regulator (percentage of rankings)



	TGA	HC	FDA	MHRA
1st	13%	13%	40%	60%
2nd	0%	27%	33%	27%
3rd	13%	47%	20%	0%
4th	73%	13%	7%	13%

Note: Key findings listed in Table 6.1 were used to derive the above figure, which indicates the percentage of first, second, third and fourth rankings on key findings for each regulator

Figure 6.2: Factor ranking by regulator



6.2.1 Legislated authority and appropriate governance enable stronger post-market risk communication

Both the FDA and the EMA are required by legislation to provide information to the public about drug safety issues. One of the six listed objectives of the EU Commission pharmacovigilance legislation of 2010 (Directive 2010/84/EU)[1,2] [3] was: "*Strengthening medicines safety transparency and communication to increase the understanding and trust of patients and health professionals in the safety of medicines and improve the penetration of key warnings*". With this explicit goal, the accompanying regulations appear to have helped legitimise the EMA's role in post-market safety communication manifesting in organisational structures, budgets and operational priorities, as well as guidelines for best practice communication.

This legislative basis, which also provides a legal authority for regulatory actions should they be challenged by industry, was absent in Canadian and Australian legislation. The absence of similar legislated authority for Health Canada and the TGA does not prevent these regulators from issuing communications, but it may influence their approach to doing so and their prioritisation of post-market safety communication activities.

The governance of both post-market safety communication and pharmacovigilance more generally, may give an indication of the relative importance of this regulatory function within each jurisdiction. Whilst this is a complex area, the EMA and FDA appear to have stronger governance structures than the smaller regulators, although hierarchical tensions between pre- and post- marketing sections may not have been completely resolved in the FDA, where staff with responsibility for post-market safety and activities are less important hierarchically than staff involved in drug approvals.[4] The EMA's pan-national structure cannot be directly compared with other regulators, nonetheless the centralisation of assessment and governance in matters relating to post-market safety is a strength not fully replicated elsewhere.

Amongst the four regulators whose use of advisories was compared, the MHRA issued advisories for more safety concerns than other regulators - both in the subset of advisories examined in 0and in the SAFER database overall.[5] This might plausibly be explained by the governance and authority of the EMA for safety communication described above, including its authority over DHPCs. While there is a popular perception that the FDA is more likely to communicate about risk due to the more litigious US environment[6], this was not evident in the current research, ranking 3rd in a simple count of the proportion of safety concerns communicated, after the MHRA and Health Canada. (Table 6.1) One explanation considered was that the FDA might be using REMS as a way of requiring company communications, which is authorised by legislation.[7]. While REMS had been excluded in the collection of data initially as they are usually required at drug approval, a sensitivity analysis conducted by Perry et al for the SAFER database found only a minor change in the proportion of safety concerns with FDA communications when REMS were included (57% vs.59%)[8] and no change in the overall ranking of regulators.

In addition, Health Canada issued far more advisories than the TGA, despite a similar lack of a clear legislative mandate. The reason may lie in a previous characterisation of Health Canada as a 'shadow regulator', whereby a lack of capacity or expertise is compensated for by 'shadowing' the decisions made by other regulators with an accepted reputation for expertise.[9] Two findings support this characterisation. Firstly, despite issuing a large number of advisories, Health Canada was less likely than both the FDA and the EMA to be the first to notify about a safety concern, (see Table 6.1) suggesting it is more likely to follow the actions of others. Secondly, Health Canada's actions in the SGLT2 inhibitor case study suggest a tendency to follow rather than lead. Although Health Canada was the only regulator to have reviewed amputation data for canagliflozin pre-approval, it approved the drug on the basis of changes describing the related risk factor of peripheral vascular insufficiency in product information. Later, when more data emerged, and at the same time that the EMA issued an advisory signalling the start of an investigation, Health Canada's

initial action was to amend its product information to include the new amputation data without an accompanying investigation and only a brief note in its newsletter. This advice was later upgraded to a boxed warning following the actions of both the FDA and the EMA. While it is not possible to know whether Health Canada would have upgraded its warnings without other regulators' actions, its initial reaction indicates a tendency to follow. Geo-political factors may explain why Health Canada acts differently to the TGA, in that Canada has both geographical proximity to the US and Commonwealth ties to the EMA and the MHRA, thus shadowing both regulators, while Australia has closer regulatory ties with the EMA through the Commonwealth.

The TGA, as noted in Chapter 2, instituted a minor change in the *Therapeutic Goods Act* to allow the release to the public of certain types of information as specified in regulation. However, unlike the EU legislation, TGA legislation does not clearly reference a public health role as the object of the Act,[10] and while this specific provision allows the release of information about safety, the TGA's responsibility is not clearly articulated.

While important, legislation does not explain all the differences between regulators. The TGA has no less provision in its act than Health Canada does, yet the way that Health Canada interprets its role in the absence of legislation is in contrast with the TGA, suggesting that individual cultural factors and historical factors may be involved.

Further, in the case study of SGLT2 inhibitors the UK MHRA issued advisories for only two of the five safety concerns identified in FDA advisories - diabetic ketoacidosis and amputation - but not for acute kidney injury, severe genitourinary infections or bone fracture risk. A lack of transparency made it difficult to determine processes in all jurisdictions, however the seriousness or novelty of the adverse event alone was not clearly a determining factor in all jurisdictions, suggesting contributing factors related to regulatory discretion in judgement and risk prioritisation.

For example, for the bone fracture risks of canagliflozin, EMA and FDA had very different interpretations of the level of risk and the need to communicate this risk, based on the same evidence. As a condition of approval, the FDA required a post-market study report about effects on bone and assessed the results as confirmatory, resulting in an update in product information and an accompanying advisory. In contrast EMA, had been sceptical of the risk at approval, considering it secondary to falls due to hypotension. Despite flagging the risk in the risk management plan at approval as an important potential risk, it did not issue an advisory when the FDA-required study was completed, rather adding information directly to the product information. The EMA risk statement was also phrased in the opposite direction to the FDA statement, noting fracture rates but reassuring about impact on bone mineral density.[11,12] Thus even with the same evidence and the same regulatory powers, the two regulators made different judgments.

In summary, while regulators may choose to act without regulation, regulation and legislation provide clear parameters for decision making, a legal basis for acting on safety and may help in the prioritisation of regulatory activities. An investigation into the workings of the FDA, which involved in depth interviews with regulators found that despite good intentions, a tendency remains to prioritise activities related to new drug approval.[4]

6.2.2 Reliance on industry to augment regulatory capacity for post-market risk communication

Policy and regulation describe expectations of industry for many aspects of post-market regulation, with varying requirements in relation to safety advisories across regulators. However, current arrangements for all four regulators are reliant on industry, indicating a need for strong regulatory parameters to avoid negative outcomes. The role of industry was reflected in observable policy outcomes including decision making in advisories and product information changes for SGLT2 inhibitors (chapter 3.4), as well as the frequency of DHPCs as regulatory communications (Table 6.1).

Paradoxically, these findings reflect changes in policy implemented in the wake of significant controversies in which drug manufacturers did not disclose post-market safety data openly to regulators. Examples include the cardiovascular risks associated with rofecoxib and later with rosiglitazone and pioglitazone, and benfluorex (Mediator) in France.[13-17] Current legislation authorises regulators to require companies to change drug product information, request or require them to conduct post-market studies and to report adverse events, as well as requiring regulators to have systems for monitoring post-market safety.[18-28] These requirements have led to the identification of several of the risks described in this thesis. However, while it is important to ensure industry accountability, some have commented on the drawbacks associated with delegating responsibility to industry for aspects of pharmacovigilance which could be carried out independently or by regulators.[29,30]

Firstly, industry collected post-market data may not be available to the public. The exception is ADR reporting databases held by regulators which have been made publicly available in all jurisdictions, often in response to public pressure.[30-32] However, unlike when ADR reporting schemes first started, most reports are now submitted by industry. While this ensures capture of events through regulation, issues have been identified with the quality of reports collected by industry and the large volume of irrelevant reports submitted, which could hamper accurate signal detection.[33,34] In addition, the design and completion of post-market studies may be less than optimal as the motivation for such studies from a company's perspective is often to expedite drug approval[4]. In both the EU and the US, post-market studies are frequently delayed[35-37] or inadequately designed.[37,38] In the US, companies have not been penalised for failing their post-market commitments.[4]

In the current thesis, reliance on industry was demonstrated when examining the process for EMA 'referral procedures' which were conducted for diabetic ketoacidosis and amputation with respect to SGLT2 inhibitors. The role of the regulator was to elicit specific information, data and proposed risk mitigation actions from pharmaceutical companies. In these examples the EMA posed questions for the companies to answer using their own internal

clinical trials and ADR report databases.[39,40] Analyses were carried out by the company and presented to the Pharmacovigilance Risk Assessment Committee (PRAC) for consideration and assessment. When the company proposed further meta-analyses as a voluntary measure, EMA agreed and advised on specific requirements for those studies. The reliance on industry to perform studies about the safety of their own products is concerning given findings suggesting that studies by sponsors are more likely to report results in favour of their products.[41] As these data remain proprietary, however, there is no obligation to publish.

A second issue relates to the involvement of industry in risk communication of various kinds, including product information (the role of DHPCs is discussed below). Industry influences on safety advice was examined in the SGLT2 case study, demonstrating how industry may contest the wording and presentation of safety information in product information; these documents in turn may influence the way that safety advisories are written. In the specific case of communicating amputation risk, the company engaged in 'extensive' efforts with the FDA to obtain its preferred wording, including an eleventh-hour teleconference on the morning of the FDA deadline. [42] Changes in wording between the initial FDA advisory and the advisory issued after changes to the product information suggest the impact of negotiations on messaging, with a weakening in the directness of statements about causality and harm (Chapter 3). These discussions occurred despite the regulator's legislated mandate to require changes to prescribing information.[42]

6.2.2.1 Role of industry DHPCs

DHPCs are a primary form of communication in the EU, UK and Canada. In both the UK and Canada, a DHPC is a letter to a health professional which may come from the regulator or from the company. In the US context, DHPCs are from industry, and in Australia the TGA does not write directly to individual prescribers using DHPCs. In Chapter 4 , all DHPCs identified were from the company.

Differences among regulators in their use of DHPCs must be considered in the context of evidence regarding how they are perceived, their accessibility to the public and the role of industry in their development. As noted in Chapter 2 , and in Table 6.1, EMA legislation provides the strongest mandate for regulation of industry DHPCs, requiring companies to inform the regulator if they are planning a safety-related DHPC, and that they co-operate with the regulator in its preparation. US regulation mandates industry compliance for REMS related DHPCs, requesting it for others. Health Canada and the TGA legislation do not refer to DHPCs, although Health Canada acknowledges the role of DHPCs in guidance materials. In Table 6.1, I have ranked countries which do not regulate industry DHPCs lower than those that do. I also ranked countries with a greater reliance on DHPCs as lower than those with less reliance. The rationale for this assessment is explained below.

Amongst new drugs advisories (Chapter 4), DHPCs made up 66% of MHRA advisories, 56% of Health Canada advisories and 0% of FDA and TGA advisories. These findings are consistent with findings from the overall SAFER database in which DHPCs made up 40% of all MHRA communications and 28.3% for Health Canada.[5] The higher numbers of DHPCs alone may account for differences amongst regulators in frequencies of advisories.

The FDA has moved away from posting DHPCs as a form of safety advisory, comprising only 9.7% of all its communications between 2007-2016 in the SAFER database, many of which occurred earlier in the time period.[5] As the FDA has a clear mandate over DHPCs issued as part of REMS and can determine the content of these letters[7,43] it may be using this avenue when seeking DHPCs from industry.

In the absence of a specific authority to require DHPCs or mandate content, companies may still follow a regulator's requirements, in response to its institutional authority. However, without a formal policy or authority, the appropriateness of safety messages may be weakened. As described above in Chapter 3, the process of negotiation with the company may change messages or delay warnings, irrespective of regulatory authority.

The high rate of DHPCs amongst Health Canada advisories occurred despite the lack of a clear provision within regulation for this to occur. This is most likely a matter of regulatory culture, with Health Canada's relationship with industry being characterised as one of 'clientele pluralism' where the regulator and industry relationship is consultative, compared to the FDA which has been described as 'managerial', with the FDA directly managing the extent of industry involvement.[44]

While DHPCs are commonly used in Europe and Canada, prescribers in the US and Australia reported mixed views on letters from companies (Chapter 5). While companies were not generally considered a trusted source of information, some believed that DHPC content might be mandated and were therefore theoretically less suspicious of a commercial motive, but in practice might just discard or delete such messages as unsolicited materials from a commercial origin. These findings are supported by European surveys of prescribers indicating that many prescribers would prefer to receive safety information from non-commercial sources including regulators, independent information providers and professional organisations.[45,46] In addition, a recent qualitative study indicates that European prescribers distrust the motivation for DHPCs, which are perceived as having a legalistic function to protect companies from risk, shifting it instead to the prescriber.[47]

As prescribers may not trust DHPCs from industry, I have rated the FDA and TGA as higher than EMA and Health Canada who rely more on DHPCs. However, there is ambiguity in the TGA's involvement with industry DHPCs, with the TGA aware of, or directly involved in such communications from industry.[48] This was confirmed by industry sponsors contacted during the development of the SAFER project, and by the TGA itself.[48] Yet the TGA has no obligation within legislation to oversee these communications, and these letters are not made public by the TGA .[48] Accordingly these DHPCs are considered commercial property.[48] There is a clear need for policy to clarify this ambiguity, as the accessibility of one-off communications is poor and important safety information should not be considered proprietary information.

A systematic review of UK regulatory interventions found that DHPCs from the regulator's advisory committee were associated with greater changes in prescribing than drug bulletin notices alone, suggesting that this communication mechanism may be important.[49] However, the impact of direct communications may be undermined by a lack of trust. Further evidence is required to assess how the form of communication interacts with other aspects of the communication, such as the source. The more important factors may include amplification through multiple and repeated sources including the media, and the clarity of the suggested action.[49,50] To avoid the possible unintended effects of DHPCs, such as a lack of trust in their advice, or a tendency to disregard them, regulators should provide evidence of their endorsement by co-signing letters (as occurs in other jurisdictions) or repeat the same messages through their own communication channels.

6.2.3 Limitations in current risk communication —the need to do better

The importance of effective communication to achieve safe medicines use has been discussed in much of the literature assessing safety advisories and other risk communication strategies.[49-56] On one side is the need to ensure reductions in harm. On the other, there is a possibility of misinterpretation of safety messages in the media, which may have unwarranted impacts on consumer health decisions,[57,58] damage institutional reputations, and - though not stated by regulators - have an economic impact on industry. The ability to effectively communicate risk and manage public perceptions of safety information is a considerable challenge for regulators and clinicians alike.

Whether prescribers act on safety advisories and other safety advice is integral to the impact of advisories on population risk. In interviews conducted both in Australia and Boston US (Chapter 5), there was disparity in awareness of regulatory advisories between specialist clinicians and primary care doctors; the latter describing high volumes of information to process. In addition it was found that clinicians sought to validate the information provided in

advisories, some were uncertain as to clinical relevance or how to advise patients about risk. Similar results have been found in other studies.[59,60]

When regulators choose to update product information rather than issue warnings it is uncertain whether prescribers will identify such changes. Few clinicians reported using product information for a meaningful assessment of safety information; they were considered relatively inaccessible as they provide long lists of adverse effects with little clarity about significance. These assessments align with the literature finding poor overall clarity of reporting of adverse effects.[61] Prescribers in the interview study preferred point-of-care, accessible, clinically relevant and non-industry sources of safety information including in Australia, the Australian Medicines Handbook and Therapeutic Guidelines, and in Boston, UpToDate[62] which was available in local clinical software

Despite a higher number of advisories overall, no MHRA advisories in the sample of new drugs advisories (section 4.4) provided information to consumers, even for non-DHPC communications. In contrast, every FDA Drug Safety Communication includes a section for consumers using a standardised format, and information for consumers was provided by the majority of communications issued by other included regulators. The possibility that post-market safety information may not reach consumers was reinforced by the findings of the prescriber interviews, with interviewees describing reluctance to describe safety concerns to consumers for fear of affecting compliance, due to the time required for explanation or uncertainty in their own ability to adequately explain the complexity of the risk information adequately, especially for low literacy consumers. Much of the advice provided in safety advisories to consumers, stated that they should not stop their medicine without medical advice, and to seek further information from their prescriber. This suggests a flaw in the logic of regulatory risk communication which expects prescribers to implement safety advice, without tailoring information to this need.

A final issue relates to organisational capacity. In at least one SGLT2 safety concern, described above, FDA updates to include fracture risk in product information occurred more than a year later than the EMA's product information change on the same data, reported as part of a post-market safety requirement implemented by the FDA. This aligns with previous findings that the FDA lacks the organisational capacity to follow up on all post-market safety commitments and requirements imposed, resulting in substantial delays in acting on reports received from companies, as well as delays in obtaining them. [63,64] Whether the TGA has the necessary organisational capacity to manage public communication for emerging safety issues has not been examined, however I noted delays of up to 33 months, with a mean delay of 11.3 months for 10 Australian advisories issued after an advisory in another country (Chapter 4).

Similarly, the investigation of safety concerns for SGLT2s took around 12 months in the EU and the US for amputation concerns, and 6-8 months for diabetic ketoacidosis changes to be finalised within product information (Chapter 3) and the risk clarified. Given the number of new drugs approved each year, and the number of approved drugs within any jurisdiction, the capacity required for ongoing monitoring and follow up is substantial, increasing the potential regulatory burden. This ongoing burden may not be adequately factored into the approvals of new medicines.

Strategic actions to improve risk communication were identified for three of the regulators examined in this thesis, most notably the EMA and the FDA who have conducted research into maximising the effectiveness of risk communication and measurement of outcome, including issuing guidance for best practice communications.[65-70] Health Canada commissioned a report on risk communication and how to evaluate it, but is not clear from publicly available documents whether that report has been implemented.[71] Communication was also addressed in a review of transparency at the TGA,[32] leading to enhanced communications by the TGA, but strategic work on risk communication was not identified.[72]

In addition, regulatory policy is based on expected outcomes of risk mitigation activities - including safety advisories - for which the evidence of effectiveness may not be available. The EMA is required under legislation "to monitor the outcome of risk minimisation measures contained in risk management plans", which includes assessing the impact of safety communications where possible, for which both the agency and industry are responsible. Similarly the FDA requires companies to submit data on the outcomes of REMS programs, although it does not have authority to require particular kinds of studies or outcome thresholds.[73] However, evidence suggests that the goals of regulatory risk mitigation interventions are not being realised,[64,73,74] making it possible that they provide 'false cover' – the appearance that risks have been managed without any actual impact on patient harm. As has been identified in other case studies, risk management approaches may be more permissive of risk to patients rather than precautionary, in cases where more restrictive action such as drug withdrawal would have more effectively managed harm.[75] While there is a broader debate about the effectiveness of risk management as a regulatory policy, the key point for safety communication is that the outcomes of safety advisories need to be measured, proportionate to both the risk and the advice provided.

6.2.4 Regulation for safety communication in Australia

Each of the studies conducted for this dissertation suggests that post-market safety communication is a lower priority for the TGA than for other regulators. This was reflected in the perceptions of Australian prescribers who did not immediately perceive the regulator as regularly communicating post-market concerns, despite a high degree of respect for its institutional role and authority.

Importantly, comparison with Health Canada suggests that regulatory size alone does not explain why the TGA differs so markedly from other regulators. It is true that smaller regulators have limited capacity to detect safety concerns particularly when using population-based ADR data and this might be one reason that Health Canada and the TGA

less often are the first to issue an advisory for a safety concern. (Table 6.1) However, Health Canada issued more safety advisories for the cohort of Australian new drugs than the TGA (39/140 [27.8%] vs.16/140 [11.4%] respectively). This demonstrates that regulators need not have their own extensive post-market monitoring systems in order to issue advisories, they may simply shadow other regulators.

My findings suggest that several factors contribute to the discrepancy between the TGA and other regulators. Firstly, the TGA lacks a clear mandate for public health in legislation to communicate emerging safety concerns for a public health and safety purpose and can therefore be selective in the issues it chooses to communicate about or allocate resources to. However, if the TGA is exercising selectivity in determining what to communicate, the specific criteria applied are not obvious, and appear to be largely a matter of discretion. Secondly, the TGA may be aware of, or support the issuing of DHPCs by companies, but is not compelled to make them publicly available or take responsibility for their content. Additionally, there may be other advisories that the TGA issues directly to professional societies and organisations, as such communications are referred to in its own guidelines.[76]

Whilst it has been proposed that the Australian regulator may exercise greater discretion in shielding prescribers from unimportant issues, this suggestion was not supported by my research (Chapter 4). For the 79% (58/73) of safety concerns without Australian advisories, 55.2% of the 58 safety concerns mentioned death, 77.6% were about a new or emerging adverse effect, and 44.8% were associated with a significant change to product information in another jurisdiction. A high proportion of advice given for safety concerns without an Australian advisory included advice to stop or avoid the medicine in certain situations, further suggesting the importance of these safety concerns and their relevance to both prescribers and medicines consumers. Australian advisories were less likely to offer specific advice to prescribers and more often provided general advice aimed at raising awareness.

As discussed earlier, another reason for fewer Australian advisories may be that companies issued DHPCs with the TGA's knowledge, that were not duplicated by the regulator publicly. During the collection of data for the SAFER database, attempts were made to identify such potential advisories by firstly contacting individual companies, and secondly submitting an FOI request to the TGA.[48] The FOI request was unsuccessful, although information was received from companies for 36 of 207 drugs without an Australian advisory. Of these, 19 (52%) confirmed that a letter had been sent (unpublished data). The low number of respondents to the request makes it impossible to assess how many letters may have been sent, but it is possible that up to 50% more advisories may have occurred as industry communications off the public record.

An alternative explanation is that the TGA preferentially authorises changes to product information without advisories. In both the SGLT2 case study (Chapter 2), and in 0 examples of serious risks for commonly used drugs were added to product information without a TGA advisory. These included cardiac failure with alogliptin and saxagliptin, and severe arthralgia with dipeptidyl peptidase-4 inhibitors, both of which were the subject of FDA advisories. Ironically the FDA has been criticised for failing to take stronger action for the former example[4], while in contrast, the TGA did not even issue a safety warning.

Regardless of the reason for the TGA's different approach, these findings warrant a review within the context of the broader policy implications, as discussed below.

6.2.5 Transparency

Pharmaceutical expenditure accounts for at least 11% of all health expenditure in Australia, about half of which is publicly subsidised.[77,78] On this basis alone, information about the safety of medicines held by regulators and industry should be publicly available.

However, transparency in post-market safety differs between regulators, and there is further divergence between public expectations of transparency and those of regulators and industry.[79-81]

I found that regulatory policy for transparency of post-market safety information was strongest for the EMA and weakest for the TGA. EU pharmacovigilance legislation requires regulatory transparency, so long as personal and commercial confidentiality are maintained. The EMA had the most comprehensive process documentation, providing rationales for all changes to the product's licensing status, product information changes and summarised minutes of PRAC meetings. While Health Canada appears to be emulating the European approach, some important details are omitted, such as the reasons for changes to product information. Many explanatory documents available are summaries which do not present detailed data. FDA transparency is inconsistent. While it provides transcripts of committee meetings, there is almost no information about decision making for safety issues. The TGA does not provide any process transparency on a routine basis for decisions about safety data. Least transparent are interactions between industry and regulators, especially for Health Canada and the TGA.

In the SGLT2s case study, I found that most, if not all steps of safety decisions were documented by the EMA and a scientific rationale – albeit brief – was available for all product information changes, with more detailed reports for referral procedures.[39,40] Much more information was available to trace the decisions made by the EMA, and the data supporting them, than for other regulators. Despite this, EMA assessment reports of referral procedures for SGLT2 inhibitors described the comprehensive clinical trials databases and global ADR databases held by companies and summarised the data provided to regulators, but fell short of providing data to the public. In each of the jurisdictions, ADR report databases are available, yet clinical trial data are not, even for the post-market safety studies requested or required by regulators. These studies may be published by companies in the research literature, but conflicts of interest are likely to affect the reporting of findings.[41]

Health Canada provided simple summaries of some decisions but for the SGLT2 examples reviewed, these were often of limited detail, for example stating that the product information had been changed, but not the nature of the change. TGA transparency was extremely limited, with information available only in advisories themselves. This transparency particularly contrasted with the extensive detail provided in AUSPAR reports. Neither the TGA nor Health Canada provided information about risk management plans, updates to those plans post-market, or details of any evaluations of impact conducted.

In the FDA memo describing decision making for canagliflozin and amputation risk, comments from the company are completely redacted. Although these documents were made available, extensive redactions on the basis of commercial sensitivity hamper understanding of the processes of safety decision making, particularly interactions between regulator and industry.

6.3 Policy implications

On the basis of the research findings discussed in this dissertation and summarised above, I propose the following policy implications.

6.3.1 Improving regulatory authority, capacity and governance

The TGA and Health Canada do not currently have a clear mandate to provide information to the public about emerging safety issues in a timely manner. Addressing this lack of a defined role in post-market safety communication could enable stronger governance and prioritisation of organisational capacity to address these issues.

Similarly, the TGA and Health Canada do not currently have the ability to mandate safety communications by industry or to review the content of those communications. While systems are in place based on institutional authority, there are limitations to such arrangements, as illustrated by the TGA's inability to provide copies of DHPCs without seeking permission from companies.[48]

Current levels of public participation in post-market safety decision making are low, especially by consumers. The EMA's PRAC and the FDA have carried out public consultation activities including public forums for specific post-market safety concerns, such as for fluroquinolones and valproate. This is an interesting development, but to date has occurred only for off-patent drugs. The most effective and appropriate ways to involve consumers and clinicians in these decisions has not been determined and would need to take into account the heterogeneity in individual values, as well as the impact of industry influences and conflicts of interest.[82-84]

6.3.2 Maximising the effectiveness of risk communication

Regulators should investigate how best to advise prescribers about new safety concerns, including using safety advisories and when changes occur in product information. User-centred research, for example comparing the utility of different presentations of product information could be considered, especially in jurisdictions where this has not been carried out or acted upon. Criteria for determining which product information changes to communicate and how best to do so is an important aspect of post-market safety communication. Identifying whether a safety concern is particularly important for decision making before prescribing (e.g. fracture risk), could be embedded in such criteria, given the finding that long, undifferentiated lists of adverse effects are not useful. These changes might not require advisories as such but could make use of electronic clinical systems to provide time-limited alerts to important changes in safety information. Moving from information-based systems to decision support could also enable more targeted use of safety data.

Policymakers should evaluate whether key safety advice is reaching consumers through its current mechanisms. This is particularly important for the MHRA, which includes only DHPCs and drug safety alerts for health professionals amongst its regulatory communications. Currently, regulators list their goals for safety advisories as including the

provision of information to support risk benefit assessments and discussions between clinicians and their patients. However, clinicians in our interview study were inconsistent in their provision of advice to consumers because of time constraints and hesitation about effects on compliance. This suggests that many consumers will be unaware of potential adverse effects unless they are proactive or health literate, with a risk that medicines information will be obtained from less reliable sources via the internet and social media.

When regulators issue advisories recommending that clinicians counsel or advise their patients about risk, greater consideration could be given to the impact of that advice on the prescriber and the consumer, so that recommendations are made in the most appropriate way to support effective communication. The EMA, for example has issued specific advice for risk communication with young people and in the face of vaccine fears.[67,68,85] Providing information about risk is also important in the context of informed consent. While informed consent for medicines with serious potential harms is addressed in some REMS as well as in risk minimisation measures in the US and the EU, it is lacking for most prescribed drugs, despite the potential for significant risks even with common medicines.

The qualitative study findings suggest that clinicians may be under-utilising the information in product information and have low awareness of regulatory safety communications, particularly in Australia. Additionally, clinicians recognised the authority of regulatory agencies but felt the need to contextualise their advice against more clinically relevant sources including their own and others' experiences, the evidence, and advice from colleagues and experts. Yet information about the place of medicines in therapy for a given condition may not be provided by regulators because of restrictions relating to commercial competition and commercial confidentiality. Policy should use evidence to optimise regulatory communications to clinicians and draw in additional agencies if appropriate.

Broader strategic approaches, such as through national medicines policies are essential. While the role of regulators is important, they may have limited clinical authority or relevance

with prescribers or consumers, and their prescribed regulatory functions may not be aligned with the skills, capacity and requirements needed to effectively implement safety communication goals. A broader systems approach would consider which public and non-government agencies are responsible for disseminating information about the safe use of medicines and monitoring the effectiveness of regulatory and industry risk mitigation strategies. Such systems would require integration of high-quality post-market surveillance data with effective assessment and action, including safety communication and advice regarding the implications for clinical practice. Further, regulatory advice to the funders of medicines, such as the Pharmaceutical Benefits Scheme (PBS) in Australia could have a greater impact on medicines use than regulatory communication alone. Regulators often have privileged access to safety data and most have the authority to require such information from industry. While this information has an important use in regulatory functions, it also has a high value for improving the quality use of medicines and avoiding medicines harm.

All regulators may need to assess their policies in relation to industry DHPCs in light of findings that many prescribers distrust industry communications. In addition, other research has found that these communications may be perceived as defensive on the part of industry, rather than for patient protection, and has important policy implications.[60] Regulators should consider issuing their own advisories to accompany DHPCs. This is particularly important in Australia, where there is a need for the TGA to clarify its position on industry communications via DHPCs. If commercial confidentiality or concerns about regulatory independence preclude the inclusion of DHPCs on the TGA website, the regulator could issue its own statement on safety concerns, rather than delegating this responsibility to industry in a way that is inaccessible to the public.

The effectiveness of safety advisories and other risk management interventions needs to be measured and monitored, proportionate to both the risk and the advice provided, in order to ensure that patient harm is avoided. The TGA and Health Canada do not have a legislated

responsibility to assess the impact of safety communication. While the FDA and EMA are required to assess effectiveness, the FDA cannot currently require assessments of the outcomes of REMS or other safety interventions. [73]

Where there is continuing evidence of harm to patients, there are no clear thresholds for determining what level of risk is acceptable and when stronger action is required, which may be hampered by inadequate measurement. A contemporary example can be seen in the opioids crisis, with limited regulatory action being taken despite evidence of dependence and other harms persisting for many years. REMS programs required by the FDA have been found by the US Inspector General audit to have uncertain benefit in achieving their primary goal of reducing serious adverse events from inappropriate prescription, misuse, or abuse of extended release and long-acting opioid analgesics.[86] An independent analysis identified that results provided by companies to demonstrate the effectiveness of the program in educating prescribers, were at odds with actual rates of prescribing in the community.[86,87]

Risk communication is central to the quality use of medicines, but if it is ineffective, then patient risk of harm may be increased. From a broader societal perspective, it is crucial that regulators maximise the impact of risk communication, measure its effectiveness and act decisively when harm continues despite communication of risk.

6.3.3 Transparency: recommendations

In response to the findings of the SAFER project[8] a senior FDA regulator stated that differences amongst regulators choices in communicating emerging harms were inevitable, due to “differing conclusions about whether a risk exists or when there is agreement on the risk assessment but a difference in the benefit-risk analysis or risk management options”. This was clearly seen in some of the examples in this thesis. He went on to advise that the basis for different decisions should be made clear to avoid confusion amongst prescribers and consumers. [88] This worthy goal can only be achieved with a commitment by all regulators to greater transparency.

Publishing records of interactions between regulators and industry in regard to post-market communications, safety advisories and product information changes could help accountability and ensure these interactions maintain a public interest focus. In the example shown in Chapter 3, the company diplomatically but consistently resisted FDA attempts to require changes to product information for canagliflozin, but these interactions are rarely in the public domain.[iv] The memo itself however was extensively redacted, suggesting that concerns about commercial confidentiality may pervade regulatory decision making. Such negotiations can weaken safety messages and delay risk communication.

While the EMA and FDA provide some procedural transparency, in that documents are publicly available, in some instances they are organised in a manner more useful to researchers than to clinicians or the general public, requiring cross-checking of dates and multiple webpages to identify relevant information. A World Health Organization report about transparency in pharmaceutical systems stated that "poor-quality information, or an overload of undigested data, may create confusion, rather than increase understanding and can actually hinder accountability."[89] The EMA website does however provide a single page for each medicine which includes its regulatory history.

Despite gains in transparency in post-market communication, regulators currently provide limited access to post-market data. While regulators may fear releasing safety data due to concerns about unintended consequences, ultimately this could help improve understanding and help mitigate concerns when accompanied by better transparency of decision making.[89] Regulators currently receive information in the form of post-market safety reports submitted by industry to regulators. Industry interactions with regulators regarding these safety data

[iv] In the document search for this case study similar documentation was not available for any other safety concern suggesting this was something of an anomaly.

should be openly available to ensure accountability and avoid undue pressure or influence. The limits of commercial confidentiality in regard to safety concerns should be explicitly stated to support greater transparency and accountability in the public interest.

6.3.4 Policy implications for Australia

A key finding in this report is the discrepancy between Australian regulation and policy and actions related to safety advisories and those of other regulators. The Therapeutic Goods Act itself does not articulate a clear public health objective for the regulator,[10] give the regulator the authority to communicate with purpose to prevent harm, or require industry to do so.

While the TGA uses risk management plans, and risk minimisation measures may include safety communications, these are largely non-transparent particularly for those which may be amended in response to post-market safety issues.

The TGA does not have a clear mandate over DHPCs, which creates considerable ambiguity and lack of transparency for these communications. When the TGA supports or requests industry dissemination of safety advice using DHPCs, it should make them publicly available on the regulator's website, as occurs in the UK, EU, Canada and the US for DHPCs as part of REMS. For a regulator to be unable to readily locate or provide safety information, and to consider such information as commercially owned, indicates a significant gap in policy.

Amongst Australian prescribers there is a concerning lack of awareness of the TGA's role in post-market safety communication, which may be a result of the low frequency of TGA advisories. It may also indicate a lack of effective risk communication and capacity to promote TGA messages. As one interviewee in Chapter 5 stated,

> *"The TGA might publish something on their website, but it just sits there. There is not a connection to the audience which is the meaningful process that needs to occur."*

These criticisms are not new. A 2011 review of the TGA recommended the TGA improve its communications to the public, health professionals and industry.[32] A comment from the Consumers Health Forum of Australia in the same review noted that:

> *"Public information about adverse events must not be limited to passive measures such as inclusion of the information on a website; there must be a hierarchy of proactive strategies for informing health professionals and the public of adverse events, with the level of the response proportionate to the severity of the adverse events and the potential risk to public health and safety."* [32]

There are many aspects of Australian regulation which may serve Australians well. Australia does not have the high rates or litigation over drug adverse effects seen in the US, which may fuel increased safety warnings there. However, Australia issued fewer advisories than both the UK and Canada as well as the US, which belies this explanation. A lack of transparency in TGA decision making about post-market safety, or about the processes involved makes it difficult to assess whether there is a rational basis for the differences seen in this dissertation.

6.4 Implications for future research

Research conducted for the FDA has provided insights into how consumers and prescribers responded to FDA warnings for two sedative drugs.[69,90] Some of these findings may be generalisable to other regulators. However, similar studies may be warranted in Australia, where cultural differences have been demonstrated in prescriber perceptions of regulators and the perceived accessibility of their advisories; and Australian and US consumers are also likely to differ. However, it is equally important that existing research be applied in the approaches to communication within policy as outlined above.

Appropriate ways to involve consumers and clinicians in decisions about post-market safety could also be examined, for example whether using deliberative participatory approaches

such as citizens juries would be appropriate for post-market safety decision making. As noted, in Chapter 2, the UK's National Institute for Health and Care Excellence (NICE) has a Citizens Council which is an independent body which can be consulted on a range of matters using a deliberative approach to inform participants and better understand community perspectives.

The reliance on industry to perform studies about the safety of their own products and to communicate their results is concerning, and it is important that research be conducted to confirm whether such studies produce reliable and relevant results, using approaches similar to assessing the impacts of conflicts of interest in other literature.[41]

The TGA has been little studied in general, with no previous examination of policy for safety communication identified. Additional research is required to better characterise the TGA's approach to safety communication in order to explain its lower rates of advisories, and the time lags associated with those communications. In addition, qualitative studies to examine regulatory culture and decision making could provide helpful context to quantitative findings, such as those conducted for the FDA and other regulators.[4,91]

6.5 Conclusion

This thesis provides important new information about the use of regulatory safety advisories and their underlying policy basis for four regulatory agencies. These questions have not been assessed previously using comparative methods and there has been little investigation of the TGA's communications efforts.

The fundamental question addressed by this thesis relates to whether regulation supports the most effective means of communication about post-market safety. To communicate effectively, regulators need adequate legislative authority and policies, the capacity and capability to communicate risk successfully, and the means to influence clinical decision making by prescribers. The role of industry in such communications requires careful

consideration and may require some regulators to change their approach to reliance on manufacturers for disseminating safety messages.

Considerable differences between Australia and other regulators exist, and while some may relate to differences in the nature of healthcare provision and governance in Australia, others may be cultural, discretionary or historical. Whether Australian health professionals and consumers have access to the information they need to make decisions about the risks and benefit of medicines use requires further assessment. The gap between risk communication science, regulatory requirements and real-world use of safety communications for all regulators requires further investigation.

6.6 References

1. European Parliament and Council of Ministers. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of the European Union, 2010.
2. European Parliament and Council of Ministers. Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance. Official Journal of the European Union, 2010.
3. European Commission. Commission staff working document. Accompanying document to the Proposal for a regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency and the Proposal for a directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Brussels: Commission of the European Communities, 2008.
4. Herder M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. *Milbank Q* 2019; epub ahead of print.
5. Perry LT, Bhasale A, Fabbri A, et al. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiol Drug Saf* 2020; 29: 1054-1063. DOI: 10.1002/pds.5072.
6. Buckley NA and Rossi S. Bringing greater transparency to "black box" warnings. *Clin Toxicol (Phila)* 2011; 49: 448-451.
7. U.S. Department of Health and Human Services Food and Drug Administration. *FDA's application of statutory factors in determining when a REMS is necessary. Guidance for industry. Draft Guidance.* Maryland: FDA, 2016.
8. Perry LT, Bhasale A, Fabbri A, et al. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med* 2019; 179: 982-984. 2019/04/30. DOI: 10.1001/jamainternmed.2019.0294.

9. Maor M. Organizational Reputations and the Observability of Public Warnings in 10 Pharmaceutical Markets. *Governance* 2011; 24: 557-582. DOI: 10.1111/j.1468-0491.2011.01536.x.

10. Sansom L, DeLaat W and Horvath J. Review of Medicines and Medical Devices Regulation. Report on the regulatory framework for medicines and medical devices., http://www.health.gov.au/internet/main/publishing.nsf/content/expert-review-of-medicines-and-medical-devices-regulation#review (2015).

11. Napp Pharmaceuticals Limited. *Invokana - Summary of Product Characteristics.* . Updated 13 Sep 2018. UK.

12. Janssen Pharmaceutical Companies. INVOKANA (canagliflozin). Revised 07/2017. Maryland: U.S. Food and Drug Administration, 2017.

13. Califf RM and Kramer JM. The balance of benefit and safety of rosiglitazone: important lessons for our system of drug development and postmarketing assessment. *Pharmacoepidemiol Drug Saf* 2008; 17: 782-786. Comment.

14. Mullard A. Mediator scandal rocks French medical community. *The Lancet* 2011; 377: 890-892. DOI: 10.1016/s0140-6736(11)60334-6.

15. Waxman HA. The Lessons of Vioxx — Drug Safety and Sales. *New England Journal of Medicine* 2005; 352: 2576-2578. DOI: 10.1056/nejmp058136.

16. Kesselheim AS and Avorn J. The role of litigation in defining drug risks. *Journal of the American Medical Association* 2007; 297: 308-311. Note. DOI: 10.1001/jama.297.3.308.

17. Krumholz HM, Ross JS, Presler AH, et al. What have we learnt from Vioxx? *BMJ* 2007; 334: 120-123. 2007/01/20. DOI: 10.1136/bmj.39024.487720.68.

18. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry postmarketing adverse experience reporting for human drug and licensed biological products: Clarification of what to report. Maryland: FDA, 1997.

19. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry. Postmarketing studies and clinical trials — implementation of section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. Maryland: FDA, 2011.

20. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry. Safety labeling changes — implementation of section 505(o)(4) of the FD&C Act. Maryland: FDA, 2013.

21. Darrow JJ, Avorn J and Kesselheim AS. Speed, Safety, and Industry Funding — From PDUFA I to PDUFA VI. *New England Journal of Medicine* 2017; 377: 2278-2286. DOI: 10.1056/NEJMhle1710706.

22. European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3)*. EMA/118465/2012 Rev 1 ed. Amsterdam: EMA, 2017.

23. European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)*. EMA/204715/2012 Rev 2* ed. Amsterdam: EMA, 2017.

24. European Medicines Agency and Heads of Medicines Agencies. *Guideline on good pharmacovigilance practices (GVP). Module XV – Safety communication.* 2013. London: EMA with HMA.

25. European Medicines Agency and Heads of Medicines Agencies. *Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2)*. 2013. London: EMA with HMA.

26. Health Canada. Amendments to the Food and Drugs Act: Guide to New Authorities (power to require and disclose information, power to order a label change and power to order a recall), https://www.canada.ca/en/health-canada/services/drugs-health-products/legislation-guidelines/amendments-food-drugs-act-guide-new-authorities-power-require-disclose-information-power-order-label-change-power-order-recall.html (2017, accessed **1 Aug 2019**).

27. Australian Government Department of Health Therapeutic Goods Administration. *Risk management plans for medicines and biologicals Australian requirements and recommendations*. Version 3.1, November 2017 ed. Woden, ACT: Commonwealth of Australia, 2017.

28. Australian Government Department of Health Therapeutic Goods Administration. Pharmacovigilance responsibilities of medicine sponsors. Australian recommendations and requirements. Version 2.0 September 2017 ed. ACT: TGA, 2017.

29. Anonymous. The reorganisation of European pharmacovigilance. Part 2. From spontaneous reports to agency reviews and decisions. *Prescrire International* 2014; 34: 692-697. Review.

30. Anonymous. European pharmacovigilance: increasingly outsourced to drug companies. *Prescrire International* 2014; 34: 536-544.

31. Lexchin J. Health Canada and drug safety: how safe are we? *Public profits vs private policy*. Toronto: University of Toronto Press, 2016.

32. Panel to Review the Transparency of the Therapeutic Goods Administration. Review to improve the transparency of the Therapeutic Goods Administration. Final Report. ACT: Commonwealth of Australia, 2011.

33. Li R, Curtis K, Zaidi STR, et al. Effect of the black triangle scheme and its online educational campaign on the quantity and quality of adverse drug event reporting in Australia: a time series analysis. *Expert Opinion on Drug Safety* 2020; 19: 747-753. Article. DOI: 10.1080/14740338.2020.1746762.

34. Klein K, Scholl JHG, De Bruin ML, et al. When More Is Less: An Exploratory Study of the Precautionary Reporting Bias and Its Impact on Safety Signal Detection. *Clin Pharmacol Ther* 2018; 103: 296-303. Article. DOI: 10.1002/cpt.879.

35. Hoekman J, Klamer TT, Mantel-Teeuwisse AK, et al. Characteristics and follow-up of postmarketing studies of conditionally authorized medicines in the EU. *British Journal of Clinical Pharmacology* 2016; 82: 213-226. Article. DOI: 10.1111/bcp.12940.

36. Woloshin S, Schwartz LM, White B, et al. The Fate of FDA Postapproval Studies. *New England Journal of Medicine* 2017; 377: 1114-1117. DOI: 10.1056/nejmp1705800.

37. United States Government Accountability Office. Drug safety. FDA expedites many applications, but data for postapproval oversight need improvement. In: Office USGA, (ed.). Washington: GAO, 2015.

38. Engel P, Almas MF, De Bruin ML, et al. Lessons learned on the design and the conduct of Post-Authorization Safety Studies: review of 3 years of PRAC oversight. *British Journal of Clinical Pharmacology* 2017; 83: 884-893. DOI: https://doi.org/10.1111/bcp.13165.

39. European Medicines Agency. *PRAC assessment report. Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data. SGLT2*

inhibitors and lower limb amputation (canagliflozin, dapagliflozin, empagliflozin-containing medicines). 2017. London: EMA.

40. European Medicines Agency. *Assessment report. Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data. SGLT2 inhibitors*. London: EMA, 2016.

41. Lundh A, Lexchin J, Mintzes B, et al. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017. DOI: 10.1002/14651858.MR000033.pub3.

42. US Food and Drug Administration Center for Drug Evaluation and Research. Approval Package for: APPLICATION NUMBER: 204042Orig1s026 Trade Name: INVOKANA Generic Name: Canagliflozin. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/204042Orig1s026.pdf (2017, accessed 02/06/2019).

43. Bhasale AL, Sarpatwari A, De Bruin ML, et al. Postmarket safety communication for protection of public health: A comparison of regulatory policy in Australia, Canada, the European Union, and the United States. *Clin Pharmacol Ther* 2020 2020/08/09. DOI: 10.1002/cpt.2010.

44. Wiktorowicz ME. Emergent patterns in the regulation of pharmaceuticals: institutions and interests in the United States, Canada, Britain, and France. *J Health Polit Policy Law* 2003; 28: 615-658. 2003/09/06.

45. de Vries ST, van der Sar MJM, Cupelli A, et al. Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences. *Drug Saf* 2017; 40: 729-742. Article. DOI: 10.1007/s40264-017-0535-0.

46. Mollebaek M, Kaae S, De Bruin ML, et al. The effectiveness of direct to healthcare professional communication - A systematic review of communication factor studies. *Res Social Adm Pharm* 2019; 15: 475-482. Review. DOI: 10.1016/j.sapharm.2018.06.015.

47. Møllebæk M and Kaae S. Why do general practitioners disregard direct to healthcare professional communication? A user-oriented evaluation to improve drug safety communication. *Basic Clin Pharmacol Toxicol* 2021; 128: 463-471. DOI: https://doi.org/10.1111/bcpt.13516.

48. Torka M, Mintzes B, Bhasale A, et al. Secret safety warnings on medicines: A case study of information access requests. *Pharmacoepidemiol Drug Saf* 2019; 28: 551-555. 2019/03/07. DOI: 10.1002/pds.4762.

49. Weatherburn CJ, Guthrie B, Dreischulte T, et al. Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: Systematic review, time series analysis and meta-analysis. *Br J Clin Pharmacol* 2019 2019/08/30. DOI: 10.1111/bcp.14104.

50. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care* 2012; 50: 466-478. DOI: 10.1097/MLR.0b013e318245a160.

51. Piening S, Haaijer-Ruskamp FM, de Vries JT, et al. Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf* 2012; 35: 373-385. DOI: 10.2165/11599100-000000000-00000.

52. Way D, Blazsin H, Löfstedt R, et al. Pharmaceutical Benefit–Risk Communication Tools: A Review of the Literature. *Drug Saf* 2017; 40: 15-36. Review. DOI: 10.1007/s40264-016-0466-1.

53. Schwartz LM, Woloshin S and Welch HG. Using a drug facts box to communicate drug benefits and harms: two randomized trials. *Annals of internal medicine* 2009; 150: 516-527. 2009/02/18. DOI: 10.7326/0003-4819-150-8-200904210-00106.

54. Schwartz LM, Woloshin S, Andrews A, et al. Influence of medical journal press releases on the quality of associated newspaper coverage: retrospective cohort study. *BMJ* 2012; 344: d8164. DOI: 10.1136/bmj.d8164.

55. Schwartz L and Woloshin. S. *FDA and the media: Lessons from Tysabri about communicating uncertainty.* 2015. Washington: National Academy of Medicine.

56. Schwartz LM and Woloshin S. The Drug Facts Box: Improving the communication of prescription drug information. *Proc Natl Acad Sci U S A* 2013; 110 Suppl 3: 14069-14074. 2013/08/13. DOI: 10.1073/pnas.1214646110.

57. Einarson A, Schachtschneider AK, Halil R, et al. SSRI'S and other antidepressant use during pregnancy and potential neonatal adverse effects: impact of a public health advisory and subsequent reports in the news media. *BMC Pregnancy Childbirth* 2005; 5: 11. 2005/05/24. DOI: 10.1186/1471-2393-5-11.

58. DeFrank JT, McCormack L, West SL, et al. Unintended Effects of Communicating About Drug Safety Issues: A Critical Review of the Literature. *Drug Saf* 2019; 42: 1125-1134. Review. DOI: 10.1007/s40264-019-00840-3.

59. Kesselheim AS, McGraw SA, Dejene SZ, et al. Patient and Physician Perceptions of Drug Safety Information for Sleep Aids: A Qualitative Study. *Drug Saf* 2017; 40: 531-542. Article. DOI: 10.1007/s40264-017-0516-3.

60. Mollebaek M and Kaae S. Why do general practitioners disregard *direct to healthcare professional communication*? A user-oriented evaluation to improve drug safety communication. 2021.

61. Sieluk J, Palasik B, dosReis S, et al. ADHD medications and cardiovascular adverse events in children and adolescents: cross-national comparison of risk communication in drug labeling. *Pharmacoepidemiol Drug Saf* 2017; 26: 274-284. DOI: 10.1002/pds.4164.

62. UpToDate. 2021.

63. United States Government Accountability Office. Drug safety. FDA has begun efforts to enhance postmarket safety, but additional actions are needed. In: Office USGA, (ed.). Washington: GAO, 2009.

64. Fain K, Daubresse M and Alexander G. The Food and Drug Administration Amendments Act and postmarketing commitments. *JAMA* 2013; 310: 202-204. DOI: 10.1001/jama.2013.7900.

65. Goedecke T, Morales DR, Pacurariu A, et al. Measuring the impact of medicines regulatory interventions - Systematic review and methodological considerations. *Br J Clin Pharmacol* 2017 2017/11/07. DOI: 10.1111/bcp.13469.

66. Briesacher BA, Soumerai SB, Zhang F, et al. A critical review of methods to evaluate the impact of FDA regulatory actions. *Pharmacoepidemiol Drug Saf* 2013; 22: 986-994. Article. DOI: 10.1002/pds.3480.

67. European Medicines Agency and Heads of Medicines Agencies. *Guideline on good pharmacovigilance practices – Product- or population-specific considerations I: Vaccines for prophylaxis against infectious diseases* 2013. London: EMA

68. European Medicines Agency and Heads of Medicines Agencies. *Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations IV: Paediatric population*. 2018. London: EMA

69. Kesselheim AS, Sinha MS, Campbell EG, et al. Multimodal Analysis of FDA Drug Safety Communications: Lessons from Zolpidem. *Drug Saf* 2019; 42: 1287-1295. Article. DOI: 10.1007/s40264-019-00849-8.

70. U.S. Department of Health and Human Services Food and Drug Administration. *Communicating risks and benefits: An evidence-based user's guide*. Maryland: FDA, 2011.

71. Council of Canadian Academies. *Health product risk communication: Is the message getting through? The Expert Panel on the effectiveness of health product risk communication*. 2015. Ottawa: Council of Canadian Academies.

72. Australian Government Department of Health Therapeutic Goods Administration. TGA Reforms: a blueprint for TGA's future. Progress report as at 31 December 2014. In: TGA, (ed.). ACT: Commonwealth of Australia, 2015.

73. United States Department of Health and Human Services Office of Inspector General. *FDA lacks comprehensive data to determine whether risk evaluation and mitigation strategies improve drug safety*. 2013. Washington: US Department of Health and Human Services.

74. Frau S, Font Pous M, Luppino MR, et al. Risk Management Plans: are they a tool for improving drug safety? *Eur J Clin Pharmacol* 2010; 66: 785-790. journal article. DOI: 10.1007/s00228-010-0848-8.

75. Davis C and Abraham J. A comparative analysis of risk management strategies in European Union and United States pharmaceutical regulation. *Health Risk & Society* 2011; 13: 413-431. DOI: 10.1080/13698575.2011.596191.

76. Australian Government Department of Health and Ageing Therapeutic Goods Administration. Trans-Tasman early warning system. Processes in Australia and New Zealand. Version 1.0 ed. ACT: TGA, 2013.

77. Australian Institute of Health and Welfare. *Health expenditure Australia 2018–19. Health and welfare expenditure series no.66. Cat. no. HWE 80.* . Canberra: AIHW, 2020.

78. OECD Health Statistics. Chapter 10. Pharmaceutical Sector. Figure 10.2. Expenditure on retail pharmaceuticals per capita, 2015 (or nearest year). *Health at a Glance 2017: OECD indicators.*: OECD Publishing, 2016.

79. Herder M. Toward a Jurisprudence of Drug Regulation. *Journal of Law Medicine & Ethics* 2014; 42: 244-262. DOI: 10.1111/jlme.12139.

80. Herder M. Reinstitutionalizing transparency at Health Canada. *Can Med Assoc J* 2016; 188: 218-219. DOI: 10.1503/cmaj.150765.

81. Sharfstein JM, Miller JD, Davis AL, et al. Blueprint for Transparency at the U.S. Food and Drug Administration: Recommendations to Advance the Development of Safe and Effective Medical Products. *The Journal of Law, Medicine & Ethics* 2017; 45: 7-23. DOI: 10.1177/1073110517750615.

82. Fabbri A, Parker L, Colombo C, et al. Industry funding of patient and health consumer organisations: systematic review with meta-analysis. *BMJ* 2020; 368: l6925. DOI: 10.1136/bmj.l6925.

83. Sismondo S. How to make opinion leaders and influence people. *Can Med Assoc J* 2015: cmaj.150032. DOI: 10.1503/cmaj.150032.

84. Lexchin J. Association between commercial funding of Canadian patient groups and their views about funding of medicines: An observational study. *PLOS ONE* 2019; 14: e0212399. DOI: 10.1371/journal.pone.0212399.

85. Bahri P and Castillon Melero M. Listen to the public and fulfil their information interests - translating vaccine communication research findings into guidance for regulators. *Br J Clin Pharmacol* 2018; 84: 1696-1705. 2018/03/25. DOI: 10.1111/bcp.13587.

86. United States Department of Health and Human Services Office of Inspector General. *FDA's Risk Evaluation and Mitigation Strategies: Uncertain effectiveness in addressing the opioid crisis*. 2020. Washington: US Department of Health and Human Services.

87. Rollman JE, Heyward J, Olson L, et al. Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products. *JAMA* 2019; 321: 676-685. DOI: 10.1001/jama.2019.0235.

88. Dal Pan GJ. Gauging the Effectiveness of Medicines Safety Communications From Global Regulatory Agencies. *JAMA Internal Medicine* 2019. DOI: 10.1001/jamainternmed.2019.0266.

89. Paschke A, Dimancesco D, Vian T, et al. Increasing transparency and accountability in national pharmaceutical systems. *Bull World Health Organ* 2018; 96: 782-791. 2018/11/21. DOI: 10.2471/blt.17.206516.

90. Kesselheim AS, Campbell EG, Schneeweiss S, et al. Methodological approaches to evaluate the impact of FDA drug safety communications. *Drug Saf* 2015; 38: 565-575. Article. DOI: 10.1007/s40264-015-0291-y.

91. Tafuri G, Stolk P, Trotta F, et al. How do the EMA and FDA decide which anticancer drugs make it to the market? A comparative qualitative study on decision makers' views. *Annals of Oncology* 2014; 25: 265-269. DOI: 10.1093/annonc/mdt512.

Appendix 1 - Additional related publications

The studies below were conducted as part of the SAFER Project funded by the NHMRC and CIHR, of which my research was also a part. A core aspect of the SAFER Project was the development of a database of safety advisories issued by the MHRA, Health Canada, the FDA and the TGA between 1 Jan 2007 and 31 December 2016.

I participated in the development of the database by assisting in the development of the database and the development of the initial coding framework. This database was used in studies 1 – 4 below.

For study 1 (Torka et al), I identified the advisories without Australian equivalents from the SAFER database. This list was included in the Freedom of Information request and determined which companies should be contacted. I also wrote and submitted the FOI request and managed communications with the regulator. I contributed to limited aspects of the analysis and provided comments on the written article.

In studies 2 and 3 (Perry et al 2019 and Perry et al 2020) I participated in coding and writing of the manuscripts.

For study 4 (Hooimeyer et al), I extracted data to identify the cardiac advisories to be studied and played a key role in designing the content questionnaire used, along with Lucy Perry. I also carried out pilot testing with multiple coders, and revised the questionnaire based on the results. With Lucy Perry I developed the questionnaire in RedCap and participated in initial coding, and reviewed drafts of the article.

1. Torka M, Mintzes B, Bhasale A, Fabbri A, Perry L, and Lexchin J. Secret safety warnings on medicines: A case study of information access requests. *Pharmacoepidemiol Drug Saf* 28: 551-555, 2019.

2. Perry LT, Bhasale A, Fabbri A, Lexchin J, Puil L, Joarder M, and Mintzes B. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med* 179: 982-984, 2019.

3. Perry LT, Bhasale A, Fabbri A, Lexchin J, Puil L, Joarder M, and Mintzes B. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiol Drug Saf* 29: 1054-1063, 2020.

4. Hooimeyer A, Bhasale A, Perry L, Fabbri A, Mohammad A, McEwin E, and Mintzes B. Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. *Pharmacology Research & Perspectives* 8: e00680, 2020.

APPENDIX 1.1

Torka M, Mintzes B, Bhasale A, Fabbri A, Perry L, and Lexchin J. Secret safety warnings on medicines: A case study of information access requests. ***Pharmacoepidemiol Drug Saf*** **28: 551-555, 2019.**

Received: 19 November 2018 | Revised: 14 January 2019 | Accepted: 11 February 2019

DOI: 10.1002/pds.4762

BRIEF REPORT

WILEY

Secret safety warnings on medicines: A case study of information access requests

Marc Torka[1,2] | Barbara Mintzes[1] | Alice Bhasale[1] | Alice Fabbri[1] | Lucy Perry[1] | Joel Lexchin[3]

[1] School of Pharmacy, Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney, Sydney, Australia

[2] Department of Sociology, Macquarie University, Sydney, Australia

[3] Faculty of Health, York University, Toronto, Canada

Correspondence
B. Mintzes, 6W75, The Hub, Charles Perkins Centre D17, The University of Sydney, NSW 2006 Australia.
Email: barbara.mintzes@sydney.edu.au

Funding information
National Health and Medical Research Council, Grant/Award Number: APP1122332; Canadian Institutes of Health Research, Grant/Award Number: 378588

Abstract

Purpose: There has been less attention to the transparency of postmarket evidence of harmful effects of medicines than of premarket clinical trial data. This is a case study of requests for Australian "direct health professional communications" (DHPCs). These letters are used by regulators and manufacturers to inform clinicians of emergent evidence of harm. DHPCs are not made public by Australia's Therapeutic Goods Administration (TGA).

Methods: We requested all DHPCs sent out in Australia from 2007 to 2016 inclusive for 207 drugs that were subject to safety advisories over this decade in Canada, the United Kingdom, and/or the United States. We contacted 39 manufacturers (February to May 2018), with repeat requests to nonrespondents, and a follow-up freedom-of-information (FOI) request to the TGA.

Results: Fifteen companies provided information, either sending DHPCs (n = 4, on five drugs) or affirming none were sent out (n = 11). The remaining 24 of 39 (62%) companies did not provide DHPCs: nine (23%) refused the request, often citing commercial confidentiality; the rest provided no answer despite repeat requests. In total, we had no information for 170 of 207 (82%) of the drugs. Our FOI request to the TGA was unsuccessful.

Conclusions: Our experience highlights unacceptable secrecy concerning safety warnings previously sent to thousands of Australian clinicians. In the absence of explicit regulatory policy supporting disclosure, companies differed in their response. These letters warn of serious and often life-threatening harm and guide safer care; full ongoing public access is needed, ideally in searchable online databases.

KEYWORDS

access to information, drug-related side effects and adverse reactions, pharmacoepidemiology, pharmacovigilance, policy-making, risk communication

Marc Torka and Barbara Mintzes contributed equally to this article and are joint first authors.

Barbara Mintzes presented a preliminary version of this study at a seminar on *Regulation of Medicines, Commercial Bias and Public Safety* at the Charles Perkins Centre, University of Sydney, on May 3, 2018.

1 | INTRODUCTION

Secrecy about serious harmful effects of medicines has no place in modern medicine and should not be accepted by regulatory agencies. Adverse effects are a frequent cause of emergency department visits[1] and hospital admissions,[2] and improved access to information about harms of medicines may help reduce these events. However, regulatory approaches to transparency of evidence on the safety of medicines remain inconsistent. Within this context, a recent experience with a request for safety letters in Australia is described below.

1.1 | The need for transparency

Selective publication of premarket clinical trials is a recognised threat to public health and to the integrity of scientific evidence.[3] Although access remains imperfect, many gains have been made to transparency, including clinical trial registries and data platforms.[4] There has been less attention to the need for transparency about emergent postmarket evidence of harmful effects of medicines. With, on average, 1000 to 3000 participants in premarket studies, which are often of short durations,[5] it is unsurprising that evidence of rare or longer-term harm often emerges only after market approval. More rapid drug approvals and provisional approval pathways compound the problem of restricted premarket exposure.[6]

Seventeen medicines eventually withdrawn for safety reasons were prescribed 112 million times in the United States (US) prior to withdrawal.[7] Safer treatment options existed in most cases, suggesting inadequate physician awareness of mounting evidence of harm despite most having been subject to prior US black box warnings[8] or safety advisories.[9]

National drug regulatory agencies regularly issue safety advisories to warn professionals and the public of new evidence of harm. These warnings often provide practical advice, such as dose reductions or cautions about at-risk patients. Individually addressed "dear health professional letters" or "direct health professional communications" (DHPCs) are a commonly used communication tool. Manufacturers usually distribute DHPCs following regulatory review, which may be explicitly noted. For example, Health Canada often releases letters jointly with manufacturers. There has been increased harmonisation of DHPCs in the European Union (EU) and most EU regulators post DHPCs on their websites (De Bruin, ML, personal communication, September 2018). With the introduction of Risk Evaluation and Mitigation Strategies (REMS) in the US in 2007,[10] the US Food and Drug Administration (FDA) has switched to publishing DHPCs on its website as a REMS component for drugs with REMS (https://www.accessdata.fda.gov/scripts/cder/rems/). The FDA uses DHPCs less often as a communication tool than web-based safety alerts.

2 | METHODS

Our team is carrying out research on postmarket regulatory safety warnings in Australia, Canada, the United Kingdom (UK), and the US from 2007 to 2016,[11] with the aim of examining consistency of safety warnings among countries. Within this study, we identified lower numbers of advisories in Australia than in the other included countries.

Unlike many regulators, the Australian Therapeutic Goods Administration (TGA) does not post DHPCs on its website.[12] We therefore contacted TGA personnel to request copies of these letters and were informed that the TGA has no central file. We were advised to request DHPCs from the manufacturers of drugs that were subject to warnings in the other countries in our study, followed by a freedom of information (FOI) request to the TGA if required. We pursued this strategy after exhausting other avenues such as drug information services.

We identified 207 drugs from 39 companies with no publicly available Australian safety advisories from January 1, 2007, to December 31, 2016, although regulators in Canada, the UK, and/or the US had issued advisories during this time period (Appendix S1). We excluded drugs with multiple generic versions and/or for which the originator drug was unclear or no longer available. Our team contacted the Australian branch of the 39 companies by email (38) or telephone (1) from February to May 2018. We sent out a repeat request to nonrespondents 2 weeks later, with further email and phone contacts to clarify initial responses. We have included all company responses received up to January 1, 2019.

KEY POINTS

- There has been less attention to the need for transparency about postmarket evidence of harmful effects of medicines than for premarket clinical trial data.
- "Direct health professional communications" (DHPCs) are a key tool used by regulators and manufacturers to inform clinicians about postmarket safety warnings. In Australia, DHPCs are not publicly accessible.
- We requested DHPCs for 207 drugs from 39 manufacturers; 15 companies provided information; 24 (62%) did not, several citing commercial confidentiality.
- Our experience highlights the need for explicit transparency policies on postmarket safety communication to ensure public access to information needed for safe prescribing and medicine use.

3 | RESULTS

3.1 | Pharmaceutical companies' responses to our requests

In the absence of a clear Australian disclosure policy for DHPCs, companies' responses varied (Table 1). In total, 24 of 39 (61.5%) companies did not provide DHPCs or clarify if they existed. Appendix S1 lists the companies and brands for which we requested information, organised according to company response.

TABLE 1 Company responses

	Response Type	Information Provided	Companies n = 39 (%)	Examples of Company Responses
No information (n = 24)	Refuse	Nondisclosure	9 (23.1)	• The documents you have requested are confidential. • Dear HCP letters not readily available through the TGA are not provided to the general public by [company]. • Unfortunately, we are unable to disclose such information for research purposes as they are Commercial in Confidence. • The safety advice outlined in these communications may be out of date, and was intended for a specific audience at the date of distribution. • With respect to your request, I have referred this to relevant [company] personnel and wish to advise that [company] will not be providing you with copies of any safety notices in relation to [products] sent directly to healthcare professionals in the period 2007 to 2016. • [Company] have investigated the feasibility of providing this information and unfortunately we are unable to fulfil your request. • We appreciate the research that you are conducting … however, currently, we are unable to prioritise answering your request due to our limited resources. • Unfortunately we are unable to assist you any further.
	Ignore	No answer	7 (17.9)	• No reply or automatic return email stating "We will get back to you soon"
	Delay	No further answer	5 (12.8)	• I have been advised that your project is being discussed by management and they will get back to you with a decision soon • I will discuss with the central safety team and get back to you. • The process involved in obtaining this information is quite lengthy and we are working on obtaining information that you require.
	Deflect	No further answer—refers to TGA	3 (7.7)	• Any [company] letters distributed to Health Care Professionals about emergent adverse drug reactions or newly identified safety concerns are done in consultation with the TGA, and information relating to these issues are accessible on the TGA website.
Information provided (n = 15)	Agree	Confirms no letters were sent	11 (28.2)	• I have been informed by our Medical Director that no new letter on [product] has been sent to the healthcare professionals (HCPs) recently. • HQ confirmed that there was no DHCP letter issued in 2007-2016.
	Agree	Letters provided	4 (10.3)	• We have reviewed the "Dear Health Care Professional" letters regarding safety concerns between 2007-2016 for [products]. There were two identified safety communications meeting these inclusion criteria. Copies of these letters are attached.

Among the 24 companies who did not provide DHPCs, the most common response was to *refuse* our request (n = 9; 23.1%). These nine companies referred to the information in DHPCs as "commercial in confidence" or "not provided to the general public." One stated that the information was "intended for a specific audience at the date of distribution" and "may be out of date" despite the research context behind our request. Three companies simply refused to provide information without a rationale.

Seven companies (17.9%) *ignored* our request, either via an automatic email reply ("We will get back to you soon") or *no answer* despite a repeat request. An additional five companies (12.8%) promised to process our request but provided *no further answer* to follow-up requests. Some companies referred to complex internal decision-making, such as the need for discussion with international headquarters. In one case, fulfilling our request was deemed too "lengthy" a process.

Three companies (7.7%) referred us back to the TGA. One company stated that "Any [company] letters distributed to Health Care Professionals about emergent adverse drug reactions or newly identified safety concerns are done in consultation with the TGA, and information relating to these issues are accessible on the TGA website." Another deflected responsibility to the TGA: "… Please also note that a copy of each DHCP letter has been sent to the TGA, who you may wish to contact."

Fifteen companies (38.5%) provided a clear answer to our request. We received eight DHPCs from four companies, on five products. The remaining 11 companies confirmed that no DHPCs were sent out.

In three cases, companies requested our research protocol before replying. Although we sent the protocol, only one of the three provided us with the requested information.

3.2 | Unsuccessful freedom of information request

Following our requests to companies, we submitted an FOI request to the TGA for remaining missing information, as advised by the TGA. After an initial refusal, we restricted the time frame of requested letters. The

TGA again refused: "Specifically the work involved in processing your request would substantially and unreasonably divert resources of the TGA from its other operations."[13]

4 | DISCUSSION

The idea that a warning letter that has gone out to thousands of individual health professionals would be considered confidential is counterintuitive. However, as is described above, this is the situation we encountered when we tried to obtain Australian DHPCs. In total, we received no response about whether a safety letter was issued in Australia for 170 of 207 (82.1%) of the drugs subject to publicly available advisories in Canada, the UK, or the US. We were also unable to obtain missing letters directly from the TGA through an FOI request.

Among the nine companies that refused to provide DHPCs (Appendix S1), eight are included in a 2016 audit of company transparency policies.[14] Seven have committed to registering all trials, all eight share summary trial results, and all have policies to share Clinical Study Reports and individual patient data. Current standards for clinical trial transparency, albeit incompletely implemented, stand in stark contrast to these companies' Australian subsidiaries' refusal to share safety warnings.

We suspect that this inconsistency reflects the limited attention thus far to the need for full disclosure of postmarket evidence on medicine safety. Many regulators, including the TGA, allow public access to adverse drug reaction databases. However, the Periodic Safety Update Reports (PSURs) required for new drugs are generally not made public. The EMA supports access to PSURs, but only on request.[15] Health Canada publishes summary safety reports, but only releases the full report on request. A report provided in 2017 in response to a request had 39 of 61 pages extensively redacted.[16]

In our opinion, a one-time mailing of a DHPC to a clinician, otherwise inaccessible, provides inadequate warning. Clinicians may overlook a mailing or forget its contents. Not all DHPCs lead to changes in product information. Piecemeal public access to communication of harms is inconsistent with the potentially lifesaving role of this communication. The safety advisories issued in the other countries often described serious and, in some cases, fatal adverse events.

5 | CONCLUSIONS AND RECOMMENDATIONS

Our experience highlights unacceptable company and regulatory secrecy concerning safety warnings previously sent to thousands of Australian clinicians. These letters often warn of serious harm and aim to guide prescribing and medicine use. Although the TGA treats DHPCs as manufacturers' property, several companies stressed joint development. The TGA does not have legislated authority over DHPCs,[17] and no public information describes the extent of the TGA's role in initiating them.

The varied response we received from manufacturers reflects a policy vacuum, in which companies are free to choose whether or not to release DHPCs. This is unacceptable from a public health perspective. Stronger, well-defined limits to commercial confidentiality are needed. A secret warning is no warning at all. To ensure ongoing access to critical safety information, a searchable online database of all postmarket safety warnings on medicines, including DHPCs, should be made publicly available.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

ACKNOWLEDGEMENTS

Funding for our team's research on regulatory safety advisories was provided by the National Health and Medical Research Council, Australia, grant number App1122332, and the Canadian Institutes of Health Research, grant number 378588.

CONFLICT OF INTEREST

B.M. was retained as an expert witness in 2015 and 2016 by the law firm representing the plaintiffs in an application for a Canadian class action on cardiovascular risks of testosterone supplements. L.P. is an employee of George Clinical, a clinical research organisation, run by the George Institute for Global Health. George Clinical receives funding for conduct of clinical trials from various pharmaceutical companies. In 2015-2018, J.L. was a paid consultant on three research projects, on indication-based prescribing (US AHRQ funding), conservative diagnosis (Gordon and Betty Moore Foundation) and a publicly funded Ontario GP formulary. He was a paid panel member on Pharmacare in Canada (Canadian Institute, non-profit) and was paid to write a brief for a law firm. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. None of the other authors have any competing interests to declare.

AUTHOR'S CONTRIBUTION

M.T. and B.M. jointly carried out the analysis, prepared initial and consecutive drafts of the paper, and are joint first authors. M.T. carried out data collection. All authors provided conceptual input on design, analysis, and reporting, edited drafts of this article, and approved the final version. B.M. is guarantor.

ORCID

Barbara Mintzes https://orcid.org/0000-0002-8671-915X

REFERENCES

1. Zed PJ, Abu-Laban RB, Balen RM, et al. Incidence, severity and preventability of medication related visits to the emergency department: a prospective study. *CMAJ*. 2008;178(12):1563-1569.
2. Phillips AL, Nigro O, Macolini KA, et al. Hospital admissions caused by adverse drug events: an Australian prospective study. *Aust Health Rev*. 2013;38(1):51-57.
3. Lemmens T. Pharmaceutical knowledge governance: a human rights perspective. *J Law Med Ethics*. 2013;41(1):163-184.

4. Goldacre B. How to get all trials reported: audit, better data, and individual accountability. *PLoS Med*. 2015;12(4):e1001821.

5. Moore TJ, Furberg CD. Development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the US FDA. *JAMA Intern Med*. 2014;174(1):90-95.

6. Arnardottir AH, Haaijer-Ruskamp FM, Straus SMJ, Eichler HG, deGraeff PA, Mol PGM. Additional safety risk to exceptionally approved drugs in Europe? *Br J Clin Pharmacol*. 2011;72(3):490-499.

7. Saluja S, Woolhandler S, Himmelstein DU, Bor D, McCormick D. Unsafe drugs were prescribed more than one hundred million times in the United States before being recalled. *Int J Health Serv*. 2016;46(3):523-530.

8. Frank C, Himmelstein DU, Woolhandler S, et al. Era of faster FDA drug approvals has also seen increased black-box warnings and market withdrawals. *Health Aff*. 2014;33(8):1453-1459.

9. U.S. Food and Drug Administration. Index to drug-specific information. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111085.htm. Accessed January 2019.

10. Rodriguez-Monguio R, Spielberger K, Seoane-Vasquez E. Examination of risk evaluation and mitigation strategies and drug safety in the US. *Res Soc Admin Pharmacy*. 2014;10:232-238.

11. National Health and Medical Research Council (NHMRC) grant, University of Sydney. How best to protect public health: a comparative analysis of regulatory safety warnings on medicines in Australia, Canada, the European Union and the United States. Available at: http://purl.org/au-research/grants/nhmrc/1122332 accessed September 2018.

12. Australian Government Department of Health, Therapeutic Goods Administration (TGA). TGA approach to disclosure of commercially confidential information (CCI). Version 1.1. May 2014. Available at: https://www.tga.gov.au/sites/default/files/regulation-basics-disclosure-cci-140514.pdf accessed September 2018.

13. Pegg, G. A/g Head, Pharmacovigilance and Special Access Branch. Therapeutic Goods Administration. Freedom of Information Request FOI 832-1819. Notice of Decision. Letter to Dr Barbara Mintzes. Oct 26, 2018. TRIM Ref: D18-11101457

14. Goldacre B, Lane S, Mahtani KR, et al. Pharmaceutical companies' policies on access to trial data, results, and methods: audit study. *BMJ*. 2017;358:j3334. https://doi.org/10.1136/bmj.j3334

15. Heads of Medicines Agencies/European Medicines Agency. HMA/EMEA recommendations on transparency. Recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs). EMEA/743133/2009. London, 23 November 2009

16. Marketed Health Products Directorate (MHPD). Health Products and Food Branch, Health Canada. Signal Assessment Addendum: Domperidone. Serious ventricular arrhythmia and cardiac death. Dated September 9, 2014.

17. Therapeutic Goods Administration (TGA). Australian Government Department of Health. Pharmacovigilance responsibilities of medicine sponsors. Australian recommendations and requirements. Version 2.1, June 2018. Available at: https://www.tga.gov.au/sites/default/files/pharmacovigilance-responsibilities-medicine-sponsors.pdf; Accessed January 2019.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Torka M, Mintzes B, Bhasale A, Fabbri A, Perry L, Lexchin J. Secret safety warnings on medicines: A case study of information access requests. *Pharmacoepidemiol Drug Saf*. 2019;1–5. https://doi.org/10.1002/pds.4762

APPENDIX 1.2

Perry LT, Bhasale A, Fabbri A, Lexchin J, Puil L, Joarder M, and Mintzes B. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med* 179: 982-984, 2019.

Letters

RESEARCH LETTER

Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom

National regulatory agencies' decisions to approve new drugs are based on limited safety evidence collected during clinical development. Often, only when a drug enters general use do rarer or longer-term adverse events become known or better understood, prompting regulators to issue safety advisories.[1] We examined how often medicines regulators in 4 countries with similar medical traditions, population health, and demographics—Australia, Canada, the United Kingdom, and the United States—were concordant in their decisions to issue safety advisories on approved prescription medicines.

Invited Commentary

Methods | We undertook a retrospective analysis of safety advisories issued by the US Food and Drug Administration (FDA), Health Canada (HC), the UK Medicines and Healthcare products Regulatory Agency (MHRA), and the Australian Therapeutic Goods Administration (TGA) from January 1, 2007, to December 31, 2016. Safety advisories were defined as notifications to prescribers and/or the public about a potential or confirmed drug risk, excluding issues of production quality, shortages, or overdoses. We obtained advisories from regulators' websites (current and archived). This project did not fall within the scope of the National Statement on Ethical Conduct in Human Research because all included data are from publicly available documents. Therefore, according to University of Sydney Research Code of Conduct, ethics approval was not required.

Each identified drug-risk issue was reviewed for concordance or discordance among regulators. Overall concordance rates were calculated for drug-risk issues for which at least 2 countries had issued an advisory.

Statistical analysis was performed from February 1, 2017, to October 1, 2018. Regulators' discordancy rates, defined as the number of drug-risk issues for which each regulator did not issue an advisory for an approved drug, were compared using χ^2 tests for independence. All P values were from 2-sided tests, and the results were deemed statistically significant at $P < .05$, and Bonferroni corrections were used for multiple comparisons.

Results | We identified 1441 advisories in the 4 countries, covering 680 drug-risk issues. The MHRA issued advisories for 344 of 657 drug-risk issues (52.4%) for medicines approved in the United Kingdom, HC issued advisories for 317 of 635 drug-risk issues (49.9%), the FDA issued advisories for 265 of 647 drug-risk issues (41.0%), and the TGA issued advisories for 183 of 619 drug-risk issues (29.6%) (**Table**).

The overall frequency with which the 4 regulators issued safety advisories differed significantly ($\chi^2_3 = 82.3$; $P < .001$). The MHRA was more likely than other regulators to issue an advisory (136 of 657 [20.7%] vs FDA, 89 of 647 [13.8%]; HC, 122 of 635 [19.2%]; and TGA, 69 of 619 [11.1%]; $P = .001$), whereas the TGA was least likely to issue an advisory ($P < .001$; Bonferroni-adjusted significance, $P = .006$). The FDA and HC did not differ significantly from expected distributions.

The Table shows a low rate of agreement in decisions to inform professionals and the public of emergent safety concerns. The TGA had the highest discordance rate, providing no warning for 436 of 619 drug-risk issues (70.4%) for drugs approved in Australia. The MHRA issued more warnings, but still failed to provide warnings on 313 of 657 relevant drug-risk issues (47.6%). For 70 of the 680 identified drug-risk issues (10.3%), regulators issued advisories in every country where the drug was marketed. For 40 of 573 drug-risk issues, all 4 countries had approved the drug and also issued advisories (**Figure**).

Discussion | Overall, we found a low level of concordance (10.3%) between regulators in the decision to warn clinicians and the

Table. Overview of Discordance in Regulators' Decisions to Issue Advisories

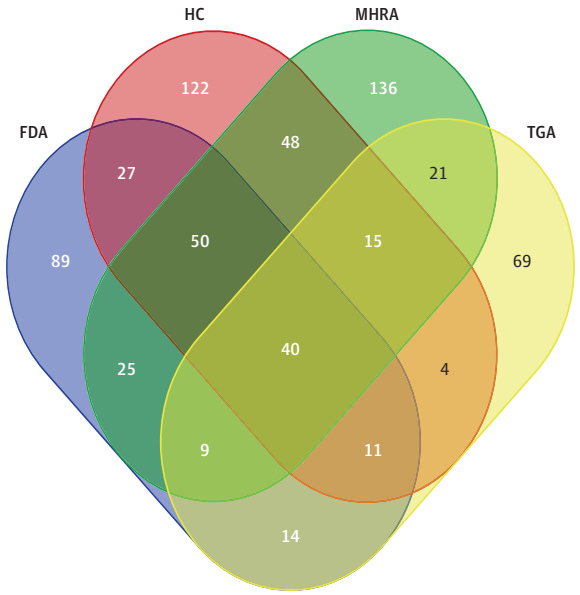
Regulator	No./Total No. (%)			
	FDA	HC	MHRA	TGA
Drug or class or drug group approved nationally	647/680 (95.2)	635/680 (93.4)	657/680 (96.6)	619/680 (91.0)
First country to release advisory (>1 regulator issued advisory)[a]	118/316 (37.3)	61/313 (19.5)	121/325 (37.2)	33/308 (10.7)
Only regulator to release an advisory[b]	89/647 (13.8)	122/635 (19.2)	136/657 (20.7)	69/619 (11.2)
Overall discordance or concordance				
Discordance rate (no advisory despite drug or drug group approval)[b]	382/647 (59.0)	318/635 (50.1)	313/657 (47.6)	436/619 (70.4)
Concordance rate (advisory released for drug-risk issue)[b]	265/647 (41.0)	317/635 (49.9)	344/657 (52.4)	183/619 (29.6)

Abbreviations: FDA, US Food and Drug Administration; HC, Health Canada; MHRA, UK Medicines and Healthcare products Regulatory Agency; TGA, Australia's Therapeutic Goods Administration.

[a] Denominators per regulator represent the number of drug-risk issues with advisories from more than 1 regulator and where the drug was approved in the country in question.

[b] Denominators per regulator represent the number of drug-risk issues based on drugs approved in the country in question.

Figure. Venn Diagram Illustrating the Level of Concordance Between Regulators in Releasing Safety Warnings, 2007-2016



Each shape indicates the number of drug-risk issues for which included regulators have issued advisories (n = 573 drug-risk issues for which all 4 regulators had approved the drug). The center (n = 40) indicates the concordant situation in which all regulators had issued an advisory. FDA indicates US Food and Drug Administration; HC, Health Canada; MHRA, UK Medicines and Healthcare products Regulatory Agency; and TGA, Australia's Therapeutic Goods Administration.

public about risks of approved prescription medicines. These results suggest widespread differences in communication patterns among included regulators.

Our findings expand on and confirm the results of a comparative analysis of direct health professional communications issued by 4 European countries.[2] That analysis reported inconsistency in decisions to issue advisories, despite national regulators' reliance on the same information from the European Medicines Agency.

This study does have some limitations. We did not consider advisories outside this 10-year window, and some warnings may have been issued before or after this period. We also did not consider other risk management tools that may have been used to communicate harm, such as the US Risk Evaluation and Mitigation Strategies. However, a sensitivity analysis including safety letters sent out within the US Risk Evaluation and Mitigation Strategies indicated little effect on results (57% vs 59% FDA discordance rate).

Our results likely reflect differences in national approaches to pharmacovigilance. National medicines policy determines the activities of the medicines regulator and resource availability, including the capacity to undertake postmarket monitoring and its administrative burden.[3] Further study into the regulators' decision making and action thresholds[4] (based on seriousness of harm or strength of evidence) and the follow-on effects of these decisions and actions is required to fully elucidate the public health implications of these policies.

Lucy T. Perry, MPharMed
Alice Bhasale, MSc (Med)
Alice Fabbri, MD, PhD
Joel Lexchin, MD
Lorri Puil, MD, PhD
Maisah Joarder, BPharm
Barbara Mintzes, PhD

Author Affiliations: Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia (Perry, Bhasale, Fabbri, Joarder, Mintzes); School of Health Policy and Management, Faculty of Health, York University, Toronto, Ontario, Canada (Lexchin); Department of Anaesthesiology, Pharmacology, and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada (Puil).

Accepted for Publication: January 26, 2019.

Corresponding Author: Barbara Mintzes, PhD, Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, D17, John Hopkins Drive, Camperdown, NSW 2006, Australia (barbara.mintzes@sydney.edu.au).

Published Online: April 29, 2019. doi:10.1001/jamainternmed.2019.0294

Author Contributions: Ms Perry had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Perry, Bhasale, Puil, Mintzes.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Perry, Lexchin.
Critical revision of the manuscript for important intellectual content: Bhasale, Fabbri, Puil, Joarder, Mintzes.
Statistical analysis: Perry.
Obtained funding: Puil, Mintzes.
Administrative, technical, or material support: Bhasale, Joarder, Mintzes.
Supervision: Lexchin, Mintzes.

Funding/Support: This research was funded by grants from the National Health and Medical Research Council of Australia (APP1122332) and the Canadian Institutes of Health Research (CIHR PJT-153275).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interest Disclosures: Ms Perry reported being employed by George Clinical Pty Ltd outside the submitted work. Ms Bhasale reported part-time employment with the Australian Commission on Safety and Quality in Health Care. Dr Lexchin reported serving as a member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. Dr Mintzes reported receiving personal fees from the legal team representing plaintiffs in a Canadian application for a class action suit on cardiovascular risks of testosterone outside the submitted work. No other disclosures were reported.

1. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care*. 2012;50(6):466-478. doi:10.1097/MLR.0b013e318245a160

2. Zeitoun J-D, Lefèvre JH, Downing N, Bergeron H, Ross JS. Inconsistencies among European Union pharmaceutical regulator safety communications: a cross-country comparison. *PLoS One*. 2014;9(10):e109100. doi:10.1371/journal.pone.0109100

3. Hirst C, Cook S, Dai W, Perez-Gutthann S, Andrews E. A call for international harmonization in therapeutic risk management. *Pharmacoepidemiol Drug Saf*. 2006;15(12):839-849. doi:10.1002/pds.1319

4. Goldman SA. Communication of medical product risk: how effective is effective enough? *Drug Saf*. 2004;27(8):519-534. doi:10.2165/00002018-200427080-00005

APPENDIX 1.3

Perry LT, Bhasale A, Fabbri A, Lexchin J, Puil L, Joarder M, and Mintzes B. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiol Drug Saf* 29: 1054-1063, 2020.

Received: 18 February 2020 | Revised: 19 May 2020 | Accepted: 5 June 2020

DOI: 10.1002/pds.5072

WILEY

ORIGINAL REPORT

A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016

Lucy T. Perry[1] | Alice Bhasale[1] | Alice Fabbri[1,2] | Joel Lexchin[3] | Lorri Puil[4] | Maisah Joarder[1] | Barbara Mintzes[1]

[1]School of Pharmacy, Faculty of Medicine and Health, and Charles Perkins Centre, University of Sydney, Sydney, New South Wales, Australia

[2]Centre for Evidence Based Medicine Odense, Odense University Hospital and University of Southern Denmark, Odense, Denmark

[3]School of Health Policy & Management, Faculty of Health, York University, Toronto, Ontario, Canada

[4]Department of Anaesthesiology, Pharmacology & Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence
Lucy T. Perry, Charles Perkins Centre, University of Sydney, D17, John Hopkins Drive, Camperdown, NSW 2006, Australia.
Email: lper0180@uni.sydney.edu.au

Funding information
Canadian Institutes of Health Research, Grant/Award Number: 153275; National Health and Medical Research Council, Grant/Award Number: 1122332

Abstract

Purpose: To determine the frequency and characteristics of safety advisories issued by medicines regulatory agencies in Australia, Canada, United Kingdom (UK) and the United States (US).

Methods: This retrospective analysis examines medicines safety warnings issued by the US Food and Drug Administration (FDA), Health Canada (HC), the Australian Therapeutic Goods Administration (TGA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) from January 1, 2007 until December 31, 2016. A database of warnings obtained from regulators' websites was developed and warnings were classified by communication type, drug, or therapeutic class focus, and the risk discussed. Advisories identifying the same drug or therapeutic class and risk were combined into groups termed "drug-risk issues" for comparisons between regulators.

Results: Over this 10-year period, 1441 advisories were identified, with the MHRA issuing the most advisories (MHRA = 469, FDA = 382, HC = 370 TGA = 220). Seventy two percent focussed on single drugs (1034/1441) and 58.7% were alerts (846/1441) posted on the regulators' websites. Diabetes drugs, smoking cessation drugs and immunomodulatory agents were the individual drug types most often subject to safety advisories, while antidepressants, antipsychotics, and proton-pump inhibitors were the top three therapeutic classes. Of 680 identified drug-risk issues, 3.8% (26/680) described a risk of death. By body system, cardiac effects were the most frequent: 10.4% (71/680).

Conclusion: We found considerable differences in the use of advisories including frequency, communication type, and focus. Disparities in communication about emergent evidence on risks may mean that clinicians and patients in some countries are less well informed about medicine safety concerns than others.

KEYWORDS

adverse reactions, Australia, Canada, drug-related side effects, pharmacoepidemiology, pharmacovigilance, risk communication, United Kingdom, United States

Lucy T. Perry presented preliminary results as a poster at the International Society for Pharmacoepidemiology Annual Conference 2018.

1 | INTRODUCTION

National medicines regulators are tasked with protecting public health by ensuring the safety of medicines that they approve. At the time of approval, there is only limited safety information available. It is often only when new drugs enter general use that rarer or longer-term adverse events are discovered or become better understood. Regulators monitor post-market risks through a variety of means including adverse event reporting systems and post-market study requirements. However, there are no consistent thresholds among regulators in the standard of evidence or the level of risk that justifies public communication of emerging potential harms. Nor is there a consistent publicly described methodology used by regulators for formulating and disseminating risk communications, determining the target audience(s), or evaluating effectiveness.

Comparison of safety advisories issued by national regulators can provide insight into differences in their decisions on management and communication of emergent risks. A previous publication from our group,[1] looking at a 10 year period (2007-2016), showed differences between four national medicines regulators' decisions to warn about risks associated with approved medicines or classes. Of the 680 different risks communicated, only 10.3% (70/680) were the subject of an advisory from all regulators where the medicine or class was approved. Other comparative studies of medicine risk communications from regulators have found differences in timing, subject, content and outcomes of these communications.[2-8] Most studies to date on emergent safety information have been limited in scope, for example addressing only specific audiences, types of warnings or drug types.

This study furthers this research by examining the spectrum of safety advisories issued by regulators over a 10-year period (2007-2016 inclusive) in four countries with similar population health, and medical standards of care - Australia, Canada, the United Kingdom (UK) and the United States (US). The aim is to compare which prescription medicines and their associated harms are being communicated and the characteristics of the safety advisories, for both health care professionals and the public, including advisory frequency, focus and communication types.

KEY POINTS

- National medicines regulatory agencies use safety advisories to communicate emergent risks of approved medicines to clinicians and the public, to support safer prescribing by healthcare professionals and medicine use by patients.
- This retrospective descriptive study found major differences in the use of safety advisories by regulators, including their frequency, content, communication type, and focus.
- Inconsistencies in communicating emergent risks may mean that prescribers and patients in some countries are less well informed about medicine safety risks than others.

2 | METHODS

2.1 | Data collection

We carried out a retrospective descriptive analysis of safety advisories issued by the US Food and Drug Administration (FDA), Health Canada (HC), the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Australian Therapeutic Goods Administration (TGA) from January 1, 2007 to December 31, 2016. Advisories were obtained from regulators' current and archived websites.

Safety advisories were defined as a notification to prescribers and/or the public about a potential or confirmed safety risk that was inherent to a medicine and not due to manufacturing problems or improper use, such as administration or dosing errors. Changes made solely within the approved product labeling or information documents did not meet our definition of a safety advisory. The following inclusion criteria were applied:

- the advisory was about one or more prescription medicines (including biologicals);
- discussed at least one safety issue or risk; and
- was released by the regulators during the study period.

Advisories were included regardless of whether risks were characterized as emergent or established or if these were "all clear" advisories (ie, further analysis indicates no risk). Where a medicine was prescription only in one country and "over the counter" in another, it was still included. We undertook duplicate independent screening for inclusion using a standardized data collection form. Differences were resolved by discussion and consensus between coders; any unresolved disagreements were discussed by the full research team.

Advisories that announced a market withdrawal, medicines shortage, or were not disseminated or made publicly available were excluded. Other regulatory safety interventions such as FDA Risk Evaluation and Mitigation Strategies (REMS) and risk management measures determined as part of a preventive framework for risks known at approval, were also excluded. While originally all FDA REMS materials were excluded, post-market Direct Healthcare Professional Communications (DHPCs) issued through REMS were included in a post-hoc analysis (see below).

In the course of data collection, we found situations in which regulators released more than one communication on the same safety issue and drug(s), for example, both an alert and a DHPC. We considered these multiple communications of a single advisory, if they were issued within 30 days of each other and recorded the number and types of communication per advisory.

TABLE 1 Categories of advisories

Category	DHPC[a]	Alert	Investigation	Bulletin	Public
Description	Letters mailed or emailed to individual health professionals, either jointly issued by regulators and industry, or solely by regulators	Notification in the safety section of the regulator's website, addressed to a broad audience and not individual clinicians	Statements regarding ongoing review or analysis of adverse reaction reports, early monitoring reviews and detailed investigation reports	Articles appearing in the regulator's newsletter or drug safety bulletin concerning safety risks associated with a drug or drug class	Message on drug safety risks directly targeting or addressing public or media
Example	Direct Healthcare Professional Letters, Dear Healthcare Professional Letters, Dear Doctor Letters	Drug Safety Communications, Safety Alerts, Safety Advisories, Safety Warnings and Message for Medicines	Monitoring communications, Summary Safety Reviews, Early Communications	ADRAC[b] bulletin, Medicines Safety Update (AU), Adverse Reaction Newsletter, Health Canada Product InfoWatch (CA), Drug Safety Update (UK),	Public Health Notifications, Media/ press releases, Information Updates

[a]Direct healthcare professional communications.
[b]Adverse drug reaction advisory committee.

2.2 | Grouping by drug and risk

Advisories were categorized into five groups: DHPCs, alerts, investigations, bulletin articles or public messages (Table 1) and were coded by drug and type of harm. For drug type, we used the Anatomical Therapeutic Chemical (ATC) classification[9] at the fourth level (chemical subgroup). Each advisory was then classified by whether the focus was on a single drug product (containing one or more active ingredients) or multiple drug products. For multiple drug products, a further sub-classification was applied: (a) "drug class/therapeutic group," if a class or therapeutic group or all drug products within a class were mentioned, (b) "multiple drugs" if the focus was several individual and distinct drug products, and (c) drug-drug interactions.

Harms were categorized by the Medical Dictionary for Regulatory Activities (MedDRA v19.1) classification to the High-Level Group Term (HLGT) and System Organ Class level (SOC). We allocated each advisory to "drug-risk issues," that is, groupings of advisories about the same drug or drug class/therapeutic group and safety concern (eg, statins - rhabdomyolysis).

In some cases, one regulator issued an advisory about an entire drug class whereas another referred to only a single drug in the class. If the same safety concern was addressed, we grouped single drug advisories with the relevant drug class advisory.

An advisory could be coded to more than one drug-risk issue, for example if it addressed both cardiovascular and hepatic adverse effects. Extracted data were verified by a second coder and reviewed by a physician team member (JL, LP, and AF) to ensure clinical similarity of grouped safety issues.

2.3 | Case study

We chose to examine a case study of safety advisories for a specific drug risk with a view to explore the differences in communication strategies between regulators in greater detail. This was intended to help identify the factors contributing to differences and plan for future research examining the reasons communications differed. Advisories for the non-vitamin K oral anticoagulant (NOAC) drug class were selected since drugs in the class were newly approved within the study period and represented a significant change in therapy for atrial fibrillation, a commonly treated condition, compared to the usual warfarin therapy.[10,11]

National approval dates were obtained from regulators' websites, and a chronology of advisories was constructed, which was used to examine similarities and differences among regulators.

2.4 | Analysis

Descriptive statistics were calculated for advisory frequencies by country, year, communication type(s), drug or drug class/therapeutic group and safety concern. Data analysis was undertaken in SAS 9.4 (SAS, Cary NC). Data collected were publicly available and did not fall within the scope of the Australian National Statement on Ethical Conduct in Human Research; therefore ethics approval was not required.

2.5 | Post Hoc analysis

While REMS were excluded from our definition of post-market safety advisories, as they are usually issued at market approval, the FDA began to use REMS more frequently during the study period, including for some post-market communications. A REMS can require DHPCs distinct from standard FDA regulatory safety advisories; therefore, review was required to ensure that we obtained a complete overview of FDA post-market advisories. This was a post hoc expansion of the source of safety advisories and was used as a sensitivity analysis in another study.[1]

3 | RESULTS

3.1 | Drugs and classes

We identified a total of 1441 advisories issued by the four regulators across the 10-year period (Table 2). Table 3 provides an overview of the top 10 single drugs/drug products and classes/therapeutic groups across the four regulators.

These 1441 advisories discussed 403 individual drugs or drug products. MHRA advisories covered the largest number of individual drugs and drug products, TGA advisories the fewest: MHRA: 221/403, HC: 208/403, FDA: 181/403 and TGA: 103/403. Rosiglitazone, a thiazolidinedione for type II diabetes (29/403), varenicline, a smoking cessation aid (28/403) and influenza vaccines (25/403) were the top three drug types. Advisories about certain antineoplastic and immunomodulatory drugs, such as natalizumab and pioglitazone, another member of the thiazolidinedione class, were also common.

Class/therapeutic group advisories were issued for 74 distinct drug classes or therapeutic groups. The MHRA again communicated about the most classes and HC the least: MHRA: 41/74, FDA: 35/74, TGA: 33/74 and HC: 30/74. Across the four regulators, the top 10 classes featured a wide mix of therapeutic areas, with three widely used classes the most common: antidepressants (all) (23/74); proton pump inhibitors (23/74) and bisphosphonates (17/74).

3.2 | Risks

Grouping of individual advisories by drug or drug class and type of harm revealed 680 drug-risk issues. "General disorders and administration site conditions" were the most frequent type of risk identified (11.6%; 79/680). This category includes a broad range of events, for example, fatigue, high temperature, death, and lack of drug effect. Within this SOC, death was the most common risk communicated with 3.8% (26/680) drug risk issues, followed by lack of effect (including drug interactions causing lack of efficacy) in 3.2% (22/680) (Table 4).

Cardiac disorders accounted for 10.4% (71/680) drug risk issues, (eg, general cardiac disorders, arrhythmias, and myocardial infarctions) followed by nervous system disorders (eg, cerebrovascular accidents, seizures, and neurological disorders) for 8.4% (57/680). "Hepatobiliary" and "skin and subcutaneous tissue disorders" were also among the top five risk types, 6.9% (47/680) and 6.0% (41/680), respectively.

3.3 | Frequency and characteristics of communications

Figure 1 documents the number of advisories released per regulator by year. The annual frequency declined for the FDA and MHRA over the study period, increased for HC and remained stable for the TGA.

TABLE 2 Overview of safety advisory characteristics (2007-2016)

Regulator[a]	FDA	HC	MHRA	TGA	Total
Advisories per regulator n = 1441 (% per country)					
Number of Advisories issued	382 (26.5)	370 (25.7)	469 (32.6)	220 (15.3)	1441 (100)
Focus of advisory n = 1441 (% per country)					
Drug/drug product	263 (25.6)	281 (27.3)	337 (32.8)	148 (14.4)	1029 (71.4)
Drug class/therapeutic group[b]	70 (28.2)	54 (21.8)	80 (32.3)	44 (17.7)	248 (17.2)
Multiple drugs[c]	26 (31.7)	15 (18.3)	20 (24.4)	21 (25.6)	82 (5.7)
Drug interaction	23 (28.1)	20 (24.4)	32 (39.0)	7 (8.5)	82 (5.7)
Communications per regulator n = 1825 (% per regulator)					
Total communications	508 (27.8)	509 (27.9)	577 (31.6)	231 (12.7)	1825 (100)
Mean communications/advisory (SD)	1.81 (1.21)	1.58 (0.62)	1.39 (0.55)	1.08 (0.29)	1.52 (0.82)
Communication type per regulator n = 1825 (% per regulator)					
Alert	363 (71.5)	78 (15.3)	337 (58.4)	68 (29.3)	846 (46.4)
Direct Healthcare Professional Communication	49 (9.7)	145 (28.5)	227 (39.3)	0 (0.0)	421 (23.1)
Bulletin article	0 (0.0)	75 (14.7)	0 (0.0)[d]	148 (64.2)	223 (12.2)
Investigation	63 (12.4)	104 (20.4)	12 (2.1)	14 (6.0)	193 (10.6)
Public	33 (6.5)	107 (21.0)	1 (0.2)	1 (0.4)	142 (7.8)

[a]Food and Drug Administration (FDA), Health Canada (HC), Medicines and Healthcare products Regulatory Agency (MHRA), Therapeutic Goods Administration (TGA).

[b]Advisory referred to the entirety of a drug class or therapeutic group.

[c]Advisory referred to multiple individual drug products not specific to a drug class or therapeutic group.

[d]The MHRA issued alerts within a monthly bulletin until 2014, after which they were issued directly on the MHRA website as alerts, accompanied by a monthly bulletin summary. These have been classified as alerts only to avoid duplication.

TABLE 3 Overview of drugs and classes identified in advisories (n = 1441)

Regulator[a]		FDA	HC	MHRA	TGA	Total
Total distinct drugs or drug products communicated about by the regulator		181	208	221	103	403
Total distinct classes or therapeutic groups communicated about by the regulator		35	30	41	33	74
Top 10	**Indication(s)**	**FDA (%) n = 382**	**HC (%) n = 370**	**MHRA (%) n = 469**	**TGA (%) n = 220**	**Total (%) n = 1441**
Single drug or drug products advisories						
rosiglitazone	Type II diabetes mellitus	9 (2.4)	7 (1.9)	9 (1.9)	4 (1.8)	29 (2.0)
varenicline	Smoking cessation	10 (2.6)	8 (2.2)	6 (1.3)	4 (1.8)	28 (1.9)
influenza vaccine	Influenza prophylaxis	3 (0.8)	0 (0.0)	6 (1.3)	16 (7.3)	25 (1.7)
mycophenolate	Transplant rejection, autoimmune disease	11 (2.9)	4 (1.1)	5 (1.1)	2 (0.9)	22 (1.5)
natalizumab	Multiple sclerosis, Crohns disease	6 (1.6)	4 (1.1)	9 (1.9)	3 (1.4)	22 (1.5)
pioglitazone	Type II diabetes mellitus	7 (1.8)	4 (1.1)	6 (1.3)	4 (1.8)	21 (1.5)
bevacizumab	Neoplasm, eye disease	2 (0.5)	10 (2.7)	7 (1.5)	1 (0.5)	20 (1.4)
rituximab	Neoplasm, autoimmune disease	3 (0.8)	6 (1.6)	8 (1.7)	2 (0.9)	19 (1.3)
fingolimod	Multiple sclerosis	4 (1.0)	6 (1.6)	7 (1.5)	1 (0.5)	18 (1.3)
clopidogrel	Heart disease, stroke	5 (1.3)	5 (1.4)	6 (1.3)	0 (0.0)	16 (1.1)
Classes or therapeutic groups advisories						
antidepressants (all)	Depressive and anxiety disorders	6 (1.6)	2 (0.5)	9 (1.9)	7 (3.2)	24 (1.7)
antidepressants (general)		*1 (0.3)*	*1 (0.3)*	*3 (0.6)*	*6 (2.7)*	*11 (0.8)*
serotonergic antidepressants		*4 (1.0)*	*0 (0.0)*	*2 (0.4)*	*0 (0.0)*	*6 (0.4)*
selective serotonin reuptake inhibitors		*1 (0.3)*	*1 (0.3)*	*2 (0.4)*	*1 (0.5)*	*5 (0.4)*
serotonin noradrenaline reuptake inhibitors		*0 (0.0)*	*0 (0.0)*	*1 (0.2)*	*0 (0.0)*	*1 (0.1)*
tricyclic antidepressants		*0 (0.0)*	*0 (0.0)*	*1 (0.2)*	*0 (0.0)*	*1 (0.1)*
proton pump inhibitors	Peptic ulcer, gastroesophageal reflux disease	5 (1.3)	7 (1.9)	7 (1.5)	4 (1.8)	23 (1.6)
bisphosphonates	Osteoporosis, bone disorders	6 (1.6)	3 (0.3)	7 (1.5)	1 (0.5)	17 (1.2)
antipsychotics (all)	Psychiatric disorders	2 (0.5)	5 (1.4)	4 (0.9)	5 (2.3)	16 (1.1)
antipsychotics (general)		*2 (0.5)*	*1 (0.3)*	*4 (0.9)*	*3 (1.4)*	*10 (0.7)*
atypical antipsychotics		*0 (0.0)*	*4 (1.1)*	*0 (0.0)*	*2 (0.9)*	*6 (0.4)*
statins	High cholesterol	2 (0.5)	2 (0.5)	6 (1.3)	3 (1.4)	13 (0.9)
tumor necrosis factor alpha inhibitors	Inflammatory disease	7 (1.8)	3 (0.3)	1 (0.2)	1 (0.5)	12 (0.8)
gadolinium containing contrast agents	Diagnostic image enhancement	5 (1.3)	3 (0.3)	3 (0.6)	1 (0.5)	12 (0.8)
angiotensin-II receptor antagonists	Hypertension, diabetic nephropathy	2 (0.5)	0 (0)	6 (1.3)	3 (1.4)	11 (0.8)
sodium glucose cotransporter 2 inhibitors	Type II diabetes mellitus	2 (0.5)	4 (1.1)	2 (0.4)	2 (0.9)	10 (0.7)
erythropoiesis stimulating agents	Anemia	6 (1.6)	1 (0.3)	2 (0.4)	1 (0.5)	10 (0.7)
non-steroidal anti-inflammatory drugs	Pain, fever	2 (0.5)	0 (0.0)	5 (1.1)	3 (1.4)	10 (0.7)

[a]Food and Drug Administration (FDA), Health Canada (HC), Medicines and Healthcare products Regulatory Agency (MHRA), Therapeutic Goods Administration (TGA).

TABLE 4 Top 10 risk types communicated (as per MedDRA system organ class)

System organ class	Total drug risk issues n = *680* (%)
General disorders and administration site conditions[a]	79 (11.6)
Death/fatal outcome	*26 (3.8)*
Lack of effect	*22 (2.9)*
Administration site conditions	*5 (0.7)*
Body temperature conditions	*5 (0.7)*
Cardiac disorders	71 (10.4)
Nervous system disorders	57 (8.4)
Hepatobiliary disorders	47 (6.9)
Skin and subcutaneous tissue disorders	41 (6.0)
Immune system disorders	36 (5.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	35 (5.2)
Vascular disorders	35 (5.2)
Infections and infestations	30 (4.4)
Blood and lymphatic system disorders	26 (3.8)
Metabolism and nutrition disorders	26 (3.8)
Renal and urinary disorders	26 (3.8)
All drug risk issues	680 (100)

[a]This SOC code contains event terminology that does not fit into more specific SOC codes or relate to nonspecific disorders.

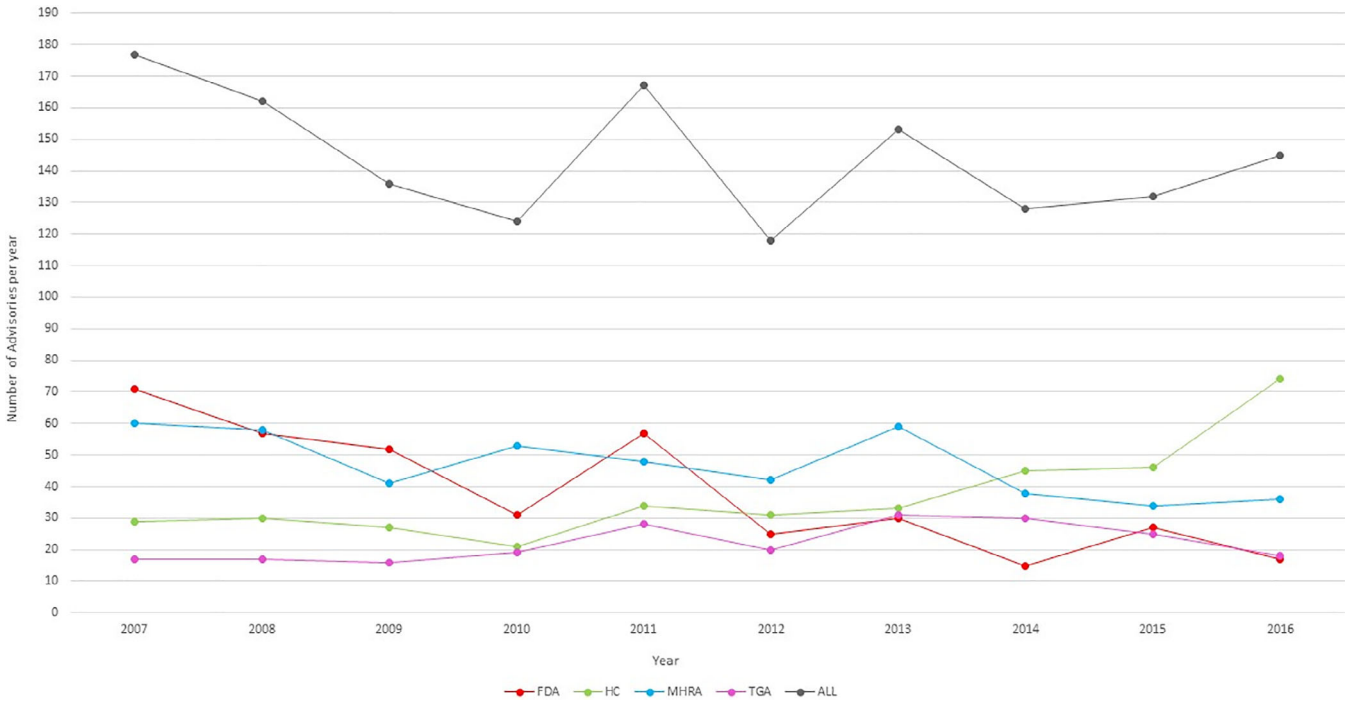


FIGURE 1 Overall frequency of safety advisories[†] issued by each regulator between 2007 and 2016. Food & Drug Administration (FDA), Health Canada (HC), Medicines and Healthcare products Regulatory Agency (MHRA) Therapeutic Goods Administration (TGA) [Colour figure can be viewed at wileyonlinelibrary.com]

The MHRA issued the most advisories (469/1441) and the TGA (220/1441) the least. Single drug advisories were the most frequent focus: 72% (1034/1441) of advisories.

There were 1825 separate communications within the 1441 advisories, that is, communications on the same drug and safety concern (s) within 30 days (Table 2). Types of communications used by

TABLE 5 Overview of non-vitamin K oral anticoagulants (NOACs) safety communications (2007–2016)

Regulator[a]	FDA	HC	MHRA	TGA	All
Total number of NOAC advisories issued	4/19 (21.1)	2/19 (10.5)	8/19 (42.1)	5/19 (26.3)	19 (100)
Focus of advisory n = 19 (% per country)					
Drug/drug product – any NOAC	4 (100.0)	1 (50.0)	5 (62.5)	2 (40.0)	12 (63.2)
dabigatran	*4*	*1*	*4*	*1*	*10*
rivaroxaban	*0*	*0*	*0*	*1*	*1*
edoxaban	*0*	*0*	*1*	*0*	*1*
Drug class/therapeutic group[b]	0 (0.0)	0 (0.0)	2 (25.0)	2 (40.0)	4 (21.1)
Drug interaction	0 (0.0)	1 (50.0)	1 (12.5)	1 (20.0)	3 (15.8)
Multiple drugs[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Communication type per regulator n = 19 (% per regulator)					
Alert	3 (75.0)	0 (0.0)	4 (50.0)	3 (60.0)	10 (52.6)
Direct Healthcare Professional Communication	0 (0.0)	1 (50.0)	4 (50.0)	0 (0.0)	5 (26.3)
Bulletin article	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	2 (10.5)
Investigation	1 (25.0)	1 (50.0)	0 (0.0)	0 (0.0)	2 (10.5)
Public	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Food and Drug Administration (FDA), Health Canada (HC), Medicines and Healthcare products Regulatory Agency (MHRA), Therapeutic Goods Administration (TGA).
[b]Advisory referred to the entirety of a drug class or therapeutic group.
[c]Advisory referred to multiple individual drug products not specific to a drug class or therapeutic group.

regulators varied as presented in Table 2. However, alerts on regulators' websites were the most common communication type (46.4%, 846/1825), followed by DHPCs (23.1%, 421/1825).

Individually, regulators differed in the types of advisories that they used. The FDA and MHRA mostly used alerts - 71.5% (363/508) and 58.4% (337/577) of their respective total communications - whereas HC used DHPCs (28.5%, 145/509) and the TGA used bulletin articles (64.2%, 148/231) most often. The MHRA issued advisories as part of a monthly bulletin until 2014 and then issued these directly on the MHRA website as alerts. HC also used bulletins, but the FDA did not use this communication type. The TGA did not issue any publicly available DHPCs. HC directed 20% (107/509) of their communications to the public; the FDA targeted 6.5% (33/1825) of communications specifically to the public, whereas the MHRA and TGA issued public communications rarely (0.2% and 0.4%, respectively). Finally, the TGA issued the fewest communications per advisory (mean 1.08 ± SD 0.29) and the FDA the most (mean 1.81 ± SD 1.21).

Post-hoc screening of FDA REMS located a total of 69 post-market REMS related DHPCs. Sixty-three (91.3%) of these focused on single drugs, 5/69 (7.2%) on multiple drugs, and 1 (1.4%) on drug class.

3.4 | Case Study: Advisories on NOACs and Hemorrhage

We examined the non-vitamin K oral anticoagulants (NOACs) as a case study of a recently approved drug class that has been subject to frequent advisories.

Four of the five NOACs (dabigatran, apixaban, rivaroxaban, and edoxaban) were available during the study period in one or more included country. Dabigatran, apixaban, and rivaroxaban were approved by the four regulators between 2007 and 2016. Edoxaban was approved by the FDA and MHRA in 2015, but was approved by HC and the TGA after the study period.

We found 19/1441 (1.3%) advisories on risks of hemorrhage with NOACs (Table 5), including 3/19 (15.8%) on interactions between dabigatran and antiarrhythmics. Of these 19 advisories, 8/19 (42.1%) were issued by the MHRA (4 DHPCs and 4 alerts), 4/19 by the FDA (21.1%,1 investigation and 3 Alerts), 5/19 by the TGA (26.3%, 2 bulletins and 3 Alerts), and 2/19 (10.5%) by HC (1 and 1 investigation).

Most advisories were about a single NOAC (12/19, 63.2%), with the TGA and the MHRA each issuing two class level advisories. The TGA was the first regulator in our sample to communicate about risks of hemorrhage with dabigatran, and the only regulator to issue an advisory on rivaroxaban. Dabigatran was the focus of the most advisories (12/19, 63.2%) and the only NOAC for which the FDA issued an advisory.

Figure 2 provides a timeline showing drug approval dates (vertical lines) and subsequent advisories (circles), illustrating that the timing of a regulator's decision to warn is not solely a function of the approval date. The TGA approved dabigatran later than the FDA and HC, but was the first to warn of risks of hemorrhage.

4 | DISCUSSION

Our study expands on previous comparative research on post-market regulatory safety advisories issued by regulatory authorities[1,2,4-6] and

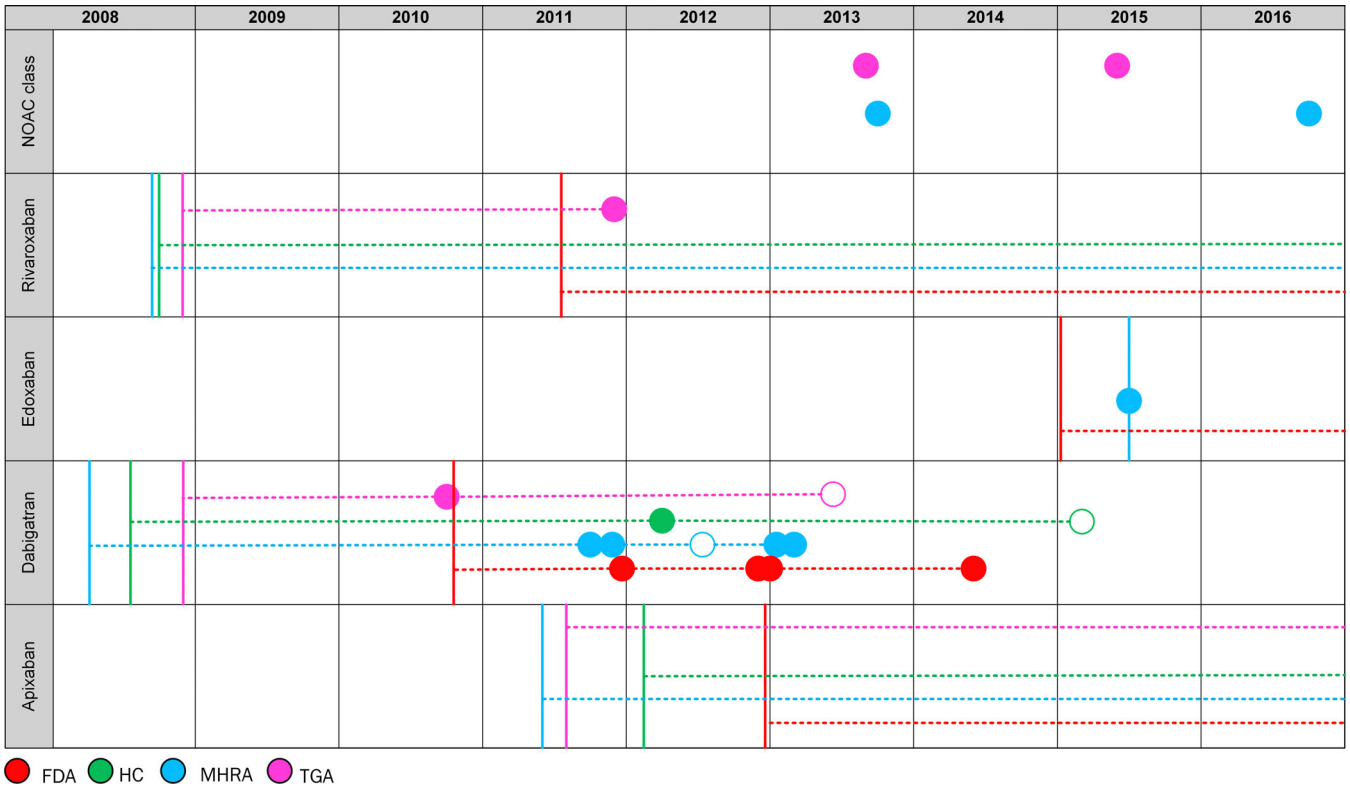


FIGURE 2 Timelines of Advisories about Non-Vitamin K Oral Anticoagulants (NOACs) and hemorrhage risk. Approval dates of each NOAC by regulator is indicated by the vertical line, whereas the communication time points are indicated by circles. Solid circles represent the advisories about NOACs and hemorrhage risk, open circles represent the advisories about hemorrhage associate with dabigatran drug interactions [Colour figure can be viewed at wileyonlinelibrary.com]

finds both similarities and differences among the FDA, HC, MHRA, and the TGA in communication (frequency, the intended audience, communication types, and focus). The MHRA issued the most advisories, as compared to the TGA that issued the least. Alerts were favored by the FDA and MHRA, while HC and the TGA more frequently issued DHPCs and bulletin articles, respectively. HC and FDA both produced public-directed advisories, whereas the other two regulators did not. For all four regulators, the majority of advisories focused on single drugs or drug products.

Across the four regulators, there was a strong focus on the diabetes drugs rosiglitazone and pioglitazone, as well as specific immunomodulatory agents such as natalizumab and bevacizumab. At a class or therapeutic group level, the focus was on widely used medicines such as antidepressants and proton pump inhibitors, as well as newer chronic disease therapeutic groups such as the SGLT-2 inhibitors, used for type II diabetes. The high frequency of drug risk issues in the "general disorders and administration site conditions," including risk of death in 26 groups, likely reflects the broad range of issues included in this risk category. Cardiac, neurological or nervous and hepatobiliary advisory groups were also prevalent.

The case study of the NOACs, one of the leading therapeutic groups in terms of spontaneous reports to the FDA Adverse Event Reporting System,[12] illustrates how much communication patterns can differ. Dabigatran was the only NOAC for which all four regulators issued an advisory; otherwise, we found differences in the type, timing, and numbers of advisories among the regulators. These differences highlight the need to further understand the effects of the frequency and characteristics of safety advisories on the actions of medicines prescribers and users (including risk awareness, comprehension, and clinical decision-making).[13]

The differences that we found suggest that health professionals and the public in a particular country may be less well informed than others about emergent evidence on the harmful effects of some prescription medicines. These differences in how much information is communicated by each regulator are especially concerning as these four countries have sophisticated pharmacovigilance systems, with similar pharmaceutical markets and population demographics. They become even more important if we look to low-to-middle income countries, with more limited resources for regulation of medicines and often extremely limited pharmacovigilance systems.[14] These nations may rely on information from key reference regulators to support local pharmacovigilance activities.[3,15]

National medicines regulatory policy dictates not only how medicines are approved (therapeutic indications, populations and timing of approval), accessed (prescription vs over-the-counter) and reimbursed,[1] but also the risk management tools available to a regulator and the extent to which information is communicated to the public.[16,17] For example, the FDA changed its approach to risk communication during the study period, consolidating multiple communications into a single Drug Safety Communication and using REMS as a tool to manage post-

approval medicine risks. In addition, unlike the other included jurisdictions, in Australia, DHPCs have never been made publicly available.[18]

How regulators judge whether, when, why, how and who to communicate to about medicines risk is not transparent to those who are most affected by this information: prescribers and patients. Improving transparency about regulatory decision-making and communications is an important part of understanding the efficacy (or lack thereof) of safety advisories in achieving desired outcomes.[13]

Discordance in the frequency, focus, and targets of warnings by regulatory bodies can lead to less than ideal communication and places a burden on prescribers in making informed treatment decisions on behalf of their patients.[13] "Message spill-over," in which, for example, a warning issued for a specific at-risk patient group influences overall prescribing, may lead to unintended consequences such as changes in or stopping of medicine use in a non-targeted population.[19] Some studies indicate that multiple communications are effective in changing behaviors, while others show specific and targeted communications are more effective.[7,8,16,20] Too much communication can lead to "alert fatigue" and the importance of these regulatory communications being lost.[21] Furthermore, health professionals often have limited awareness of warnings and only a subset reports changes in prescribing behavior.[22]

Our study has several limitations. We did not investigate the effects of differences between regulators in issuing advisories on awareness of emergent risks, eventual changes in prescribing, or ultimately, patient outcomes. It is also worth noting that our results do not provide clarity on how best to communicate risk information to the intended end users or the most appropriate tool for these communications. Additionally, in some cases risk management tools other than safety advisories may be the primary communication method used. We did not consider advisories outside the 10-year time frame; hence warnings may have been issued before or after our study period. Our 30-day period for grouping communications on the same safety concern into a single advisory is arbitrary and other time periods could be used. Finally, the advisory category framework was constructed by our team for the purposes of this research.

5 | CONCLUSION

We found marked variation in the characteristics of medicines safety advisories issued by four medicines regulators between 2007 and 2016, in terms of frequency, the intended audience, communication types, and focus. We acknowledge that a "one-size-fits-all" approach is not practicable nor appropriate for medicines risk management, and while regulatory decision-making occurs within a national policy context and some differences are expected, successful risk communication requires transparency in methods, rationales, and goals in order for communications to deliver intended outcomes.[23] Engagement and empowerment of all stakeholders in risk communications should be a priority for regulators. Allowing prescribers and patients in all countries to have equitable access to appropriate medicines safety information is key to making informed treatment choices and quality use of medicines.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

ACKNOWLEDGEMENTS

The authors would like to thank Christiane Klinner and Marc Torka for their assistance with data collection and coding, Emily Karanges for data management support and Marie Louise De Bruin and Christine Hallgreen for their comments and advice. Funding for this research was provided by the National Health and Medical Research Council (Grant ID: 1122332), Australia and the Canadian Institutes of Health Research (Grant ID: 153275).

CONFLICT OF INTEREST

LTP is an employee of George Clinical, a contract research organization conducting research on behalf of the pharmaceutical industry. BM in 2020 acted as an expert witness for Health Canada in a legal case related to marketing of an unregistered product in Canada. JL received payments for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and a second brief on the role of promotion in generating prescriptions for Goodmans LLP. He is a member of the Foundation Board of Health Action International. AB, AF, LP and MJ have no conflicts of interest to declare.

ORCID

Lucy T. Perry https://orcid.org/0000-0002-3337-1321
Alice Bhasale https://orcid.org/0000-0002-5387-8760
Alice Fabbri https://orcid.org/0000-0001-8413-0440
Joel Lexchin https://orcid.org/0000-0001-5120-8029
Lorri Puil https://orcid.org/0000-0003-4021-5500
Maisah Joarder https://orcid.org/0000-0003-1176-9790
Barbara Mintzes https://orcid.org/0000-0002-8671-915X

REFERENCES

1. Perry LT, Bhasale A, Fabbri A, et al. Comparative analysis of medicines safety advisories released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med*. 2019;179(7):982-984. https://doi.org/10.1001/jamainternmed.2019.0294.
2. Zeitoun J-D, Lefèvre JH, Downing N, Bergeron H, Ross JS. Inconsistencies among European Union pharmaceutical regulator safety communications: a cross-country comparison. *PLoS ONE*. 2014;9(10):e109100.
3. Hirst C, Cook S, Dai W, Perez-Gutthann S, Andrews E. A call for international harmonization in therapeutic risk management. *Pharmacoepidemiol Drug Saf*. 2006;15(12):839-849.
4. Bjerre LM, Parlow S, de Launay D, et al. Comparative, cross-sectional study of the format, content and timing of medication safety letters issued in Canada, the USA and the UK. *BMJ Open*. 2018;8(10):e020150. https://doi.org/10.1136/bmjopen-2017-020150.
5. Giezen T, Mantel-Teeuwisse A, Straus SM, Schellekens H, Leufkens H, Egberts A. Safety-related regulatory actions for biologicals approved in the United States and the European Union. *JAMA*. 2008;300(16):1887-1896.

6. Heemstra HE, Giezen TJ, Mantel-Teeuwisse AK, de Vrueh RLA, Leufkens HGM. Safety-related regulatory actions for orphan drugs in the US and EU: a cohort study. *Drug Saf*. 2010;33(2):127-137.
7. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care*. 2012;50(6):466-478.
8. Piening S, Haaijer-Ruskamp FM, de Vries JTN, et al. Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf*. 2012;35(5):373-385. https://doi.org/10.2165/11599100-000000000-00000.
9. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC - Home. ATC Classification Index with DDDs. Published 2018. Retrieved on 18 September 2018 from https://www.whocc.no/. 2018.
10. Fanaroff AC, Ohman EM. Non–vitamin K antagonist oral anticoagulants in the treatment of atrial fibrillation. *Annu Rev Med*. 2019;70(1):61-75. https://doi.org/10.1146/annurev-med-042617-092334.
11. Yeh CH, Hogg K, Weitz JI. Overview of the new oral anticoagulants: opportunities and challenges. *Arterioscler Thromb Vasc Biol*. 2015;35(5):1056-1065. https://doi.org/10.1161/atvbaha.115.303397.
12. Moore TJ, Furberg CD, Mattison DR, Cohen MR. QuarterWatch. Published online Q42015. Retrieved from https://www.ismp.org/quarterwatch/annual-report-2014.
13. Dal Pan G. Gauging the effectiveness of medicines safety communications from global regulatory agencies. *JAMA Intern Med*. 2019;179(7):984-984. https://doi.org/10.1001/jamainternmed.2019.0294.
14. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. *Drug Saf*. 2010;33(8):689-703. https://doi.org/10.2165/11536390-000000000-00000.
15. Bollyky T, Stergachis A. A Report of the Safety and Surveillence Working Group. Published online 2014. https://docs.gatesfoundation.org/documents/SSWG%20Final%20Report%2011%2019%2013_designed.pdf. 2014.
16. Buckley NA, Rossi S. Bringing greater transparency to "black box" warnings. *Clin Toxicol*. 2011;49(6):448-451.
17. Bhasale A, Mintzes B, Sarpatwari A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. *BMJ*. 2020;369:m1107. https://doi.org/10.1136/bmj.m1107.
18. Torka M, Mintzes B, Bhasale A, Fabbri A, Perry L, Lexchin J. Secret safety warnings on medicines: a case study of information access requests. *Pharmacoepidemiol Drug Saf*. 2019;28(4):551-555. https://doi.org/10.1002/pds.4762.
19. DeFrank JT, McCormack L, West SL, Lefebvre C, Burrus O. Unintended effects of communicating about drug safety issues: a critical review of the literature. *Drug Saf*. 2019;42(10):1125-1134. https://doi.org/10.1007/s40264-019-00840-3.
20. Roughead EE, Gilbert AL, Primrose JG. Improving drug use: a case study of events which led to changes in use of flucloxacillin in Australia. *Soc Sci*. 1999;48:845-853.
21. Baseman JG, Revere D, Painter I, Toyoji M, Thiede H, Duchin J. Public health communications and alert fatigue. *BMC Health Serv Res*. 2013;13(1):295. https://doi.org/10.1186/1472-6963-13-295.
22. Kesselheim AS, McGraw SA, Dejene SZ, et al. Patient and physician perceptions of drug safety information for sleep aids: a qualitative study. *Drug Saf*. 2017;40(6):531-542. https://doi.org/10.1007/s40264-017-0516-3.
23. Council of Canadian Academies, Council of Canadian Academies, expert panel on the effectiveness of health product risk communication. Health product risk communication: Is the message getting through? Published online 2015. Retrieved on 9 September 2018 from http://www.deslibris.ca/ID/247032. 2015.

How to cite this article: Perry LT, Bhasale A, Fabbri A, et al. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiol Drug Saf*. 2020;29:1054–1063. https://doi.org/10.1002/pds.5072

APPENDIX 1.4

Hooimeyer A, Bhasale A, Perry L, Fabbri A, Mohammad A, McEwin E, and Mintzes B. Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. *Pharmacology Research & Perspectives* 8: e00680, 2020.

Received: 4 August 2020 | Revised: 17 September 2020 | Accepted: 19 September 2020

DOI: 10.1002/prp2.680

ORIGINAL ARTICLE

Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies

Ashleigh Hooimeyer[1] | Alice Bhasale[1] | Lucy Perry[1] | Alice Fabbri[1,2] | Annim Mohammad[1] | Eliza McEwin[1] | Barbara Mintzes[1]

[1]Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia

[2]Centre for Evidence-Based Medicine Odense (CEBMO), Odense University Hospital and University of Southern Denmark, Odense, Denmark

Correspondence
Barbara Mintzes, Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia.
Email: barbara.mintzes@sydney.edu.au

Funding information
This study is part of a project funded by the National Health and Medical Research Council of Australia (APP 1122332) and the Canadian Institute of Health Research (CIHR PJT-153275).

Abstract

Information on rare adverse effects is often limited when a medication is initially approved for marketing. Medicines regulators use safety advisories to warn health professionals and consumers about emerging harms. This study aimed to identify characteristics and advice provided in cardiac safety advisories released by regulators in Australia, Canada, the United Kingdom, and the United States. This was a retrospective study of safety advisories about cardiac-related adverse events issued by these four international medicines regulators between 2010 and 2016. A descriptive overview was followed by a more detailed content analysis, focusing on recommended actions for health professionals, including monitoring advice. For the latter, we applied the systematic information for monitoring (SIM) scale to assess adequacy. Over this period, 164 safety advisories about cardiac harms were issued by the four regulators. There were 61 drugs with advisories of cardiac risk, only 9 (14.7%) of which had advisories from all regulators in countries where the drug was approved. The most common adverse events were cardiac arrhythmias (n = 97, 59.1%) and coronary artery disorders (n = 39, 23.8%). The most frequent advice to prescribers was to monitor patients (n = 74, 45.1%), although only 41.2% of these advisories provided detailed advice on how monitoring should occur. We found many differences in the decision to warn and the advice provided. Patient monitoring was most often recommended, but key information such as frequency or thresholds for action was often lacking. Healthcare professionals and consumers need consistent information about rare serious harms so that they can make informed decisions.

KEYWORDS

cardiac harm, drug-related side effects and adverse reactions, pharmaceutical policy, pharmaceutical regulators, risk communication

Abbreviations: COX-2, cyclooxygenase type 2 receptors; DHPC, direct health professional communication; FDA, Food and Drug Administration; HC, Health Canada; HLGTs, higher-level group terms; MedDRA, Medical Dictionary for Regulatory Activities; MHRA, Medicines and Healthcare products Regulatory Agency; NSAIDS, non-steroidal anti-inflammatories; ICC, intra-class correlation coefficient; SIM, systematic information for monitoring; TGA, Therapeutic Goods Administration; US, United States.

1 | INTRODUCTION

Decisions to approve new drugs by medicines regulators are often made based on limited information about safety collected during clinical trials. Longer-term or rare adverse events are often detected only once a drug is on the market.[1] Post-market safety advisories are issued by national medicines regulators when new information about a drug's effects become known after regulatory approval, for a drug already on the market. They are one key means with which safety messages can be communicated to healthcare professionals and consumers. Regulators use various forms of safety advisories to communicate about emerging risks, including letters (direct health professional communications or DHPCs), website alert notices, and drug safety bulletins. Advisories may be accompanied by other regulatory actions such as updates to product information or prescribing guidelines and inclusion of black box warnings.

Our team previously compiled all the post-market safety advisories issued by the US United States (US) Food and Drug Administration (FDA), Health Canada (HC), the Australian Therapeutic Goods Administration (TGA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA), between 1 January 2007 and 31 December 2016. A previous publication from our group identified a low level of concordance between these four regulators in their decisions to warn healthcare professionals and the public, with all regulators issuing warnings about an approved medicine in only 10% of cases.[2]

A number of commonly prescribed drugs are associated with increased risks of cardiac adverse events.[3] These include non-steroidal anti-inflammatories (NSAIDs), antihyperglycaemics, and antiemetics.[3] For example, in observational studies domperidone has been found to increase the risk of ventricular arrhythmia and sudden cardiac death.[4-7] NSAIDs have also been extensively studied for their increased risk of ischemic heart disease,[8-14] and those which are more selective for cyclooxygenase type 2 receptors (COX-2) have been shown to be associated with an increased risk.[15]

This study aims to provide an overview of safety advisories about cardiac-related adverse events (referred to from here on as cardiac advisories) issued by four international regulators between 2010 and 2016, investigating:

- Which regulators issued advisories about which drugs?
- How often did all countries where a drug was marketed issue warnings?
- Which types of cardiac adverse effects featured most often?

We further aimed to investigate the content of these advisories and where these regulators concurred or differed in the information provided, specifically detailing:

- The advice provided to health professionals.
- Whether patient monitoring advice was provided, and whether it included key information elements needed for effective implementation.
- Evidence cited in the advisories.

What is already known about this subject

- Medicines safety advisories are one way in which new information about adverse drug reactions are communicated to healthcare professionals and the public.
- Efficacy of these warnings has previously been shown to be variable.
- Many drugs are associated with cardiac adverse effects which may have a high mortality and morbidity burden.

What this study adds

- Between 2010 and 2016, there were few cases where regulators from Australia, the United Kingdom, Canada, and the United States all issued advisories about the same drug.
- The most frequent advice for health professionals was to monitor for adverse effects although often this advice was too limited to provide useful clinical guidance

2 | MATERIALS AND METHODS

2.1 | Sample selection

All advisories issued by the TGA, FDA, HC, or MHRA between 2007 and 2016 had been previously compiled into a database, as described by Perry et al[2,16] Safety advisories were defined as communications to prescribers and/or the public about potential or confirmed drug safety risks due to the medicine itself, not problems with manufacturing or improper use. These were categorized into four types: Alerts, Investigations, DHPCs, and Bulletins. Advisories were downloaded from regulators' websites and were coded by drug (using Anatomical Therapeutic Chemical classifications)[17] and type of harm (using the Medical Dictionary for Regulatory Activities [MedDRA version 19.1]).

From this database, a subset of advisories was selected for inclusion. Only advisories released between 1 January 2010 and 31 December 2016 were included. Cardiac advisories were selected by filtering listed adverse events using MedDRA higher-level group terms (HLGTs) within the system order class grouping of "cardiac disorders". Early warning advisories and notices about investigations of possible adverse events were excluded as these described unconfirmed risks.

2.2 | Data collection and coding

A data extraction tool was created using REDCap (Research Electronic Data Capture).[18] Key areas of interest included:

- Nature of the safety concern and outcomes (adverse events, risk of death)

- Source of evidence of harms (eg, randomized controlled trials, case reports, etc)
- Advice to health professionals (eg, dosage advice, patients who should not receive the medication, monitoring, etc)

Five rounds of pilot testing the data extraction tool preceded data collection. In order to test reliability of data coding, 49 advisories were double coded. Reliability was calculated using the intraclass correlation coefficient (ICC).[19] A threshold of ≥0.75[19] was pre-specified as indicating sufficient reliability to support single coding of advisory content.

2.3 | Analysis

Descriptive statistics were calculated for advisory frequencies by country, year, communication method(s), drug, and safety concern, with differences between regulators compared using the χ^2 statistic. Data analysis was performed using SPSS (Version 24).

As warnings about cardiac risks often mention monitoring, we used the systematic information for monitoring (SIM) score to assess the usefulness of the monitoring advice (Table 1).[20-23] The SIM score has previously been used to assess advice in Summaries of Product Characteristics. The scoring system focuses on the quality of monitoring advice provided for six criteria: what to monitor, when to start monitoring, when to stop monitoring, how frequently to monitor, a "critical value," and how to respond. Each of these components were scored 0 or 1, depending on whether the advice was specified and sufficient. (Table 1).

2.4 | Case study

An illustrative case study of citalopram and escitalopram was used in order to compare the content of advisories between regulators. This example was chosen because all regulators had issued warnings about cardiac arrhythmia risks with citalopram and/or escitalopram, and these closely related antidepressants are commonly used in primary care.[24]

3 | RESULTS

3.1 | Reliability testing

Based on the 49 double-coded advisories, the calculated ICC was 0.878 (95% CI 0.784-0.931). This was well above the threshold of 0.75 for reliability and was considered adequate for single coding of the remaining advisories.[19]

3.2 | Overview of cardiac advisories

A total of 164 advisories were identified about cardiac risks (Figures 1 and 2). Of these, 57 (34.8%) were issued by the MHRA, 40 (24.4%) by the FDA, 35 (21.3%) by the TGA, and 32 (19.5%) by HC (Table 2). There was a significant difference between the number of advisories issued by each country over this timeframe ($\chi^2 = 9.12$, $P = .028$).

The regulators varied in the types of communication used ($\chi^2 = 91.22$, $P < .001$), with the FDA using mostly alerts, HC using DHPCs, and the TGA using bulletin articles (Table 2). For Canada, the US, and the UK, we were able to access DHPCs from the regulators. In Australia, however, DHPCs are not made publicly available and our team was unable to obtain a comprehensive set via requests to companies or a freedom of information request to the TGA.[25] Therefore, DHPCs from Australia have not been included in this study.

The most commonly reported adverse events based on MedDRA HLGT classification were cardiac arrhythmias (n = 97, 59.1%), coronary artery disorders (n = 39, 23.8%), and cardiac disorders, signs, and symptoms (n = 21, 12.8%; Table 2). Cardiac arrhythmias included adverse events such as increased heart rate, QT prolongation, and

TABLE 1 SIM criteria and examples

SIM Criteria	Examples of adequate advice (scored 1)	Examples of inadequate advice (scored 0)
What to monitor	ECG, heart rate, blood pressure, electrolytes	Cardiac monitoring (no additional detail)
When to start monitoring	At the beginning of treatment, before treatment	Not stated
When to stop monitoring	After 12 hours, when ceasing medication, 6 weeks after ceasing	Not stated
How frequently to monitor	Every 2 weeks, every month	Frequent monitoring
Critical Value	QT interval >470 milliseconds, heart rate <45 bpm	QT prolongation, bradycardia
How to respond	Cease medication, reduce dose, extended/increased monitoring	Not stated

cardiac arrest. Coronary artery disorders primarily consisted of myocardial infarction, while cardiac disorders, signs, and symptoms included a large range of cardiac symptoms.

There were 61 drugs in total with advisories on cardiac risks, only nine (14.7%) of which had advisories from all regulators in countries where the drug was approved.

3.3 | Common drugs featuring in cardiac advisories

Table 3 describes the top 11 drugs featuring in cardiac advisories. The aim was to describe the top 10 drugs; 11 are included as four drugs had equal numbers of advisories. In total, 87/149 (58.4%) cardiac advisories were about these drugs. Four have been removed from the market in some countries, rosiglitazone in the UK, dextropropoxyphene in all countries, ondansetron (in certain formulations) in the US, and strontium ranelate in the UK and Australia. Dextropropoxyphene had already been removed from the market in all of the countries except Australia by the time of the first advisory.[26] Domperidone was never approved in the US, while strontium ranelate was never approved in the US or Canada.

It is important to note that these numbers do not necessarily reflect the risk of the medication but can also reflect how much regulatory activity occurred during the timeframe. Dextropropoxyphene is a good example of this, as the TGA attempted to remove it from the market several times but the manufacturer appealed these attempts.[26] This led to a series of advisories that provided updates on the regulatory status, rather than new safety information about the drug.

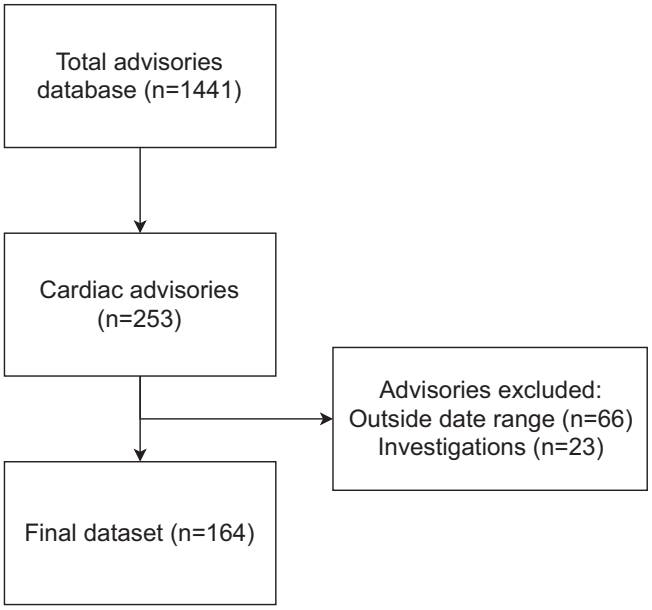


FIGURE 1 Flow chart of study sample selection from the full advisories database

3.4 | Advice provided to health professionals

Most advisories (n = 149, 90.9%) provided information for health professionals (Table 4). Of these advisories, 109 (73.2%) advised prescribers to take specific actions, while 39 (26.2%) provided awareness information only (ie, provided information about the adverse event without any actions for health professionals).

The FDA provided the most advice to educate, counsel, or advise patients (FDA = 18 (54.5%), HC = 7 (24.1%), MHRA = 14 (25.9%), TGA = 9 (27.3%), $\chi^2 = 9.749$, $P = .021$).

Australian advisories were most likely to inform prescribers to follow the product information (FDA = 8 (24.2%), HC = 8 (27.6%), MHRA = 10 (18.5%), TGA = 19 (57.6%), $\chi^2 = 15.877$, $P = .001$).

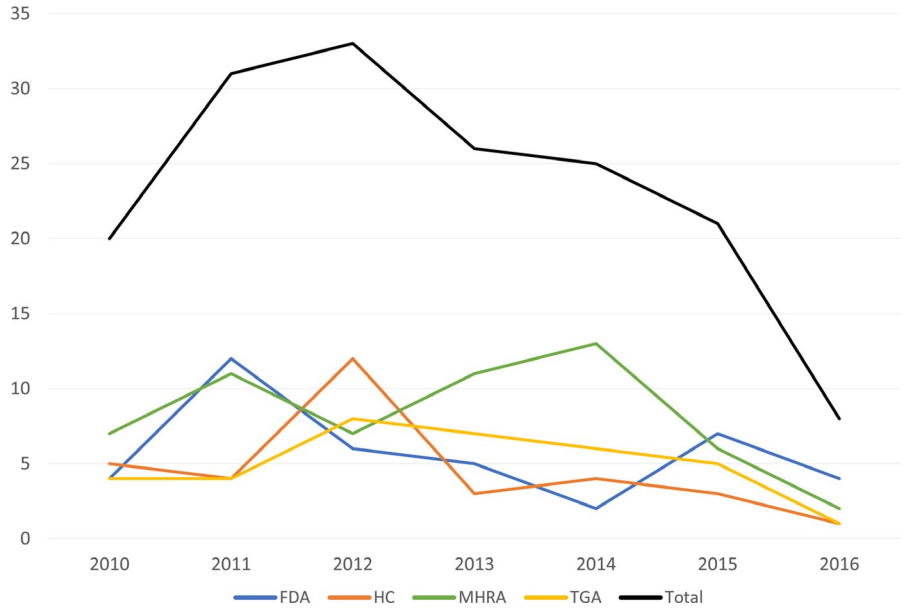


FIGURE 2 Number of advisories on cardiac harms issued per year by each regulator

TABLE 2 Characteristics of cardiac advisories

	FDA	HC	MHRA	TGA	Total
Total	40 (24.4%)	32 (19.5%)	57 (34.8%)	35 (21.3%)	164 (100%)
Adverse event type (percentages are of country total)					
Cardiac arrhythmias	18 (45%)	23 (71.9%)	34 (59.6%)	22 (62.9%)	97 (59.1%)
Coronary artery disorders	16 (40%)	6 (18.8%)	6 (10.5%)	11 (31.4%)	39 (23.8%)
Cardiac disorders, signs, and symptoms	5 (12.5%)	2 (6.3%)	11 (19.3%)	3 (8.6%)	21 (12.8%)
Heart failures	6 (15%)	3 (9.4%)	6 (10.5%)	2 (5.7%)	17 (10.4%)
Cardiac valve disorders	1 (2.5%)	2 (6.3%)	3 (5.3%)	1 (2.9%)	7 (4.3%)
Myocardial disorders	1 (2.5%)	0	1 (1.8%)	1 (2.9%)	3 (1.8%)
Congenital cardiac disorders	0	0	1 (1.8%)	0	1 (0.6%)
Communication type					
Alert	30 (75%)	10 (31.3%)	29 (50.9%)	19 (54.3%)	88 (53.7%)
DHPC	10 (25%)	22 (68.8%)	28 (49.1%)	0[a] (0%)	60 (36.6%)
Bulletin	0 (0%)	0 (0%)	0 (0%)	16 (45.7%)	16 (9.8%)

[a]We were unable to access Australian DHPCs.

The MHRA was most likely to recommend that a medication be stopped in patients on therapy (FDA = 5 (15.2%), HC = 4 (13.7%), MHRA = 16 (29.6%), TGA = 2 (6.1%), $\chi^2 = 8.618$, $P = .035$).

3.5 | Monitoring advice

Of the 109 (73.2%) advisories that advised prescribers to take action, 74 (67.9%) provided advice about testing or monitoring, but six were only about assessing suitability for treatment. Monitoring advice was assessed for the remaining 68 advisories using the SIM score (n = 68, 45.6%; Table 5).[20-23] The type of monitoring varied depending on the adverse event, but included clinical investigations such as electrocardiographs (ECGs) (60.8%), signs and symptoms (43.2%), and blood tests (17.6%).

The average total SIM score for advisories which provided monitoring advice was 2.57/6 (95% CI 2.17-2.95). In total, 28 (41.2%) of the advisories had a score ≥3, which has been considered by other studies to represent a minimum threshold for actionable advice.[20,21,23] Only two of the information items were provided in over half of advisories; what to monitor (75.0%) and when to start monitoring (55.9%).

Four advisories (5.9%) recommended monitoring without providing any details of what to monitor. There was no statistically significant difference between countries. However, there may not have been adequate power to detect a difference.

3.6 | Information about sources of evidence

Regulators reported a range of types of evidence for the harm, from systematic reviews to case studies (Table 6). While there was no statistically significant difference between the regulators on the types of cited evidence, the FDA was the only regulator that always reported the evidence used in decision-making.

3.7 | Case study: citalopram/escitalopram

Advisories for racemic citalopram and its S-enantiomer escitalopram, which belong to the selective serotonin reuptake inhibitor class of antidepressants and are widely used, were examined as an illustrative case study.[24] They present the highest risk for QT-prolongation and Torsades de Pointes among the drugs of this class.[27]

Between the four regulators, seven advisories were issued for citalopram and escitalopram between 2011 and 2012 (File S2). The FDA was the first regulator to issue a safety warning. The four regulators provided very similar information on risks of QT prolongation and on a change in recommended dose.

Despite all four regulators warning of the risk of Torsades de Pointes, only the FDA and HC mentioned the risk of death in their advisories. In all four countries, regulatory warnings were accompanied by a change to the product information advising prescribers to use lower doses. In their second advisory, the FDA mentioned more

TABLE 3 Top 11 drugs[a] by number of advisories

	Indication	FDA (n = 40)	HC (n = 32)	HC (n = 32)	TGA (n = 35)	Total (n = 164)
Rosiglitazone	Type 2 Diabetes	5 (12.5%)	4 (12.5%)	2 (3.5%)	1 (2.8%)	12 (7.3%)
Withdrawal		No	No	2010	No[c]	
Dextropropoxyphene	Mild-to-moderate pain	0	0	1 (1.8%)[d]	9 (25.7%)	10 (6.1%)
Withdrawal[b]		2010	2010		2012[e]	
Fingolimod	Multiple sclerosis	3 (7.5%)	3 (9.4%)	3 (5.3%)	1 (2.8%)	10 (6.1%)
Domperidone	Nausea	N/A	2 (6.3%)	6 (10.5%)	1 (2.8%)	9 (5.5%)
Denosumab	Osteoporosis	2 (5.0%)	1 (3.1%)	3 (5.3%)	2 (5.7%)	8 (4.8%)
Dronedarone	Cardiac arrhythmias	3 (7.5%)	2 (6.3%)	2 (3.5%)	0	7 (4.3%)
Ondansetron	Nausea	2 (5.0%)	2 (6.3%)	2 (3.5%)	1 (2.8%)	7 (4.3%)
Withdrawal[b]		2012[f]	No	No	No	
Citalopram	Depression	2 (5.0%)	1 (3.1%)	2 (3.5%)	1 (2.8%)	6 (3.7%)
Dabigatran	Venous thromboembolism	1 (2.5%)	2 (6.3%)	2 (3.5%)	1 (2.8%)	6 (3.7%)
Saquinavir	HIV infection	1 (2.5%)	2 (6.3%)	3 (5.3%)	0	6 (3.7%)
Strontium ranelate	Osteoporosis	N/A	N/A	3[g] (5.3%)	3[g] (8.6%)	6 (3.7%)

Note: N/A—not applicable as the drug was never marketed in that country or was not on the market between 2010 and 2016.

[a]The aim was to describe the top 10; 11 are included as 4 had equal numbers of advisories.

[b]Year of market withdrawal if withdrawn during the study period (2010-2016); the UK issued an advisory on dextropropoxyphene, despite its 2005 withdrawal.

[c]Rosiglitazone was later withdrawn in 2019 post-study period.

[d]Withdrawn in 2005 prestudy period.

[e]Dextropropoxyphene was withdrawn in 2012 in Australia but reintroduced in 2013 and later withdrawn again.

[f]32 mg single-IV dose withdrawn.

[g]Withdrawn in 2017 post-study period.

types of patients who should not receive the drug, in addition to patients who had congenital QT prolongation.[28]

Of the seven advisories, six mentioned the results of Thorough QT (TQT) studies as evidence to support the cardiac risks of citalopram and escitalopram.[29-33] One advisory by HC cites only 'clinical trial data' without further detail.[34] In 2004, the FDA published a guidance including standard language to describe cardiac risks identified in TQT studies, which is reflected within the FDA advisories, such as incorporation of a precautionary statement about the risk and recommendations for patient dosage and monitoring.[35] Other regulators differed in the amount of detail provided. For example, although the TGA advisory did not mention a TQT study, the cited results were the same as those in a MHRA advisory citing TQT study results.[29,31]

Four of the six advisories about citalopram and escitalopram advised health professionals to monitor patients, although they varied in their recommendations. All regulators advised ECG monitoring, but while the TGA, MHRA, and FDA advised health professionals to monitor electrolytes, HC only mentioned that "Hypokalemia and hypomagnesemia should be corrected before administering Celexa". The regulators also differed in their advice on when ECGs should be done. The MHRA recommended only performing ECGs in patients with cardiac disease before initiation of treatment, and in patients who experience cardiovascular symptoms, while other regulators advised "more frequent" ECG monitoring in patients at risk of QT prolongation, without further specifying the frequency. SIM scores for the four advisories ranged from 1/6 to 5/6, with two regulators only telling health professionals what to monitor (ie, ECG monitoring) but providing no further advice.

4 | DISCUSSION

In this analysis of regulatory advisories on cardiac risks by the TGA, FDA, HC, and MHRA from 2007 to 2016, we found inconsistencies between regulators in which safety issues they provided warnings about and how many advisories each regulator published. This supports the findings of other studies.[2,36] Of the 61 different drugs for which advisories were issued on cardiac risks, only nine had warnings issued in all of the countries in which they were approved.

While some safety issues lead to the drug being removed from the market, as with dextropropoxyphene, for others, the regulators decided that updating health professionals on the risk, and providing mitigation strategies, was sufficient to ensure that the benefits of the drug continued to outweigh these risks. An example is domperidone, where use at low doses for short periods of time in low-risk patients was decided to be reasonably safe.[37] Instead of removing this drug from the market, each of the regulators changed dosing recommendations and contraindicated it in patients with underlying cardiac conditions.

TABLE 4 Advice provided to health professionals

	FDA (n = 33)	HC (n = 29)	MHRA (n = 54)	TGA (n = 33)	Total (n = 149)
General advice					
Recommended actions	24 (72.7%)	22 (75.9%)	45 (83.3%)	18 (54.5%)	109 (73.2%)
Awareness raising	9 (27.3%)	7 (24.1%)	9 (16.7%)	14 (42.4%)	39 (26.2%)
No recommendations	0	0	0	1 (3.0%)	1 (0.7%)
Focus of advice					
Avoid use in certain patients	15 (45.5%)	15 (51.7%)	31 (57.4%)	13 (39.4%)	74 (49.7%)
Test/monitor patients	16 (48.5%)	16 (55.2%)	30 (55.6%)	12 (36.4%)	74 (49.7%)
Educate/counsel/advise patients	18 (54.5%)	7 (24.1%)	14 (25.9%)	9 (27.3%)	48 (32.2%)
Follow the product information/label	8 (24.2%)	8 (27.6%)	10 (18.5%)	19 (57.6%)	45 (30.2%)
Changes in dose	5 (15.2%)	8 (27.6%)	19 (35.2%)	5 (15.2%)	37 (24.8%)
Drug interactions	5 (15.2%)	10 (34.5%)	13 (24.1%)	5 (15.2%)	33 (22.1%)
Stop use in certain patients	5 (15.2%)	4 (13.7%)	16 (29.6%)	2 (6.1%)	27 (18.1%)
Change duration of use	2 (6.1%)	2 (6.9%)	9 (16.7%)	2 (6.1%)	15 (10.1%)
Switch to another medicine	2 (6.1%)	0	2 (3.7%)	2 (6.1%)	6 (4.0%)
Formulation change	1 (3.0%)	1 (3.4%)	2 (37.0%)	0	4 (2.7%)
Discontinue and restart as required	1 (3.0%)	0	0	1 (3.0%)	2 (1.3%)
Do not start new patients on therapy	1 (3.0%)	0	1 (1.9%)	0	2 (1.3%)

TABLE 5 Monitoring advice for prescribers: Systematic information for monitoring (SIM) scores[a]

Items of information	FDA (n = 15)	HC (n = 15)	MHRA (n = 30)	TGA (n = 8)	Total (n = 68)
What to monitor	12 (80%)	13 (86.7%)	18 (60%)	8 (100%)	51 (75.0%)
When to start monitoring	8 (53.3%)	8 (53.3%)	18 (60%)	4 (50.0%)	38 (55.9%)
When to stop monitoring	5 (33.3%)	6 (40%)	7 (23.3%)	0	18 (26.5%)
How frequently to monitor	8 (53.3%)	5 (33.3%)	9 (30%)	4 (50.0%)	26 (38.2%)
Critical value	5 (33.3%)	4 (26.7%)	8 (26.7%)	1 (12.5%)	18 (26.5%)
How to respond	5 (33.3%)	5 (33.3%)	13 (43.3%)	1 (12.5%)	24 (35.3%)
Average total score	2.87	2.73	2.43	2.25	2.57

[a]SIM score calculated based on papers by Ferner et al (2005), Geerts et al (2012), Nederlof et al (2015), and Højer et al (2020).

Monitoring advice, where provided, was fairly limited. Information about the critical value (the threshold representing a potential risk to the patient) and when to stop monitoring was usually absent (only provided in 26.5% of advisories each). This may create ambiguity for prescribers in clinical decision making as to when therapy should be changed or ceased. A 2020 study of Danish DHPCs also found that key needed detail was often lacking in these communications: only 16% of DHPCs stated the critical value and only 20% provided information about how often monitoring should occur.[23]

TABLE 6 Information on supporting evidence

	FDA (n = 40)	HC (n = 32)	MHRA (n = 57)	TGA (n = 35)	Total (n = 164)
Any evidence cited	40 (100%)	26 (81.3%)	47 (82.5%)	30 (85.7%)	143 (87.2%)
Systematic review	3 (7.5%)	1 (3.1%)	4 (7.0%)	1 (2.9%)	9 (5.5%)
Clinical trials	20 (50%)	11 (34.4%)	25 (43.9%)	11 (31.4%)	68 (41.5%)
Observational studies	3 (7.5%)	5 (15.6%)	5 (8.8%)	3 (8.6%)	16 (9.8)
Case reports	8 (20%)	11 (34.4%)	18 (31.6%)	12 (34.4%)	49 (29.9%)
Literature (unspecified)	1 (2.5%)	2 (6.3%)	1 (1.8%)	2 (5.7%)	6 (3.7%)
Post-market data (unspecified)	1 (2.5%)	1 (3.1%)	4 (7.0%)	1 (2.9%)	7 (4.3%)

The FDA generally provided more information in their advisories than other regulators. This is reflected in the format of the advisories. Advisories from the FDA contained four sections: nature of the concern, advice for patients, advice for health professionals, and a data summary. In this sample, a more structured approach tended to result in more details being provided.

The case study of citalopram and escitalopram showed that all four regulators provided fairly similar advice, although there were differences in the amount of detail provided, especially on monitoring. Advisories from all four countries referred to clinical trial evidence but did not cite a specific reference to a published or unpublished trial report. However, all of the regulators provided broadly similar recommendations. One important difference was the mention of risk of death in the advisories. The FDA and HC both mentioned that there was a risk of death, while the TGA and MHRA did not.

The extent to which differences in content of advisories may affect their impact in clinical practice is not certain. Current research on the effectiveness of advisories is mixed and has mostly focused on individual advisories and regulators. There have been a small number of systematic reviews which have investigated the effects of these advisories on rates of prescribing.[38-42] These have generally found that the current evidence is mixed, as advisories may have intended or unintended effects, to varying degrees, emphasizing that more research is required to understand why these effects are seen. One review which looked into papers on FDA advisories found that there was a mixed impact depending on the type of advisory.[38] Advisories which recommended patient monitoring had a minimal impact on prescribing and some advisories may have had unintended effects such as deceased use in patients not targeted by the advisory. Another review looking at papers on MHRA advisories found that the communication type made a difference, as DHPCs had more of an impact on prescribing than other types of advisories.[39]

Several studies have investigated the effectiveness of rosiglitazone advisories in a number of countries.[43-49] All of these studies found that there was a decrease in use following an advisory. Interestingly, an Australian study found that a decrease in use occurred after the initial European Medicines Agency and FDA warnings, but that there was no significant decline after a later TGA advisory or subsequent warnings.[46]

While it may appear beneficial to issue more advisories, there has been some research into the effects of public health communications and the risk of "alert fatigue". A 2013 study found an inverse relationship between number of communications and the ability to recall specific information.[50] Regulators need to balance the need to provide enough information to health professionals against oversaturating them with too much information.

Further research is needed to compare the effects of these advisories on prescribing, as well as how they affect doctors' and consumers' awareness of cardiac risks. A comparison of changes in prescribing between these countries might show how differences in advisory content may or may not have an effect. It would also be helpful to understand how regulators decide when to issue safety warnings, as in this study, we observed that regulators did not always issue the same warnings.

4.1 | Limitations

Our study has several limitations. Firstly, we used an otherwise comprehensive dataset of all advisories issued by the four included countries within a specified period, but we were unable to access DHPCs from Australia. This might explain some of the differences between the TGA and other regulators. Secondly, we were limited to only four regulators. Thirdly, we did not consider advisories outside the chosen time frame, and warnings may have been issued shortly before or after this time frame.

5 | CONCLUSIONS

In this overview of cardiac safety advisories, there was a low level of concordance between regulators in the decision to warn clinicians, leading to potential differences in knowledge and care between patients in different countries. Monitoring information was also often inadequate. This is particularly concerning considering the potentially fatal nature of many cardiac adverse effects.

ACKNOWLEDGEMENTS

The authors would like to thank Emily Karanges for assistance with data management and Joel Lexchin for his help in developing the data extraction tool.

DISCLOSURE

Lucy Perry is employed by George Clinical Pty Ltd a contract research organization that provides services to pharmaceutical companies.

AUTHOR CONTRIBUTIONS

AH, BM, and AF contributed to the conception, design, and interpretation of data. AH, AB, LP, AM, and EM contributed to data collection and the development of the data extraction tool. All authors reviewed the manuscript, give final approval, and agree to be accountable for all aspects.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ashleigh Hooimeyer https://orcid.org/0000-0002-8526-1837
Alice Bhasale https://orcid.org/0000-0002-5387-8760
Lucy Perry https://orcid.org/0000-0002-3337-1321
Alice Fabbri https://orcid.org/0000-0001-8413-0440
Annim Mohammad https://orcid.org/0000-0003-3744-2219
Barbara Mintzes https://orcid.org/0000-0002-8671-915X

REFERENCES

1. Psaty BM, Meslin EM, Breckenridge A. A Lifecycle approach to the evaluation of FDA approval methods and regulatory actions: opportunities provided by a new IOM report. *JAMA*. 2012;307(23):2491-2492.
2. Perry LT, Bhasale A, Fabbri A, et al. Comparative analysis of medicines safety advisories released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med*. 2019;179(7):982-984.
3. Hopper I. Cardiac effects of non-cardiac drugs. *Aust Prescr*. 2011;34(2):52-54.
4. Arana A, Johannes CB, McQuay LJ, Varas-Lorenzo C, Fife D, Rothman KJ. Risk of out-of- hospital sudden cardiac death in users of domperidone, proton pump inhibitors, or metoclopramide: a population-based nested case-control study. *Drug Saf*. 2015;38(12):1187-1199.
5. Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case- control study. *Pharmacoepidemiol Drug Saf*. 2010;19(9):881-888.
6. Smolina K, Mintzes B, Hanley GE, Oberlander TF, Morgan SG. The association between domperidone and ventricular arrhythmia in the postpartum period. *Pharmacoepidemiol Drug Saf*. 2016;25(10):1210-1214.
7. van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Saf*. 2010;33(11):1003-1014.
8. Fosbøl EL, Gislason GH, Jacobsen S, et al. Risk of myocardial infarction and death associated with the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clin Pharmacol Ther*. 2009;85(2):190-197.
9. Gudbjornsson B, Thorsteinsson SB, Sigvaldason H, et al. Rofecoxib, but not celecoxib, increases the risk of thromboembolic cardiovascular events in young adults-a nationwide registry-based study. *Eur J Clin Pharmacol*. 2010;66(6):619-625.
10. de Abajo FJ, Gil MJ, García Poza P, et al. Risk of nonfatal acute myocardial infarction associated with non-steroidal antiinflammatory drugs, non-narcotic analgesics and other drugs used in osteoarthritis: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2014;23(11):1128-1138.
11. Schjerning Olsen A-M, Fosbøl EL, Lindhardsen J, et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among myocardial infarction patients–a nationwide study. *PLoS One*. 2013;8(1):e54309.
12. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes*. 2009;2(3):155-163.
13. Schjerning Olsen A-M, Fosbøl EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation*. 2011;123(20):2226-2235.
14. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR study group. *N Engl J Med*. 2000;343(21):1520-1528.
15. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296(13):1633-1644.
16. Perry L, Bhasale A, Fabbri A, et al. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Canada, Australia, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiol Drug Saf*. 2020.29 1054–1063.
17. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC. ATC classification index with DDDs. 2020. https://www.whocc.no/. Accessed September 15, 2020.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
19. Koo TK, Li MY. A Guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15(2):155-163.
20. Nederlof M, Stoker LJ, Egberts TC, Heerdink ER. Instructions for clinical and biomarker monitoring in the summary of product characteristics (SmPC) for psychotropic drugs: overview and applicability in clinical practice. *J Psychopharmacol*. 2015;29(12):1248-1254.
21. Geerts AF, De Koning FH, Van Solinge WW, De Smet PA, Egberts TC. Instructions on laboratory monitoring in 200 drug labels. *Clin Chem Lab Med*. 2012;50(8):1351-1358.
22. Ferner RE, Coleman J, Pirmohamed M, Constable SA, Rouse A. The quality of information on monitoring for haematological adverse drug reactions. *Br J Clin Pharmacol*. 2005;60(4):448-451.
23. Højer M-MG, De Bruin ML, Boskovic A, Hallgreen CE. Are monitoring instructions provided in direct healthcare professional communications (DHPCs) of sufficient quality? A retrospective analysis of DHPCs sent out between 2007 and 2018. *BMJ Open*. 2020;10(5):e036498.
24. PBS Information and Management Section, Pricing and PBS Policy Branch, Technology Assessment and Access Division. *Expenditure and Prescriptions Twelve Months to 30 June 2019*. Pharmaceutical Benefits Scheme; 2019.
25. Torka M, Mintzes B, Bhasale A, Fabbri A, Perry L, Lexchin J. Secret safety warnings on medicines: a case study of information access requests. *Pharmacoepidemiol Drug Saf*. 2019;28(4):551-555.

26. Buckley NAF, Thomas A. Trials and tribulations in the removal of dextropropoxyphene from the Australian register of therapeutic goods. *Med J Aust*. 2013;199(4):257-260.
27. Funk KA, Bostwick JR. A Comparison of the risk of QT prolongation among SSRIs. *Ann Pharmacother*. 2013;47(10):1330-1341.
28. US Food and Drug Administration. FDA Drug Safety Communication: revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. US Food and Drug Administration. 2012. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-revised-recommendations-celexa-citalopram-hydrobromide-related. Accessed 15 September, 2020.
29. Therapeutic Goods Administration. Medicines Safety Update, Volume 3, Number 1, February 2012. Therapeutic Goods Administration (TGA). 2012. https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-3-number-1-february-2012. Accessed 15 September, 2020.
30. Gagné M. Celexa (citalopram) - Association with abnormal heart rhythms - For Health Professionals - Recalls and safety alerts. Health Canada. 2012. https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/14672a-eng.php. Accessed 15 September, 2020
31. Medicines and Healthcare products Regulatory Agency. Citalopram and escitalopram: QT interval prolongation. Medicines and Healthcare products Regulatory Agency. 2011. https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-qt-interval-prolongation. Accessed September 15, 2020.
32. Jones A. Association of Cipramil (citalopram hydrobromide) with dose-dependent QT interval prolongation. Lundbeck. 2011. https://webarchive.nationalarchives.gov.uk/20141206114903/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con134754.pdf. Accessed September 15, 2020.
33. US Food and Drug Administration. FDA Drug Saftey Communication: abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). US Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-abnormal-heart-rhythms-associated-high-doses-celexa-citalopram. Accessed 15 September, 2020.
34. Health Canada. Antidepressant Cipralex (escitalopram): updated information regarding dose-related heart risk - Recalls and safety alerts. Health Canada. https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/13674a-eng.php. Accessed 15 September, 2020.
35. US Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry - E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. 2005.
36. Zeitoun JD, Lefevre JH, Downing N, Bergeron H, Ross JS. Inconsistencies among European union pharmaceutical regulator safety communications: a cross-country comparison. *PLoS One*. 2014;9(10):e109100.
37. Pharmacovigilance Risk Assessment Committee. *Domperidone-Containing Medicinal Products Assessment Report*. European Medicines Agency; 2014.
38. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care*. 2012;50(6):466-478.
39. Weatherburn CJ, Guthrie B, Dreischulte T, Morales DR. Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: systematic review, time series analysis and meta-analysis. *Br J Clin Pharmacol*. 2020;86(4):698-710.
40. Georgi U, Lämmel J, Datzmann T, Schmitt J, Deckert S. Do drug-related safety warnings have the expected impact on drug therapy? A systematic review. *Pharmacoepidemiol Drug Saf*. 2020;29(3):229-251.
41. Piening S, Haaijer-Ruskamp FM, de Vries JTN, et al. Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf*. 2012;35(5):373-385.
42. Goedecke T, Morales DR, Pacurariu A, Kurz X. Measuring the impact of medicines regulatory interventions - systematic review and methodological considerations. *Br J Clin Pharmacol*. 2018;84(3):419-433.
43. Herdeiro MT, Soares S, Silva T, Roque F, Figueiras A. Impact of rosiglitazone safety alerts on oral antidiabetic sales trends: a country-wide study in Portugal. *Fundam Clin Pharmacol*. 2016;30(5):440-449.
44. Hsu JC, Cheng C-L, Ross-Degnan D, et al. Effects of safety warnings and risk management plan for thiazolidinediones in Taiwan. *Pharmacoepidemiol Drug Saf*. 2015;24(10):1026-1035.
45. Leal I, Romio SA, Schuemie M, Oteri A, Sturkenboom M, Trifirò G. Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. *Br J Clin Pharmacol*. 2013;75(3):861-868.
46. Niyomnaitham S, Page A, La Caze A, Whitfield K, Smith AJ. Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings. *BMC Health Serv Res*. 2014;14(1):151.
47. Noh Y, Kang DR, Kim DJ, Lee KJ, Lee S, Shin S. Impact of clinical evidence communications and drug regulation changes concerning rosiglitazone on prescribing patterns of antidiabetic therapies. *Pharmacoepidemiol Drug Saf*. 2017;26(11):1338-1346.
48. Qato DM, Trivedi AN, Mor V, Dore DD. Disparities in discontinuing rosiglitazone following the 2007 FDA safety alert. *Med Care*. 2016;54(4):406-413.
49. Ruiter R, Visser LE, van Herk-Sukel MPP, et al. Prescribing of rosiglitazone and pioglitazone following safety signals. *Drug Saf*. 2012;35(6):471-480.
50. Baseman JG, Revere D, Painter I, Toyoji M, Thiede H, Duchin J. Public health communications and alert fatigue. *BMC Health Serv Res*. 2013;13(1):295.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Hooimeyer A, Bhasale A, Perry L, et al. Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. *Pharmacol Res Perspect*. 2020;e00680. https://doi.org/10.1002/prp2.680

Appendix 2: Published papers in journal format

Appendix 2.1

Bhasale A, Mintzes B, and Sarpatwari A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. *BMJ* 369: m1107, 2020. doi: 10.1136/bmj.m1107

1 University of Sydney Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, 6W75, The Hub, Charles Perkins Centre D17, University of Sydney, NSW 2006, Australia

2 School of Population and Public Health, University of British Columbia, Vancouver, Canada

3 Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

Correspondence to: A Bhasale
abha9370@uni.sydney.edu.au

Additional material is published online only. To view please visit the journal online

Cite this as: *BMJ* 2020;368:m1107
http://dx.doi.org/10.1136/bmj.m1107

Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators

Alice Bhasale, [1] Barbara Mintzes, [1,2] Ameet Sarpatwari[3]

As new risks of SGLT2 inhibitors have emerged, how have regulators responded? Alice Bhasale and colleagues compare the number, timing, strength, and transparency of public safety communications across leading medicines regulators

Key messages

- Sodium glucose co-transporter-2 (SGLT2) inhibitors came to market amid heightened concern over the safety of diabetes drugs
- The drugs have received several serious safety warnings since approval, but the number, timeliness, and strength of these safety communications have differed between American, Australian, Canadian, and European regulators
- One regulator identified the risk of lower limb amputation during routine pre-market assessment, but three years passed before any regulator issued a public warning
- In some instances, the wording of warnings was weakened after interactions with industry
- Greater transparency is required to assure the public of the impartiality of evidence assessment and ensure that decisions reflect public values

Medicines regulators have an important role in ensuring that newly uncovered risks of approved drugs ("post-market" risks) reach prescribers and patients. Such information is conveyed through safety advisories (such as online alerts, bulletin articles, letters to health professionals) and changes to official drug prescribing information (box 1). Based on reviews of post-market safety controversies over the past two decades,[1-4] the public expects regulators to communicate post-market risks promptly and transparently, prioritising public over commercial interests.

Box 1: How regulators identify and communicate post-market risks

Post-market risks are identified through various means

- Studies designed to test for specific safety outcomes, sometimes as a requirement of licensing (such as FDA post-market requirements, EMA post-authorisation safety studies).
- Spontaneous adverse drug reaction reports collected and monitored by regulators
- Medical literature
- Notification or reporting by companies, as mandated by regulation
- Other regulators

Post-market risks are communicated using:

- Safety advisories
  - Website alerts, direct health professional communications (letters to health professionals), drug safety bulletins, and notices of safety investigations
  - Can be initiated by regulators or industry. Direct health professional communications, commonly used in the EU and Canada, are jointly developed by the company and regulator. FDA drug safety communications are developed by the FDA
- Prescribing information*
  - The approved statement of safety, efficacy, and authorised use may be updated to include new safety information.
  - Companies must apply to regulators to make updates.
  - Can be initiated by companies or when requested or required by a regulator. Companies can propose wording that regulators must assess and approve.

Safety advisories included were those related to drug adverse effects, not to administration errors, misuse, or manufacturing quality problems. FDA=US Food and Drug Administration; EMA=European Medicines Agency.
*Referred to as product information (Australia), product monograph (Canada), summary of product characteristics (UK), and informally as the drug label (US).

Assessing fidelity to these goals, we examined how the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), Health Canada, and the Australian Government Therapeutic Goods Administration (TGA) communicated emerging risks for a relatively new class of oral diabetes drugs—the sodium glucose co-transporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin—from first approval until June 2018. There are good reasons to expect timely communication of this information.

First, given the high prevalence of diabetes, even infrequent adverse effects from SGLT2 inhibitor use could have a large impact on the population. Second, SGLT2 inhibitors came to market amid heightened safety concerns over diabetes drugs. In 2010, accumulating evidence about the cardiovascular risks of rosiglitazone led to its loss of marketing authorisation in the EU and to strong regulatory warnings in the US.[5 6] Ensuing debate resulted in new FDA requirements for long term cardiovascular safety trials for all new diabetes drugs.[7] As trials like CANVAS have identified a cardiovascular benefit of SGLT2 inhibitors,[8 9] prescribing of this class of drugs is likely to rise.

We found that the regulators varied considerably in their propensity to communicate five serious risks of SGLT2 inhibitors—diabetic ketoacidosis, lower limb amputation, severe genitourinary infections, and fracture—and in the timeliness and strength of their warnings. Although most regulators provided some information about their risk assessments, the level of detail was inadequate to alleviate concerns about industry influence. Greater transparency is required to assure the public of the impartiality of evidence assessment and to ensure that decisions reflect public values.

Differences in the use and timing of safety warnings

The FDA issued advisories about the most risks, communicating all five safety concerns, compared with four by Health Canada, and two each by the EMA and TGA. Each regulator released advisories about lower limb amputation and diabetic ketoacidosis. The FDA and Health Canada also warned about acute kidney injury and fracture; only the FDA warned about severe genitourinary infections.

Time lags between regulators issuing advisories for the same safety issue ranged from 19 days to over 13 months (table 1), with Health Canada and the TGA usually following the EMA and FDA. The gap between the first and last regulator was shortest for diabetic ketoacidosis (FDA and TGA) and longest for bone loss and fracture (Health Canada and FDA).

Table 1 | Time to advisories and prescribing information changes (April 2012 to June 2018).

	Time from lead advisory (days)			
	FDA	EMA	Health Canada	TGA
Initial advisory				
Diabetic ketoacidosis	0	42	38	90
Amputation	19	0	216	39
Fracture risk	0	–	402	–
Severe genitourinary infections	0	–	–	–
Acute kidney injury	242	–	0	–
Follow-up advisory (within jurisdiction)				
Diabetic ketoacidosis	203	262	329	–
Amputation	367	327	279	–
Product information change				
Diabetic ketoacidosis	203	348	453	Changed*
Amputation (canagliflozin)†	453	360	180‡ 558§	Changed*
Fracture risk (canagliflozin)	0	–532	469	NA
Severe genitourinary infections:				
canagliflozin	0	–102	189	NA
dapagliflozin	0	173	415	Changed*
empagliflozin	0	768	–	Changed*
Acute kidney injury:				
canagliflozin	217	63	213	NA
dapagliflozin	175	No change	117	No change

o indicates the first advisory by any regulator; – indicates no advisory; a negative number indicates the action occurred before the first advisory; NA=not applicable. *The TGA does not provide an archive of previous prescribing information or a record of changes, so changes were identified by comparing current and initial prescribing information, dates of change unknown. †The EMA investigated across the class and added warnings to all prescribing information with more specific warnings for canagliflozin. The FDA and Health Canada added warnings for canagliflozin only. ‡Health Canada's initial response to the EMA advisory was a change in the adverse reactions section of the prescribing information. §Health Canada later added a boxed warning in line with the FDA's boxed warning.

Regardless of whether advisories were issued, most official drug prescribing information documents were updated to include these adverse effects, although the timing of these updates differed both between regulators and between drugs within a jurisdiction. The EMA, for example, added severe genitourinary infections to the prescribing information for canagliflozin and empagliflozin three years apart, whereas the FDA did so simultaneously (table 1).

Delayed action on amputation risk

That a new diabetes drug might increase the risk of a disease related complication such as lower limb amputation should have interested all regulators, particularly after the rosiglitazone controversy.[2 3] Yet, several years elapsed between the first identification of a signal by Health Canada and regulatory action.

In 2013, Health Canada cited the risk of lower limb amputation in its initial rejection of marketing approval for canagliflozin, seemingly based on interim results from the ongoing CANVAS trial.[10] It subsequently granted approval 10 months later, referring in approval documents to a non-statistically significant increase in amputations but explaining that text about peripheral ischaemia and skin ulcers had been added to the prescribing information.[10] The word "amputation," however, was not used (see supplementary file).

At least four years of data from the trial had been reviewed by regulators at the time of canagliflozin's approval.[11-14] Yet no other regulatory documents in the public domain described amputation until a 2016 EMA advisory that flagged the risk as a "new signal" after reviewing a report from the CANVAS programme's independent data safety committee.[15] Notably, the EMA had continued to receive monitoring reports every six months as the trial progressed and later confirmed that "the imbalance [in amputations] occurred as early as the first 26 weeks of therapy,"[16] suggesting that the risk had been evident in unblinded data for some time.

After the EMA identified the signal, the EMA and FDA each issued "early warning" advisories to alert clinicians and patients that the possible risk was being investigated. The initial FDA advisory reported that "amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo" but stated that the agency had "not determined whether canagliflozin increases the risk of leg and foot amputations."[17] The EMA said that the issue was "under investigation, and any mechanism behind the events is as yet unknown." But 10-12 months elapsed before findings were announced (table 1). Health Canada's eventual boxed warning came 16 months after the first EMA advisory and four years after Health Canada first assessed the data on lower limb amputation before approval.

Differences in clarity and strength of warnings

After assessing the CANVAS lower limb amputation data, the FDA communicated the risk in stronger terms than the EMA. The risk was described by the EMA as affecting "mainly toes" and "toe amputation," but by the FDA as "leg and foot amputations." Both regulators were factually correct as 30% of amputations for both placebo and canagliflozin in CANVAS were above the foot, but the EMA focused on the less severe outcome.[18]

The FDA also ascribed causality to canagliflozin in its post-assessment advisory ("canagliflozin causes an increased risk"), whereas the EMA and Health Canada advisories were more neutral (increased risk "has been observed"). The TGA advisory implied that the risk was probably a disease related complication, stating that "it should be noted that CANVAS involves patients at high risk of problems with the heart and blood vessels and that lower limb amputations occurred in both the canagliflozin and placebo groups in the study" (see supplementary file).

Not all key language in the FDA advisory was carried through to canagliflozin's prescribing information (box 2). Statements regarding causality and the advice to "inform patients that canagliflozin is associated with an increased risk of amputations" were omitted. FDA documents reveal extensive negotiations between the agency and the drug's manufacturer over revisions to the prescribing information and patient medication guide. Among other changes, the FDA agreed to delete the "numbers needed to harm" calculations, which the manufacturer argued was "not a metric commonly used by providers" and "not interpretable unless put in the context of benefit." The FDA did, however, resist repeated requests to change the patient warning about multiple amputations, citing the strength of evidence and need for clear communication. For prescribers it warned that "some patients had multiple amputations, some involving both limbs" [19]

Box 2: Changes after negotiation with company: canagliflozin prescribing information.

FDA drafted changes before company negotiation

- In CANVAS, use of Invokana increased the risk of lower limb amputations from 2.8 amputations per 1000 patients per year to 5.9 amputations per 1000 patients per year (number needed to harm: 323).
- In CANVAS-R, the use of Invokana increased the risk of lower limb amputations from 4.2 amputations per 1000 patients per year to 7.5 amputations per 1000 patients per year (number needed to harm: 270).

FDA approved changes after company negotiation

- In CANVAS, Invokana-treated patients and placebo-treated patients had 5.9 and 2.8 amputations per 1000 patients per year, respectively.
- In CANVAS-R, Invokana-treated patients and placebo-treated patients had 7.5 and 4.2 amputations per 1000 patients per year, respectively.

Emphasis added to indicate changes

The EMA's prescribing information, meanwhile, emphasised the similar distribution of major, minor, and multiple amputations in both canagliflozin and placebo groups rather than the overall doubling of amputation risk with canagliflozin, stating that "multiple amputations (some involving both lower limbs) were observed infrequently and in similar proportions in both treatment groups" (see supplementary file).

Regarding fracture risk, the EMA was more reticent than the FDA to attribute the effect to canagliflozin and in communicating this risk to prescribers. Unlike the other regulators, the EMA did not include fracture risk in the prescribing information at approval (see supplementary file). When it later tackled this inconsistency at the company's request, the EMA did not issue an advisory despite the risk being mentioned in the prescribing information for the first time.

At approval, the EMA, FDA, and TGA had required post-market research clarifying canagliflozin's effects on bone mineral density. The final study results spurred an FDA advisory announcing that "canagliflozin caused greater loss of bone mineral density at the hip and lower spine than a placebo" at two years, with stronger warnings on fracture risk.[20] By contrast, the prescribing information approved by the EMA reassured prescribers that canagliflozin "did not adversely affect bone mineral density after 104 weeks of treatment." Although no references are listed in the prescribing information, both regulators apparently examined the same data but reached opposing conclusions (box 3). Additionally, the EMA prescribing information implies that the 104 week bone density data came from a pooled dataset of over 5800 people, rather than the actual 714 person trial population (box 3). Despite the FDA's stronger warning, its advisory came nearly 18 months after the EMA prescribing information update.

Box 3: FDA and EMA—contradictory views regarding canagliflozin and possible effects on bone mineral density

FDA prescribing information—updated 10 Sep 2015

Bone mineral density (BMD) was measured by dual energy x ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years). At 2 years, patients randomised to Invokana 100 mg and Invokana 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively.*

EMA prescribing information—updated 10 Apr 2014

In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of approximately 5800 patients, no difference in fracture risk was observed relative to control.† After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.*

*A study required by regulators and undertaken by the sponsor describes two year (104 week) follow-up of 714 patients with serial bone mineral density measurement.[21]

†A study undertaken by the sponsor describes a pooled dataset of fracture risk in 5840 patients but no measurement of bone mineral density.[22]

Reasons for differences in communication and their implications

What are the reasons for these differences in safety communications? Compared with the detailed data released when drugs are approved, limited information is available about how regulators assess post-market risks. Summaries of some assessments were made publicly available by the EMA, FDA, and Health Canada but many lacked explanatory detail or the ability to link to the original data, and assessment material was not provided by the TGA. Regarding fracture, we found no information on the EMA's assessment or the reasons for the FDA's delayed response. Most lacking was transparency as to interactions between industry and regulators.

Some differences in safety communications might reflect intentional policy choices—for example, fewer safety advisories could arise from regulators' uncertainty about the strength of post-market findings or from perceived drawbacks of frequent notification, such as alert fatigue or excessive alarm. To determine whether these approaches are appropriate, better evidence is needed on the effects of safety advisories and the degree to which prescribers recognise changes to prescribing information without additional warnings.

Relative constraints in regulatory capacity probably contributed to the differences we observed. Regulators must balance the resources they assign to post-market safety with the attention they give to new drug approvals.[23] In attempting this balance, the FDA has struggled to ensure that companies fulfil post-market study obligations.[24] Smaller regulators, meanwhile, are hampered by smaller operating budgets and population sizes for identifying adverse effects.[25 26] Unsurprisingly, the timing of Health Canada and the TGA's responses indicates some reliance on the FDA and EMA to identify and respond to safety issues.[27 28] As a supranational agency, the EMA relays safety communication decisions to 28 member states. Accordingly, for "practical" reasons, EMA policy is to centrally coordinate and translate direct health professional communications for only limited types of safety updates, such as new contraindications and EU-wide investigations.[29 30] This could explain the lack of an EMA safety advisory for fracture, despite being previously described by the agency as an "important potential risk."[31]

Finally, the relative involvement of sponsors in drafting and disseminating safety communications might have had an important role in substance and timing. Current models of post-market safety regulation in most jurisdictions rely heavily on industry capacity. Commentators have noted the intrinsic paradox of relying on industry to collect, analyse, and report data that might negatively affect business goals.[32 33] Regulators have the authority to unilaterally compel industry to make safety related changes to prescribing information, but surrounding negotiations can weaken safety messages—as seen with lower limb amputation—and delay risk communication.[34] Such discussions are largely conducted in confidence and should be more transparent. Additionally, the issuance of safety communications by sponsors might affect the trust with which they are received.[35 36] Although European doctors have indicated that they prefer to receive safety advisories from regulators rather than industry,[35 36] a key form of safety advisory in the EU are letters from sponsors with text agreed by regulators.

Conclusions

Decisions about when to issue safety communications are largely discretionary and might depend on regulators' ability to detect post-market risks, their perception of the significance of those risks, and their propensity to communicate.[23 34 37 -39] In our review of post-market safety communications for SGLT2 inhibitors, we found that the FDA issued more safety advisories but was not always the first to act. Time lags between regulators were common, suggesting limitations in capacity.

Although regulators are not required to harmonise safety decisions,[40 41] a senior FDA official, responding to evidence of differences between regulators' safety alerts,[42] acknowledged that "with the increasing global reach of communications . . . discordance can create confusion if the basis for the differing conclusions is not made clear."[41] In addition to detailed explanatory summaries, we think that regulators should provide public access to post-market safety reports submitted by industry to regulators.[43] Industry interactions with regulators regarding the interpretation of safety data should likewise be a matter of public record. Such records are currently either unavailable or extensively redacted beyond what might justifiably be considered commercially in confidence. Greater transparency in decision making would increase the accountability of both regulators and industry and allow more informed treatment choices to be made.

Contributors and sources: This paper was developed as a case study of safety advisories for AB's doctoral research on regulatory post-market safety policy and is related to an Australian government National Health and Medical Research (NHMRC) funded research project on safety advisories. BM is the chief investigator on the NHMRC funded project and has a longstanding interest in regulatory and pharmaceutical policy; AS is a co-investigator on the NHMRC funded project and an epidemiologist and lawyer with research expertise in US pharmaceutical policy. AS's work is also funded by Arnold Ventures and the Harvard-MIT Center for Regulatory Science. Research and writing of the article were supported by funding provided by the University of Sydney and Harvard University Mobility Scheme. AB conducted the documentary review and preliminary analysis. All three authors contributed to the interpretation and synthesis of the findings and the writing of the manuscript. Colleen Fuller and Ellen Reynolds provided helpful comments and perspectives on an earlier draft of this paper.

Patient involvement: Colleen Fuller, a Canadian researcher and writer with patient advocacy experience in diabetes, provided helpful comments on an earlier draft, including a perspective on the significance of diabetic ketoacidosis associated with the use of SGLT2s for type 1 diabetes.

Competing interests: We have read and understood BMJ policy on declaration of interests and have the following interests to declare: None

Provenance and peer review: Not commissioned; externally peer reviewed.

1 US Institute of Medicine. Committee on the Assessment of the US Drug Safety System. The future of drug safety—promoting and protecting the health of the public. In: Baciu A, Stratton K, Burke SP, eds. *Committee on the Assessment of the US Drug Safety System, Board on Population Health and Public Health Practice*. The National Academies Press, 2006.

2 Moynihan R. Rosiglitazone, marketing, and medical science. *BMJ* 2010;340:c1848. doi: 10.1136/bmj.c1848 pmid: 20375091

3 Califf RM, Kramer JM. The balance of benefit and safety of rosiglitazone: important lessons for our system of drug development and postmarketing assessment. *Pharmacoepidemiol Drug Saf* 2008;17:782-6. doi: 10.1002/pds.1617 pmid: 18655016

4 Hugman B. The Erice declaration: the critical role of communication in drug safety. *Drug Saf* 2006;29:91-3. doi: 10.2165/00002018-200629010-00007 pmid: 16454537

5 European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. 2010. https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-suspension-avandia-avandamet-avaglim.

6 Woodcock J, Sharfstein JM, Hamburg M. Regulatory action on rosiglitazone by the US Food and Drug Administration. *N Engl J Med* 2010;363:1489-91. doi: 10.1056/NEJMp1010788 pmid: 20942663

7 US Department of Health and Human Services Food and Drug Administration. Guidance for industry. Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. 2008. https://www.federalregister.gov/documents/2008/12/19/E8-30086/guidance-for-industry-on-diabetes-mellitus-evaluating-cardiovascular-risk-in-new-antidiabetic

8 Neal B, Perkovic V, Mahaffey KW, etalCANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-57. doi: 10.1056/NEJMoa1611925 pmid: 28605608

9 Zinman B, Wanner C, Lachin JM, etalEMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-28. doi: 10.1056/NEJMoa1504720 pmid: 26378978

10 Health Canada. Summary Basis of Decision. Invokana. Health Canada Ottawa: Health Canada, 2014. https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00255#Brandname4 .

11 US Department of Health and Human Services Food and Drug Administration. Canagliflozin Summary Review. 204042Orig1s000. 2013. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042orig1s000sumr.pdf

12 US Department of Health and Human Services Food and Drug Administration. *Application Number: 204042orig1s000 Medical Review(s).* FDA, 2013.

13 Australian Government Department of Health Therapeutic Goods Administration. *Australian Public Assessment Report for Canagliflozin (as hemihydrate).* TGA, 2014.

14 European Medicines Agency. Assessment report. Canagliflozin. EMA/374133/2013 Committee for Medicinal Products for Human Use (CHMP) ed. London: EMA, 2013.

15 European Medicines Agency. *Pharmacovigilance Risk Assessment Committee (PRAC). Minutes of the PRAC meeting on 11-14 April 2016.* EMA, 2016.

16 European Medicines Agency. *PRAC assessment report. Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data. SGLT2 inhibitors and lower limb amputation (canagliflozin, dapagliflozin, empagliflozin-containing medicines). EMA/PRAC/637349/2016.* EMA, 2017.

17 US Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate. 18 May 2016. 2016. https://www.fda.gov/Drugs/DrugSafety/ucm500965.htm.

18 Napp Pharmaceuticals. Invokana. Summary of product characteristics. Updated 13 Sep 2018. UK.

19 US Food and Drug Administration Center for Drug Evaluation and Research. Approval Package for: Application Number: 204042Orig1s026 Trade Name: INVOKANA Generic Name: Canagliflozin. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/204042Orig1s026.pdf.

20 US Department of Health and Human Services Food and Drug Administration. FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. 09 October 2015. 2015. https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm.

21 Bilezikian JP, Watts NB, Usiskin K, etal. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. *J Clin Endocrinol Metab* 2016;101:44-51. doi: 10.1210/jc.2015-1860 pmid: 26580234

22 Watts NB, Bilezikian JP, Usiskin K, etal. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2016;101:157-66. . doi: 10.1210/jc.2015-3167 pmid: 26580237

23 Herder M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. *Milbank Q* 2019;97:820-57. doi: 10.1111/1468-0009.12413 pmid: 31407412

24 United States Government Accountability Office. Drug safety. FDA expedites many applications, but data for postapproval oversight need improvement.GAO, 2015.

25 Jain AB, Mollet A, Szucs TD. Regulatory watch: structural and procedural characteristics of international regulatory authorities. *Nat Rev Drug Discov* 2017;16:594. doi: 10.1038/nrd.2017.135 pmid: 28799542

26 OECD Data. Population Paris: OECD. 2019https://data.oecd.org/pop/population.htm.

27 European Medicines Agency. *Connecting the dots. Towards global knowledge of the international medicine regulatory landscape: mapping of international initiatives.* EMA, 2016.

28 Health Canada. *Health product vigilance framework.* Health Canada, 2012.

29 European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP). Module IX Signal management (Rev 1).* EMA with HMA, 2017.

30 European Medicines Agency. *Questions & answers on Article 31 pharmacovigilance referral procedures.* EMA, 2015.

31 European Medicines Agency. *Assessment report. Dapagliflozin. EMA/689976/2012.* EMA, 2012.

32 Anonymous . European pharmacovigilance: increasingly outsourced to drug companies. *Prescrire Int* 2014;23:302-3, 305-7.pmid: 25629153

33 Lexchin J. *Public profits vs private policy.* University of Toronto Press, 2016.

34 Health Canada and the Public Health Agency of Canada. Evaluation of the Human Drugs Program 1999-2000 to 2011-2012. 2014.

35 De Vries ST, van der Sar MJM, Cupelli A, etalSCOPE Work Package 6. Communication on safety of medicines in Europe: Current practices and general practitioners' awareness and preferences. *Drug Saf* 2017;40:729-42. doi: 10.1007/s40264-017-0535-0 pmid: 28540672

36 Piening S, Haaijer-Ruskamp FM, de Graeff PA, Straus SM, Mol PG. Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. *Drug Saf* 2012;35:1061-72. doi: 10.1007/BF03261992 pmid: 23061782

37 Eichler H-G, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat Rev Drug Discov* 2008;7:818-26. doi: 10.1038/nrd2664 pmid: 18787530

38 Kesselheim AS, Franklin JM, Avorn J, Duke JD. Speaking the same language? International variations in the safety information accompanying top-selling prescription drugs. *BMJ Qual Saf* 2013;22:727-34. doi: 10.1136/bmjqs-2012-001704 pmid: 23620531

39 Zeitoun J-D, Lefèvre JH, Downing N, Bergeron H, Ross JS. Inconsistencies among European Union pharmaceutical regulator safety communications: a cross-country comparison. *PLoS One* 2014;9:. doi: 10.1371/journal.pone.0109100 pmid: 25333986

40 Dal Pan GJ, Arlett PR. The US Food and Drug Administration-European Medicines Agency collaboration in pharmacovigilance: common objectives and common challenges. *Drug Saf* 2015;38:13-5. doi: 10.1007/s40264-014-0259-3 pmid: 25539878

41 Dal Pan GJ. Gauging the effectiveness of medicines safety communications from global regulatory agencies. *JAMA Intern Med* 2019;179:984-5. doi: 10.1001/jamainternmed.2019.0266 pmid: 31034034

42 Perry LT, Bhasale A, Fabbri A, etal. Comparative analysis of medicines safety advisories released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med* 2019;179:982-4. doi: 10.1001/jamainternmed.2019.0294 pmid: 31033999

43 Sharfstein JM, Miller JD, Davis AL, etal. Blueprint for transparency at the US Food and Drug Administration: recommendations to advance the development of safe and effective medical products. *J Law Med Ethics* 2017;45:7-23doi: 10.1177/1073110517750615.

Supplementary information: Supplementary tables

Appendix 2.2

Bhasale AL, Sarpatwari A, De Bruin ML, Lexchin J, Lopert R, Bahri P, and Mintzes BJ. Postmarket safety communication for protection of public health: A comparison of regulatory policy in Australia, Canada, the European Union, and the United States. ***Clinical Pharmacology and Therapeutics*** **2020. doi: 10.1002/cpt.2010**

Postmarket Safety Communication for Protection of Public Health: A Comparison of Regulatory Policy in Australia, Canada, the European Union, and the United States

Alice L. Bhasale[1], Ameet Sarpatwari[2,*], Marie L. De Bruin[3,4], Joel Lexchin[5], Ruth Lopert[6], Priya Bahri[4,7] and Barbara J. Mintzes[1]

In the wake of the withdrawal of the nonsteroidal anti-inflammatory drug rofecoxib, regulators worldwide reconsidered their approach to postmarket safety. Many have since adopted a "life cycle" approach to regulation of medicines, facilitating faster approval of new medicines while planning for potential postmarket safety issues. A crucial aspect of postmarket safety is the effective and timely communication of emerging risk information using postmarket safety advisories, commonly issued as letters to healthcare professionals, drug safety bulletins, media alerts, and website announcements. Yet regulators differ in their use of postmarket safety advisories. We examined the capacity of regulators in the United States, Europe, Canada, and Australia to warn about postmarket safety issues through safety advisories by assessing their governance, legislative authority, risk communication capabilities, and transparency.

A key aim of postmarket regulation of medicines is to protect public health when new safety issues arise. Regulatory warnings in the form of letters to healthcare professionals, drug safety bulletins, media alerts, and public website announcements have long played a role in informing healthcare professionals and consumers of emerging adverse effects and other safety issues. These postmarket safety advisories, the focus of this review, are a key component of regulators' postmarket safety communication toolkit. Safety advisories may accompany other mechanisms for communicating postmarket safety such as changes to the approved product information (e.g., adding new contraindications), risk minimization activities (e.g., mandatory prescriber training), and suspension or withdrawal of marketing approval. More broadly, regulators' use of safety advisories may be indicative of their individual cultural and institutional characteristics, including their degree of risk aversion, propensity to act, and transparency.

Controversies over the adequacy of postmarket safety communication have been a key driver of change in regulation. Following the withdrawal of rofecoxib in 2004, the United States (US) Institute of Medicine commented that the US Food and Drug Administration (FDA) and the pharmaceutical industry did not "consistently demonstrate accountability and transparency to the public by communicating safety issues in a timely and effective fashion."[1] Similar concerns about postmarket safety communication were described in an independent study completed for the European Commission in 2007, which highlighted the "low levels of transparency relating to pharmacovigilance and relatively limited European Union (EU) coordination of communication about the safety of medicines, plus complex product information with poor penetration of key warnings."[2]

Since the rofecoxib controversy, postmarket regulation has changed considerably in the United States and the European Union,[3,4] underpinned by significant legislative amendments.[5–8] With international convergence and harmonization in pharmaceutical policy and standards,[9,10] these changes have had a global influence on other agencies, including Australian and Canadian regulators. An approach known as "life cycle regulation" now dominates, characterized by data collection and risk minimization planning in the premarket period and an expanded range of capabilities post marketing to identify, assess, and respond to evolving risks, including mandatory postmarketing studies and stronger conditions for safer use (**Box 1**).

Part of the rationale for life cycle regulation is that excessive risk aversion on the part of regulators could prevent patients from receiving the benefits of drug treatment. Accordingly, proponents of life cycle regulation contend that uncertainties about safety should not delay access to medicines, particularly as some adverse effects can only be identified post marketing.[3,11,12] Instead, patient harm can be avoided or minimized by proactive risk management.[1,12] Postmarket studies, monitoring, and communication of emerging

[1]School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, NSW, Australia; [2]Program on Regulation, Therapeutics, and Law (PORTAL) Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [3]Copenhagen Center for Regulatory Science, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [4]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [5]York University, Toronto, Ontario, Canada; [6]George Washington University, Washington, DC, USA; [7]European Medicines Agency, Amsterdam. *Correspondence: Ameet Sarpatwari (asarpatwari@bwh.harvard.edu)

Received March 16, 2020; accepted July 25, 2020. doi:10.1002/cpt.2010

Box 1 Features of life cycle risk management regulation

At Marketing Approval

Risks that are not fully characterized at the time of approval, for example, because of limitations in data, can be addressed through the following means:

- Further research (i.e., postmarket studies)
  - For the EMA and national EU regulators, this includes "postauthorization safety studies" and patient/disease registries (which may be voluntary or mandated)
  - For the FDA, this includes "postmarket requirements" (mandated) and "postmarket commitments" (agreed/voluntary).
- Routine or intensive monitoring of cases in ongoing trials or more detailed collection of spontaneous adverse event reports
- Labeling in the product information[a] (e.g., contraindications, dose restrictions, limiting indications and safety information)
- Educational and other interventions
  - Programs to influence and control the use of drugs by clinicians (e.g., DHPC[b] letters, consumer guides, educational materials and interventions, controlled distribution, and programs to prevent pregnancy in women taking teratogenic drugs, e.g., isotretinoin (called additional risk minimization measures by EU regulators and risk evaluation and mitigation strategies (REMS) by the FDA).

Risk Management Plans are used by EU regulators, Health Canada, and the Australian TGA to document risks and mitigation strategies.

Post Marketing

Regulatory interventions include (as above):

- Changes to the usage authorized by the approved product information for healthcare professionals and consumers (e.g., new contraindications, boxed warnings, and adverse reactions)
- Postmarket studies
- Active surveillance and/or passive surveillance with enhanced review (e.g., additional requirements for research or risk mitigation when specific events are reported)
- New risk mitigation interventions: e.g., new FDA REMS, or new EU risk minimization measures
- Postmarket safety advisories from regulators including DHPCs demanded by regulators from industry
- Suspension (temporary) or withdrawal of marketing approval

[a]Product information encompasses the approved prescribing information (for healthcare professionals), consumer information, and in some cases, package inserts and labeling. Prescribing information is known in Australia as "Product information," in Canada as the Product Monograph, in the European Union as the "Summary of Product Characteristics," and in the United States as "Prescribing information."

[b]DHPC, Direct healthcare professional communications (European Union) – also known in the United States as "Dear Health Care Provider Letters" and in Canada as "Dear Health Care Professional Letters." EMA, European Medicines Agency; FDA, US Food and Drug Administration (United States); TGA, Therapeutic Goods Administration (Australia).

safety issues are key safeguards intended to ensure that unexpected harms are detected quickly and their impact is minimized.

Yet there is debate about the extent to which speed to market and postmarket safety are appropriately balanced.[13,14] While life cycle regulation has resulted in faster drug approvals,[15,16] it has also been associated with lower evidentiary requirements before market approval that may increase the likelihood of previously undetected safety issues emerging post marketing.[17,18] Medicines approved using expedited approval processes such as priority reviews have been associated with higher rates of postmarket safety warnings and withdrawals in North American studies,[14,19] though not in Europe.[20] The FDA has been found to lack data demonstrating that postmarket safety actions are effective in decreasing harms.[21]

Only a small proportion of postmarket risks are anticipated by regulators in the premarket phase,[22,23] while between 15% and 30% of new drugs are associated with serious postmarket safety issues or withdrawn within 10–12 years of approval.[19,24,25] Against this background, effective communication to healthcare professionals and the public is critical.

In previous research, our group found that medicines regulators in Australia, Canada, the United Kingdom (UK), and the United States differed substantially in their use of postmarket safety advisories.[26] All four regulators issued advisories for only 7% (40/573) of the risks communicated, for medicines approved in all countries.[26] These regulators were chosen for their comparable regulatory standards and diversity in size and global influence (the UK being part of the EU regulatory network coordinated by the European Medicines Agency (EMA) until March 2020). Similar discrepancies have been found in the use of direct healthcare professional communications (DHPCs) by different EU member states,[27] and in EU and US prescribing safety information.[28] Such divergence could lead to important differences in risk awareness and avoidance.

BASIS FOR THIS REVIEW

Aims

Differences in regulatory policy may explain some variance in safety warnings, but major regulators' policies have not been compared in the scientific literature to date. Here we review relevant policies of the EMA, the FDA, Health Canada, and the Australian Therapeutic Goods Administration (TGA). Our objective was to assess current regulatory policies for postmarket

safety advisories and the related regulatory contexts focusing on governance, legislated authority, capability, and transparency of regulatory actions.

Approach to the review

We defined regulatory postmarket safety advisories as notices issued or authorized by regulators to inform healthcare professionals or the public about medicine safety issues emerging post marketing. There is no standardized regulatory terminology for such communications, which can occur via DHPCs, drug safety bulletins, media alerts, and public website announcements. Communications pertaining to medication errors, manufacturing or quality issues, drug shortages, or product recalls were not the focus of this review, as such issues are qualitatively different in terms of their impact on patient safety and treatment choices. However, the communication modalities discussed in this review could be used in such situations.

Excluded from the review were also other mechanisms that regulators use for postmarket safety communication, mainly changed wording in product information and "risk minimization" measures, such as educational resources.[29,30] Safety advisories differ from these forms of communication in their more expedited nature, attempting to actively communicate and publicize new information, sometimes before the risk is fully understood.

Box 2 Analytical framework for postmarket safety communication policies

Governance:
- Responsibility for assessing safety issues
- Responsibility for communicating and disseminating postmarket safety information
- Mechanisms and extent of public participation in decision making about postmarket safety and communications

Legislative authority:
- Authority to issue warnings and postmarket safety advisories
- Authority to require companies to issue direct healthcare professional communications

Role of industry:
- Industry involvement in postmarket safety communication and related regulatory activity

Risk communication capability:
- Goals of regulatory communication, in particular regarding behavior change
- Methods of communicating postmarket issues
- Monitoring and measurement of effectiveness
- Guidelines for writing and communicating risk
- Risk communication priority/strategy

Transparency:
- Minutes of expert committee meetings
- Documents explaining how regulatory decisions were made
- Accessibility of postmarket safety data

Our analytical framework (**Box 2**) was broadly informed by previous analyses of regulatory policy.[12,31–34] We considered:

- Governance for postmarket safety communication and the extent of public participation in decision making about advisories
- Legislative authority for regulators to issue postmarket safety advisories or require industry to issue DHPCs
- The role of industry
- Risk communication capability, including how regulators communicate postmarket safety issues and their emphasis on behavioral change[35,36]
- Policy support for transparency regarding postmarket safety issues

Information for our review was gathered from relevant governing legislation related to safety advisories and systematic searches of government and regulators' websites for policy documents, guidelines for industry, information for the public, reports, and evaluations of relevant policies. (**Supplementary Materials – MethodsS1**).

GOVERNANCE FOR POST MARKET SAFETY AND RISK MINIMIZATION

Within regulatory agencies, responsibility for postmarket safety communication can span different units according to their function (**Figure 1**). Safety advisories may form part of an overall communication strategy or may accompany other risk minimization measures as indicated in **Box 1**.

Postmarket safety monitoring and medicines' life cycle risk management are typically handled by a dedicated postmarket surveillance unit within the regulatory agency. This monitoring can include postmarket studies, typically by industry (voluntary or mandated), adverse drug event reporting, and active surveillance of large data sets.

Agency structure can contribute to fragmentation in awareness and decision making. For example, to update prescribing information with new postmarket safety data, companies must apply to regulators, either on their own initiative or when required to do so by regulators. In some agencies, these changes are managed by the unit that approved the drug, which is not responsible for either postmarket monitoring or postmarket safety advisories.

Where emerging evidence of a safety issue points to the possibility of an error or oversight in the premarket evaluation, cognitive bias may compromise an objective review of the decision. Additionally, units responsible for surveillance or postmarket safety have traditionally had less power or recognition in the institutional hierarchy than those responsible for new drug approval, and in some jurisdictions may be less well resourced.[12,31,34] Finally, regulatory action can be delayed by governance issues, including complex decision-making structures, unclear accountability, and legal hurdles.[37]

Poor clarity in roles and power imbalances have both been identified as weaknesses.[1,12] Stronger systems would allocate responsibilities clearly, and have coordinating mechanisms and oversight in place.

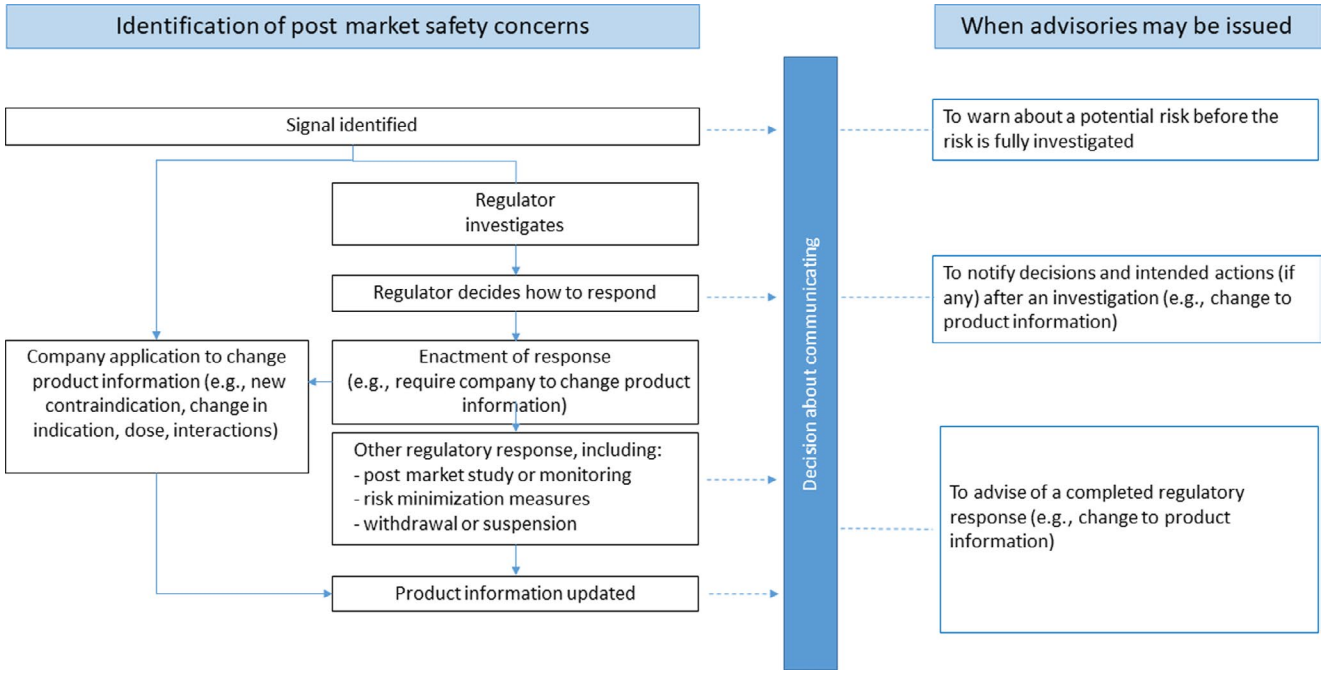


Figure 1 Timing of advisories and identification of postmarket safety issues.

Differences among regulators

FDA. At the FDA, new drug assessment and postmarket surveillance are managed by separate units. At new drug approval, FDA staff can mandate postmarket studies and/or interventions to manage risk, known as risk evaluation and mitigation strategy (REMS) programs.[38]

Post marketing, safety decision making occurs internally using a cross-team approach involving new drug assessors (Office of New Drugs), postmarket surveillance staff (Office of Surveillance and Epidemiology), and communications experts (Office of Communications).[38,39] This multidisciplinary approach has been specifically adopted to overcome internal disagreements regarding the significance of postmarket safety evidence arising from different methods of assessing harm,[40] but means that no single unit is responsible overall.[12,41]

The Office of New Drugs is still responsible for making postmarket product information changes, either before or after safety advisories are issued. Operationally, the Office of Communication prepares and disseminates drug safety messages.[42] The Office of Surveillance and Epidemiology does not therefore have full responsibility for postmarket safety.

At its discretion, the FDA may consult expert advisory committees on postmarket issues.[43] Public participation and representations are allowed as part of these committee meetings.[44]

EMA. Since enactment of the 2012 EU pharmacovigilance legislation, responsibility for postmarket safety has been centralized in the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), replacing the Pharmacovigilance Working Party that advised the Committee for Medicinal Products for Human Use (CHMP).[45] Before the 2012 legislation, final decision making for pharmacovigilance was largely managed by EU countries' national regulatory agencies, with less consistency between countries.[46] The PRAC comprises representatives of EU regulatory agencies, individual scientific experts, and consumer and healthcare professional representatives. PRAC members take "rapporteur" roles for specific products, supported by their respective national regulatory agency and EMA staff. The PRAC makes recommendations to governing bodies within the EMA: to the CHMP for products centrally authorized across the European Union (after assessment by the EMA on behalf of all member states) by the European Commission, and to the Coordination Group for Mutual Recognition and Decentralized Procedures—Human for nationally authorized medicines, for which national EU regulators are the competent authorities.

This arrangement separates responsibilities for medicines approval from postmarket safety assessment and allows for a coordinated, centralized assessment of pharmacovigilance considerations before and after approval. At the time of approval for centrally authorized products, PRAC advice on risks, surveillance requirements, and postmarket studies are included in the drug's risk management plan initially proposed by the company. Post marketing, for both centrally and nationally authorized products, the PRAC assesses pharmacovigilance signals and data and recommends actions, including product information changes, which are then executed following acceptance by governing bodies. Any national authority, company, or the PRAC itself can refer an issue posing a "potential serious risk to public health" to the EMA for investigation. This process is called a "referral procedure" and can result in changes to or withdrawal of marketing authorization for both centrally and nationally authorized medicines.[6] Postmarket safety decisions made by the EMA for centrally authorized products and referral procedures are legally binding in all member states.

For the EMA, public participation in regulatory decisions includes consumer, healthcare professional and additional expert representation on the PRAC, and public hearings. Public hearings are authorized by EU legislation but are held only when regulators consider them appropriate.[5] Public hearings have been held to discuss consumer perspectives on risk management of valproate teratogenicity and serious adverse effects of fluoroquinolones.[47,48]

Importantly, the EMA differs from other regulators in that it is a supranational agency, sharing pharmacovigilance responsibilities with national regulatory agencies. The EMA has primary authority for centrally authorized products and is responsible for maintaining their marketing authorizations, product information, and risk management plans. For products authorized centrally or nationally, the EMA supports signal management and coordinates other activities, including maintaining EudraVigilance, a centralized repository of adverse event reports across the European Union and worldwide, and a process for EU-wide single assessment of periodic safety update reports to be submitted by marketing authorization holders according to standard or enhanced schedules. National authorities are responsible for signal detection, risk management plans, and maintaining marketing authorizations and product information for nationally authorized products.[49]

Safety communications are prepared by EMA staff and discussed and endorsed by PRAC as part of their assessments and decisions, and the EMA coordinates consistent communications across the European Union. National authorities are in charge of translations and local adaptations of PRAC-agreed materials as well as national communication strategies.[50]

Health Canada. Health Canada's governance of postmarket safety is shared across different directorates within the Health Products and Food Branch. The Marketed Health Products Directorate is responsible for postmarket issues including surveillance and risk communication (which is managed by the Office of Policy, Risk Advisory, and Advertising).[51,52] Responsibility for changes to prescribing information rests elsewhere, with the directorates responsible for premarket assessments and approval (the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate). Decisions regarding whether, for example, a postmarket prescribing information change necessitates an advisory therefore relies on consultation between different directorates.

A 2011 Auditor General's report found that this division of responsibility and inadequate processes for implementing recommendations were contributing to inaction and delays. Different departments were responsible for making safety-related recommendations and liaising with companies to ensure changes were made, with companies having discretion about whether or not to implement recommendations.[37]

Health Canada convenes short-term expert advisory panels for specific issues, including postmarket safety issues, which include members of the public.[53] Examples include panels to consider safety risks of opioids and selective serotonin reuptake inhibitor antidepressants.[54]

TGA. As with other regulators, responsibilities for medicine approvals and licensing are separated from postmarket surveillance functions. New approvals and applications to change prescribing information post marketing are assessed within one branch (Prescription Medicines Authorization), while postmarket surveillance and advisories are the responsibility of the Pharmacovigilance and Special Access Branch. The latter also evaluates and provides preapproval advice on risk management plans decided before approval and monitors their implementation.

TGA staff are primarily responsible for assessing postmarket safety issues and determining the appropriate response. The TGA had a dedicated expert advisory committee for postmarket safety until 2017, when it was abolished and its functions integrated into a single committee dealing with both prescription and nonprescription medicines. The current Advisory Committee on Medicines is consulted not only on premarket matters, primarily drug approvals, but also postmarket safety matters including emerging safety signals and risk management plans. The membership includes one consumer representative.[55] TGA regulations require public consultation for changes in scheduling (rules governing restrictions on access such as classification of medicines to prescription-only or over the counter), for which a separate committee provides advice, but not for other safety-related actions.[56,57]

LEGAL AUTHORITY FOR POSTMARKET SAFETY ADVISORIES AND THE ROLE OF INDUSTRY

Life cycle regulation allows drugs to be approved or retained on the market despite uncertainties about safety, because of enhanced regulatory control over postmarket studies and monitoring. Safety advisories play a key role in communicating postmarket events; we therefore examined regulators' mandate to communicate, their authority over industry communications, and the role of industry in safety communication.

Differences among regulators

Table 1 describes the types of safety advisories used by each regulator, including DHPCs issued by industry. Various dissemination methods are used as shown in **Table 1**, including targeting of professional societies and consumer groups, or directly to individual healthcare professionals. Each regulator's authority for issuing advisories is described below.

FDA. The FDA Amendments Act of 2007 (FDAAA) required the FDA to maintain a website providing "information, alerts, and recalls" as well as granting FDA the power to require REMS programs, strengthening the FDA's role of providing information to the public.[7] Prior to FDAAA, the Food, Drug, and Cosmetic Act described how drug safety warnings letters should be formatted typographically, but had no requirements for when they should be issued or their content. FDAAA required the FDA "to develop robust and multifaceted systems to communicate emerging postmarket drug risks."[7]

FDA *Drug Safety Communication,* the FDA's primary postmarket safety communication, includes information for both healthcare professionals and consumers. It is disseminated via the FDA's website, email, and social media and described as "FDA's independent analysis of emerging information and FDA's scientific judgment as to the appropriate communication of this emerging

drug safety information to the public." Industry's role is limited to providing factual accuracy checks where required, with companies given 24 hours' notice prior to FDA issuing advisories.[58,59] *Drug Safety Communications* focus on emerging safety issues and can be issued early in regulatory investigation or after a product information change.[59]

DHPCs are regulated by the FDA in a limited way. Companies may choose to issue DHPCs voluntarily but cannot be compelled to do so by the FDA except as part of a REMS. REMS-related DHPCs may be imposed before or after drug approval, as a component of a communication plan.[21,30] FDA review of DHPC content is mandated when the DHPC is part of a REMS but can only be requested for letters issued voluntarily by companies;[60,61] only REMS DHPCs are available on the FDA website.

EMA. EU legislation requires regulators to provide "important information to the public on pharmacovigilance concerns . . . in a timely manner" (Article 102, Directive 2001/83/EU).[62] Companies must advise regulators of any planned safety communications (Article 106a) and must ensure that any safety communication is "presented objectively and is not misleading" (Table 1).[62]

The EMA issues safety announcements on its website, which are shared under embargo across the European regulatory network prior to publication so that they can be translated and disseminated by national authorities if they choose to do so. The PRAC is responsible for risk communication at the EMA level. However, each member state determines how to disseminate communications, for example, via drug safety bulletins or website information. Apart from adjustments for local context (for example drug names or available doses), safety decisions made by the EMA cannot be reassessed by an individual member state, and core content cannot be changed.[50]

EMA guidance[50] states that only certain communications are likely to be coordinated centrally for practical reasons related to capacity and workload. The list of such communications is not proscriptive, but it prioritizes new contraindications, restrictions of indications, changes in dosing, and the outcomes of referral procedures.[50]

The outcomes of all referral procedures are communicated through the EMA website, and the EMA issues media releases and information for consumers and healthcare professionals as well as detailed information about the decision-making process, all of which are accessible through a single location on its website.

Table 1 Types of postmarket safety advisories used by regulators

	Primary advisory type	Additional advisory types	DHPCs used?	Dissemination
EMA/European Union	DHPC[a]	Web alerts National authorities' bulletins or alerts	Yes Company writes; EMA approves	DHPCs: Companies distribute to healthcare professionals. Some national regulators and EMA[b] post on their websites. National regulators may target professional societies, healthcare and consumer organizations.
FDA	*Drug Safety Communication* (online alert)	Podcasts	Only within postapproval REMS; company writes; FDA approves	REMS DHPCs are distributed by companies to healthcare professionals; available on FDA website. *Drug Safety Communication*: FDA website, media, and digital channels to reach specific health professionals and consumers; distributed to some US federal authorities.[58]
Health Canada	Multiple forms including DHPC and online alerts/ notices	*Health Product Infowatch* (online drug bulletin) Information Update (website alert) Notice to hospitals Public communication (must accompany any DHPC and is put on Health Canada website)	Yes, Health Canada or company may issue	DHPCs: Companies distribute to healthcare professionals and hospitals. Health Canada posts advisories on its website and may target distribution to professional associations, health and consumer groups.[69]
TGA	Alert	*Medicine Safety Update* (online drug bulletin) Direct communications to professional medical organizations and colleges (may not be publicly available)	No	DHPCs: not regulated, company distribution is not described in guidance or regulation (informal process).[74] TGA may selectively disseminate information to professional societies and consumer groups.[145]

EMA, European Medicines Agency; FDA, US Food and Drug Administration; REMS, risk evaluation and mitigation strategy; TGA, Therapeutic Goods Administration.
[a]EMA posting of DHPCs started February 2020. [b]Different terms are used by individual regulators for letters directly sent to health professionals as follows: EMA: Direct Health Professional Communication (DHPC); FDA: Dear Health Care Provider (DHCP) letters; Health Canada: Dear Health Care Professional Letter (DHCPL) for direct letters to health professionals, Health Professional Communication (HPC) includes letters to health professionals and notices to hospitals.

DHPCs are commonly used in Europe,[63] and according to EMA guidance,[16] should be developed in cooperation between companies and regulators. The final text is approved by EMA's PRAC,[50] whose agreement with the wording is noted in the letter, although EMA approval is not formally required by regulation. The DHPC is then disseminated by the company directly to healthcare professionals in their national language and may additionally be posted on EU regulators' websites.

Health Canada. Postmarket safety communications are not specifically described in Canada's Food and Drugs Act or the Food and Drug Regulations.[64,65] Significant reform to drug safety regulation in Canada occurred with the *Protecting Canadians from Unsafe Drugs Act of 2013* (Vanessa's Law), requiring companies to report safety-related actions undertaken by international regulators, including those leading to regulatory risk communications or actions such as recalls or withdrawals. Further, Vanessa's Law provides Health Canada with the mandate to obtain safety data held by companies, along with powers to recall products where there is a "serious or imminent risk of injury to health," authorities previously lacking.[66] Despite this, Vanessa's Law has no additional provisions for postmarket safety communication.[67]

In guidance documents, Health Canada states that companies have the "primary responsibility to monitor the continued safe use of its products and communicate new information on the safety of a product in an effective and timely manner."[68] However, the recommendations in guidance documents are not enforceable. Health Canada has several different forms of risk communication, including DHPCs and website notices[69] (see **Table 1**). High-urgency communications, when "death or other serious adverse health effects" are "reasonably probable," are led by Health Canada. Otherwise a risk communication could be led by either a company or Health Canada.[68]

As with other regulators, Health Canada expects companies to provide DHPC content for review but does not have the force of law to require it. When a company issues the communication, Health Canada's agreement with the content is indicated in the letter. Accompanying notices may also state that Health Canada did not conduct its own review as it agreed with the actions taken by the company.[70] According to guidance, Health Canada will take the lead if "industry refuses to issue or refuses to issue in a timely manner" or if the "company disagrees with or will not discuss with Health Canada content of industry-issued communication." Healthcare professional communications should be accompanied by a consumer notice on the regulator's website.[71]

TGA. A legislative basis for postmarket safety advisories in Australia was formally introduced via a 2009 amendment to a section of the *Therapeutic Goods Act 1989* allowing the release of "specified information," with safety alerts newly specified as a form of regulatory information.[72] Prior to this, the regulator had issued a regular drug safety bulletin intended for healthcare professional audiences.

Companies must notify the TGA of any "significant safety issues," which include any development that in the professional judgment of the company warrants the "urgent attention of the TGA . . . because of the seriousness and potential major impact on the benefit–risk balance of the medicine and/or on patient or public health," including those that might require "prompt regulatory action and/or communication to patients and healthcare professionals." Any issue leading to action by a foreign regulator is considered reportable and must be notified to the TGA within 72 hours of the company becoming aware of it.[73]

There is no formal requirement in Australian regulation or guidance for the TGA to oversee postmarket safety communications by industry, but discussions about DHPCs occur informally.[74] The TGA does not publish DHPCs issued by industry or provide them to parties requesting them.[74]

The TGA formally adopts many EMA guidelines (for example for risk management plans), and these may be adopted unchanged or with modifications. Public consultation occurs prior to adoption.

RISK COMMUNICATION CAPABILITY AND MONITORING EFFECTIVENESS

Whether regulator-authorized risk minimization strategies actually reduce harm to patients has not been conclusively demonstrated, and the impact of postmarket safety advisories and DHPCs on prescribing behavior is uncertain.[36] Systematic reviews examining the effects of postmarket warnings on prescribing have had mixed results,[75–78] with one review finding that FDA warnings had only modest impacts on prescribing rates in 50% of studies.[75] Regulators responding to these studies have challenged whether changes in drug prescribing volume are an appropriate outcome measure,[79] raising questions about the goals of postmarket safety communication and how its effectiveness is assessed.

Communications may not achieve their intended effect due to inadequate dissemination or poor translation of knowledge into practice. While 60–90% of healthcare professionals report receiving regulatory communications,[63,80–82] their knowledge of specific messages may be less than 50%.[82,83] Repeat communications or media attention have been shown to amplify the impact of warnings on both knowledge and prescribing.[76,83,84]

Behavioral-based theories of risk communication acknowledge that people do not make entirely rational decisions about risk information.[35,85] Communication is not just the transmission of information but depends on context, including the beliefs, knowledge, and attitudes of the recipient.[35,85]

Numerous examples demonstrate the variable responses to safety warnings. The rosiglitazone case saw regulators blamed for secrecy, delayed action, and delayed communication.[86] In contrast, regulatory warnings about increased suicidality with the use of antidepressants in young people were met by some physicians with disbelief and even hostility.[87,88] Natalizumab was reapproved after initial withdrawal because patients were willing to accept the risk of serious brain infections in return for the possible benefits in the treatment of multiple sclerosis.[89] Although these cases may also reflect disagreement with regulators' benefit–risk assessments, they indicate the importance of framing, context, and values in communication.

Table 2 Differences in regulatory policy for postmarket safety advisories (also see Supplementary Materials – Table S2)

	EMA	FDA	Health Canada	TGA
1. Governance and decision making				
Separation of authority for postmarket decision making	Yes. PRAC responsible for postmarket assessment and recommendations.	No. Multiteam approach.[95]	No. Multiple departments involved.	No. Approvers assess applications to change product information.
Public involvement in postmarket safety governance	Consumer and healthcare representatives on PRAC.	Not routinely.[44]	Not routinely.	Not routinely.
2. Legislative authority, industry responsibility and requirements				
Regulators' responsibility for postmarket safety communication: described in regulation/legislation	Yes Article 102, Directive 2001/83/EC on the Community code relating to medicinal products for human use.[5]	Yes FDA Amendments Act (*FDAAA 2007*)	No	Partial (allows information release) Subsection 61(5C) of the *Therapeutic Goods Act 1989* (amended 2010)
Regulatory requirements for industry postmarket safety communication	Regulation: Company must inform the regulator about safety announcements. (Article 106a)[5] Information to the public must be presented objectively and not be misleading. (Article 106a)[5] Guidance: Company should cooperate with regulator in preparing DHPCs.[50]	Regulation: Company can be required to issue a DHPC as part of REMS. (*FDAAA*)[7] Format of markings (e.g., "Drug safety warning") for DHPCs and envelopes are legislated but not when to issue. (CFR 200.5)[146] Guidance: REMS DHPCs must be approved by the FDA. For non-REMS DHPCs, companies are encouraged to collaborate with the FDA.[61]	Regulation: Not described in regulation. Guidance: Company "encouraged" to inform Health Canada about DHPCs. Health Canada may request DHPCs and will issue a Health Canada alert if the company disagrees or delays.[71]	DHPCs are not regulated by TGA and no guidance is in place.
Industry involvement in regulator-issued alerts	Companies draft DHPCs for EMA review and approval.	No role of industry stated beyond fact-checking.[147]	Companies draft DHPCs for Health Canada review.	Company may review alerts for fact-checking.[145]
3. Risk communication capacity				
Regulatory goals for safety advisories	Inform and change behavior[50]	Inform[59]	Inform[35,69]	Inform[148]
Risk communication criteria, guidelines, and resources	Guidelines for regulators and industry[50]; specific guidelines for vaccine risk communications and young people.[101,102]	Guidance for industry and FDA for DHPCs.[61] Guidance for classifying postmarket safety concerns.[147] Risk communication guidance.[96]	Guidance for industry and template for DHPCs.[71,149] Process, criteria, and description of all risk communication products (2008).[69]	Process, criteria, description, and template for regulatory alerts.[145]
Risk communications strategic activity and planning	Yes[150,151]	Yes[152]	Yes (2006, 2015)[36]	Not in public domain
Activities for monitoring effectiveness of advisories	Described in regulation, guidance, and strategy.[5,50,153] Research undertaken.[63,99,100]	Required by regulation for REMS only. Required by legislation to develop robust systems in partnership with academics and professionals.[7] Research to examine effectiveness of *Drug Safety Communication* alert.[42,84,93,154]	Not described in regulation. Evaluation framework published but unclear if implemented.[36]	Not described in legislation or guidance.

Perceptions of the messenger can also play a role. Poor public awareness of, or a lack of confidence in, the regulator may affect the salience of safety messages.[36,90] Perceived commercial influence on regulators can reduce trust in messaging and cause reputational damage to regulators,[91] although healthcare professionals appear to prefer receiving safety advisories from regulatory authorities rather than pharmaceutical companies.[63,83,92]

In addition to providing information to support clinician and patient decision making, some regulators specify behavioral goals for safety advisories (**Table 2**).

Differences among regulators

FDA. The FDA's goal in communicating risk information is primarily to enable informed decisions by patients and clinicians. (**Table 2**) The agency has sponsored research into the impact of FDA safety communications[42,93–95] and issued guidance regarding best practice in risk communication for industry and regulators.[61,96] Since 2006, the FDA's Risk Communication Advisory Group has provided strategic oversight but is rarely involved in individual communications.

The FDA asks companies to provide assessment plans containing information about the effectiveness of REMS programs (which often include communications), yet the FDA does not have enforcement authority if companies do not submit the information requested, and the methods for evaluating effectiveness continue to evolve, according to FDA guidance.[21,97] An independent evaluation found that reliable methods for assessing effectiveness had not been established. Of 49 REMS assessments reviewed, only 7 were considered to be meeting FDA goals.[21] REMS communication plans included in the review were rated poorly; patient and prescriber awareness of the communicated drug risks was low or not measured.[21]

The FDA has conducted research to help identify appropriate methods for assessing the impact of risk communication.[75,98]

EMA. EMA goals for safety communication include changing behavior, attitudes, and decisions of physicians and patients, and increasing public confidence in regulators (see **Table 2**). The EMA has conducted research to understand clinicians' and other stakeholders' preferences for communication,[63,99,100] and it systematically reviewed the impact of regulatory interventions.[77] Published guidance describes best practice in risk communication for industry (including DHPC templates) and national EU regulators, and advice for tailoring safety communications for vaccines and to younger people.[50,101,102]

EU regulations require regulators "to monitor the outcome of risk minimization measures contained in risk management plans,"[5] while guidance[50] states that the effectiveness of safety communications should be measured where possible, generally using a research-based approach, to measure outcomes "including behavior, attitudes, and knowledge."

The EMA has conducted research to help identify appropriate methods for improving risk communication[100] and assessing its impact.[77]

Health Canada. Health Canada's goals for advisories relate primarily to enabling better decisions by healthcare professionals and patients. It has developed guidance and a DHPC template for industry use and has recently established a risk communication section within the Marketed Health Products Directorate. Health Canada guidance states that it may request follow-up information after a safety communication,[71] or recommend evaluation of risk minimization as part of a risk management plan,[103] but neither appears to be an enforceable requirement. Under Vanessa's Law, Health Canada can require companies to compile information or studies about therapeutic products, but not specifically of the effectiveness of risk mitigation.

Health Canada commissioned an external review to examine how it could measure and evaluate the effectiveness of risk communications (published in 2015),[36] but whether any further steps have been taken towards implementing recommendations is not communicated on its website.

TGA. While the TGA formally adopts many EMA guidance documents, including those for the development of risk management plans,[104] to date it has not published any guidance to industry on how it should undertake risk communication. Like the EMA, the TGA requires risk management plans to describe how the effectiveness of risk mitigation activities will be evaluated. For drugs approved in Europe earlier than in Australia, the Australian Risk Management Plan is substantively the EMA Risk Management Plan, adapted as required for the Australian context.[105] While EMA guidance suggests new risk mitigation requirements may be requested post marketing, as is authorized under EU law, there is no similar authority within TGA legislation. Updates to risk management plans are not made publicly available, nor are details of any evaluations conducted by companies, if these are in fact occurring.

TRANSPARENCY

Many of the changes in the information available about postmarket safety since 2005 have arisen because of public demands for transparency. For example, the 2006 Institute of Medicine Report stated that the life cycle approach would require industry's "increased transparency toward the FDA in the process of elucidating and communicating emerging information about a drug" and further that the "FDA's credibility is intertwined with that of the industry."[1] Transparency refers to processes and features which allow the disclosure of information, decisions and rationales, interactions between public bodies and the regulated industry, and dissenting views.[32,106–108] While safety advisories publicize risks in order to raise awareness or change behavior, transparency is a matter of public accountability[35] and may improve public participation in value-setting through better understanding of decision making.[32]

A considerable body of literature examines the extent to which regulatory actions and regulations may be shaped more by industry needs than those of the public,[9,33,108–112] arising in part because of industry's role in developing and manufacturing medicines and hence its direct participation in the regulatory process. Transparency can enhance confidence that decisions are made in the public interest.[32,106]

After the rofecoxib withdrawal, the FDA undertook to provide the public with access to information on safety signals even before their significance had been determined, allowing independent researchers to review and interpret the data.[91] However the availability of postmarket safety data remains limited and has not kept pace with improvements in the transparency of premarket data

Table 3 Transparency of decision making and postmarket safety data

	EMA	FDA	Health Canada	TGA
Postmarket safety advisories				
Sources describing decision making and background to advisory	• PRAC minutes • PRAC assessment report for Referral procedures (include descriptions of data reviewed) • Scientific conclusions: for product information changes; and for PSUR single assessments (PSUSA) • PRAC recommendations for changes to product information following signal assessment translated in all EU languages	Data summary within each *Drug Safety Communication*	Summary safety reviews published if advisory arises from data investigated by Health Canada, but not by sponsors. If a sponsor is compelled to provide safety information, it must be made publicly available.[64] Vanessa's Law allows Health Canada disclosure of evidence and reasoning supporting decision making on serious risks.[125]	Meeting statements for the Australian Committee on Medicines when postmarket safety issues are discussed.
Sponsor's contributions to process and decision making for advisories	The sponsor's role and views of the safety concern may be described in "Scientific Conclusions" for PSURs or PRAC assessment reports for referral procedures. Industry DHPCs note that content has been agreed with the regulator.	No	Industry DHPCs published by regulator have a note that Health Canada agrees with the action taken. No details of discussions with industry.	No
Risk evaluation activities				
Risk minimization activities, current and historical	The summary RMP is continually updated with changes. Resolved issues not listed.	Databases of: • REMS goals, materials, messages, & archives • postmarket requirements (PMRs), postmarket commitments (PMCs) and their completion No centralized list of all requirements for a single drug.	No	Summary Risk Management Plan at approval only. Updates are not publicly available.
Postmarket safety studies required by regulators described	• Descriptions in RMP • Protocols and abstracts of results published in EU postmarket study registry (ENCEPP). Provision of data is voluntary	The study is briefly described in Summary Review at approval and on FDA website as "Post market commitments and completions." No details of study results are available	No	Descriptions in AUSPAR at approval only. Protocols available via EU ENCEPP (only where the same protocol applies in Australia)
Description of changes to product information and other approval history	• Yes[155] • Procedural steps taken and scientific information after the authorization. • Descriptions of the nature of label changes provided in EPAR for individual drugs—steps after authorization. • List of all signals assessed and discussed by the PRAC and resulting changes to product information listed by meeting.[156] • Outcomes of PSUR assessments: for centrally authorized medicines, EPAR; for nationally authorized medicinal products and "mixed" procedures, the Community register maintained by the European Commission[157]	No Response letter from the FDA briefly describes change required. Some FDA review memos published (e.g., canagliflozin, amputation).	Partial: Post Authorization activity table (PAAT) for new drugs and subsequent entry biologics since 2012. States that a change has occurred and the date but not the nature of the change.	No

	EMA	FDA	Health Canada	TGA
All revisions of product information available	Yes	Yes	No (Current version only)	No (Current version only. For drugs approved after 2010 the original is in the AUSPAR.)
Surveillance data				
Signals being tracked	EMA provides a spreadsheet of all signals tracked, discussed, and whether they resulted in label changes. The internal EPITT database is not public.	List of issues being tracked in FAERS, but not the internal DARTTS database.	No	No
PSURs published	No (provided on request in person to EU citizens)	No	No	No
Adverse drug event reports	Eudravigilance: yes	FAERs: yes	Canada Vigilance adverse reaction online database	DAEN: yes

For EMA, see: <https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-when>
AUSPAR, Australian Public Assessment Report; DAEN, Database of Adverse Event Notifications (database of adverse event reports submitted to the TGA); DARTTS, Document Archiving, Reporting, and Regulatory Tracking System (used to track significant safety issues related to marketed prescription and over-the-counter drugs); DHPC, direct healthcare professional communications; EMA, European Medicines Agency; ENCEPP, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; EPAR, European Public Assessment Report; EPITT, European Pharmacovigilance Issues Tracking Tool (a web-based system that tracks and monitors the safety of medicinal products); EU, European Union; FAERS, FDA Adverse Event Reporting System (FDA's database containing information on adverse event and medication error reports submitted to FDA); FDA, US Food and Drug Administration; TGA, Therapeutic Goods Administration (Australia); PRAC, Pharmacovigilance Risk Assessment Committee (EMA); PSUR, Periodic Safety Update Report; PSUSA, PSUR single assessments (the PSUR is reviewed once for all EMA member states); REMS, risk evaluation and mitigation strategy; RMP, Risk management plan.
[a] Vanessa's Law enabled the Minister to release certain confidential business information to certain people to protect or promote public health and safety. The results of any postmarket safety examination undertaken by the regulator must be made publicly available on the Government of Canada website. Health Canada intends to make meeting minutes available, and to include adverse event reports with decisions and product monograph on product register.[124]

in the form of clinical study reports.[113,114] Most regulators allow public access to spontaneous adverse report databases, but other postmarket data, including periodic safety update reports and results of postmarket studies undertaken as a condition of marketing approval, are often unavailable.[107,115]

Commercial confidentiality concerns can result in the suppression of information including that which is ostensibly made public (e.g., through redaction).[107] There are instances where drug safety information has been withheld to protect a company from the potential financial impact of reducing consumer and healthcare professional confidence.[31,107,116] Financial conflicts of interest have been shown to be associated with decisions and voting patterns of expert advisory committee members and representations of consumer viewpoints that favor industry interests, reducing the objectivity of advice.[117–119]

Differences among regulators

Table 3 describes the documents available from each regulator in relation to postmarket safety. **Table 4** lists documentation available for two advisories for sodium glucose co-transporter -2 inhibitors. There was more documentation for EMA decisions than for all other regulators.[120]

FDA. The FDA's *Drug Safety Communication* includes a data summary in each advisory, but little other information regarding data or decision-making processes is published by the FDA. Summary reviews, similar to those published about new drug approvals, are not routinely available for postmarket safety changes. In situations where an FDA advisory committee is consulted about a postmarket safety issue, all meeting papers and transcripts are available as per usual committee processes.[44]

For individual drugs, archives of previous prescribing information and the letters from the FDA to companies approving changes are published online. Since only the FDA approval letter is published, without any details of correspondence or review processes, the impact of negotiations with the company cannot usually be ascertained.

The FDA documents all postmarket requirements and commitments and their fulfillment dates but does not publish the final reports or data from postmarket studies.

EMA. The EU pharmacovigilance legislation places requirements on regulators for transparency, as long as they do not breach personal data protection or commercial confidentiality, defined broadly as "any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information."[121]

Information is provided on many aspects of postmarket safety decision making, including PRAC meetings, summaries of PRAC assessments of postmarket signals, recommendations resulting in product information changes, and actions taken on postmarket safety reports (**Table 3**). Meeting materials, including draft documents for discussion and meeting transcripts are not available, and items may be omitted from summaries when considered necessary for commercial confidentiality. Detailed assessment reports are available for EMA referral procedures (specific postmarket investigations undertaken by the PRAC in response to an identified

Table 4 Case study: transparency of decision making in SGLT2 inhibitor advisories for DKA and acute kidney injury

		EMA	FDA	Health Canada	TGA
Advisories	Acute kidney injury	No	Alert (*Drug Safety Communication*)	Bulletin/Investigation report	No
	DKA	DHPC (before investigation) Alert (on identification)	Alert × 2 (*Drug Safety Communication): before and after investigation*	Information Update (Web alert) DHPC	Alert
Product information changed	Acute kidney injury	Yes (canagliflozin)	Yes (all SGLT2s)	Yes (canagliflozin and dapagliflozin)	Unknown
	DKA	Yes	Yes (boxed warning)	Yes (boxed warning)	Yes
Information about decision making	Acute kidney injury	• PRAC agendas and minutes • PRAC scientific conclusion: PSUSA Individual drug information: • Risk Management Plan summary (updated) • EPAR Procedural steps taken after authorization • Web page listing full assessment history • Revised product information and date of change (in EU languages)	*Drug Safety Communication* data summary section Individual drug information: • Letters to sponsors approving safety-related product information change (but not what was requested) • All historical product information	Summary Safety Review Individual drug information: Postauthorization Activity Table (Summary basis of decision): lists changes made after approval, including when applications made by sponsors (content of request not provided)	N/A
	DKA	• PRAC Minutes and agendas • Referral procedure documents: ○ rationale for starting the review ○ timetable for procedure ○ PRAC list of questions to the sponsor ○ PRAC Assessment Report: Scientific conclusion ○ Press release ○ Information for prescribers and the public Individual drug information: • Risk Management Plan summary (updated) • EPAR Procedural steps taken after authorization • Web page listing full assessment history • Revised product information and date of change (in EU languages)	As above	As above	N/A

DHPC, direct health professional communication; DKA, diabetic ketoacidosis; EMA, European Medicines Agency; EPAR, European Public Assessment Report; EU, European Union; FDA, US Food and Drug Administration; N/A, not applicable; PRAC, Pharmacovigilance Risk Assessment Committee (EMA); PSUR, Periodic Safety Update Report; PSUSA, PSUR single assessment (the PSUR is reviewed once for all EMA member states); RMP, risk management plan; SGLT2, sodium glucose cotransporter-2; TGA, Therapeutic Goods Administration (Australia).

signal or issue on behalf of all EU member states). For these procedures, the PRAC assessment report describes the trigger for the safety concern, data, and decision-making rationales, along with descriptions of companies' contributions to the procedure. There is no equivalent documentation in other jurisdictions.

For individual drugs, the European Public Assessment Report (EPAR) is a single collection of documents for centrally approved medicines. It includes a summary of preauthorization information, all changes made to a medicine's product information and regulatory status after approval, details of postmarket studies, and requirements introduced after marketing, including a summary of the risk management plan, assessment reports, and a medicine overview written in lay language. The EPAR "Procedural Steps after Authorisation" document describes changes to product information and when they occurred. Rationales for these changes, dates, and previous versions in EU languages are available (**Table 3**).

A register of postmarket studies by companies and others is maintained by the EMA, with companies required to document details of any studies required by regulators.[122] EMA guidance asks companies to provide details of voluntarily conducted studies and to include interim and final study reports on the register, but this is not mandated.[123]

Health Canada. Published *Summary Safety Reviews* explain some regulatory postmarket safety decisions but appear to be published only for reviews undertaken by Health Canada, not by industry. Health Canada–approved risk management plans are not publicly available.[103] As part of its Regulatory Transparency and Openness Framework and Action Plan 2017–2018, Health Canada has said it will publish decisions made by Scientific Advisory Panels and Scientific Advisory Committees, as well as aggregated regulatory decision documents with product monographs and adverse

event reports.[124] Vanessa's Law requires the regulator to provide information about postmarket safety investigations it mandates or information it requests from companies.[125] Currently, limited information and meeting minutes are available for some postmarket safety decisions.

Vanessa's Law additionally allows Health Canada (as the representative of the Minister or her/his delegate) to disclose confidential business information "if the Minister believes that the product may present a serious risk of injury to human health" (section 21.1 (2)) or if the disclosure is "related to the protection or promotion of human health" and the disclosure is to a suitably qualified person (health or research qualifications or experience).[125,126] A guide to the legislation states that the Minister will provide reasoned decisions to companies, justifying her/his actions when making any order (e.g., changes to prescribing information) based on the new provisions.[125]

Health Canada provides a summary of changes to the product monograph in a postauthorization activity table, modeled on EMA's EPAR Steps After Approval for new drugs and biosimilars approved since 2012. Health Canada's table provides limited detail, describing, for example, the date of a prescribing information change, but not the nature of the change.

TGA. In 2009, amendments to the Therapeutic Goods Act (the Therapeutic Goods Amendment (Medical Devices and Other Measures) Act 2009) allowed the TGA to release more information to the public, including TGA and Expert Committee evaluations of new medicines, committee minutes, and details of pharmacovigilance activities required of companies.[72] The provisions allow a broad range of information to be released to the public referring to "any decision or action taken under this Act or the regulations." Despite this, there is little postmarket information in the public domain documenting safety-related decision making, changes to prescribing information, or risk management plans. Published meeting statements very briefly summarize Advisory Committee on Medicines discussions on those postmarket issues,[127] with the TGA stating that for postmarket safety discussions "the information referred to, and relied on, by the Advisory Committee on Medicines does not usually contain commercial-in-confidence material."[127]

CONSIDERATIONS

Postmarket safety governance and risk minimization frameworks

Governance structures and lack of clear accountability within regulatory agencies can contribute to regulatory communication failures and delays.[1,37,66,128] Among the four regulators, EMA had the most focused governance structure for pharmacovigilance, with the PRAC responsible for postmarket safety under legislation. The PRAC's sphere of activity encompasses the whole life cycle from premarket pharmacovigilance and risk minimization planning to monitoring ongoing benefit–risk balance and withdrawing marketing approval. However, EMA's supranational role means that its structure cannot be directly compared with national regulators, and it is not possible to say whether this more holistic arrangement results in better decision making or timeliness.

The PRAC's inclusion of both regulators and public representatives in postmarket safety decision making also contrasts with other regulators, who draw on nonregulatory healthcare professional expertise and consumer representation on an ad hoc basis (e.g., public consultations on opioid prescribing (Canada), fluoroquinolones and tendon rupture (FDA), valproate and birth defects (EMA), and codeine safety (TGA)).

The depth of public engagement in drug safety decisions varies,[129] and the most effective methods have not been determined. Techniques include consumer testing of patient communications, public consultation, public hearings, and consumer representation on advisory committees. There is growing concern about the independence of consumer voices due to evidence that industry funding may influence patient group representations to regulators.[118,130,131] Mechanisms for public participation must therefore provide safeguards against conflicts of interest as well as ensure adequately informed consumer input. An alternative model could be similar to the United Kingdom's National Institute for Health and Care Excellence (NICE) Citizens Council, an independent body of consumers consulted on a range of specific matters using a deliberative approach, to better understand community perspectives.[132]

Legal authority and the role of industry

The EMA and the FDA have a legislative mandate for postmarket risk communication, giving them authority to issue their own safety alerts. A similar public health role in postmarket risk communication is absent from TGA and Health Canada legislation. Australian advisories are legitimated in the Therapeutic Goods Act by defining them as a type of information authorized for release, while Health Canada relies on guidance documents. Calls to revise Australian legislation have criticized the Therapeutic Goods Act for not including public health as an object of the legislation.[133]

DHPCs issued by industry are a common form of advisory in Europe and Canada.[27,63,80,134] The EMA and, to a lesser extent, the FDA are more empowered to determine the content of DHPCs than Health Canada and the TGA, with EU legislation requiring that company communications are objective and not misleading and that companies collaborate with regulators, while the FDA can mandate content in REMS-related DHPCs, but not in other circumstances.[5,61]

However no regulator has complete authority under legislation over all DHPCs issued by industry, and potential problems exist with their use as safety warnings. First, discussions over the wording of safety warnings can contribute to delays.[51] Second, companies can contest proposed wording in DHPCs. A Canadian evaluation found that "developing a risk communication involves a considerable amount of negotiation between Health Canada and the Marketing Authorization Holder, and that drafting and posting of a risk communication may be delayed until appropriate changes have been made to the product's labeling.[51] Such situations may lead to compromise and dilution of wording, as seen with FDA negotiations regarding canagliflozin and amputation risk.[120] Most regulatory messages include information targeted to the public, but when the chosen form of communication is an industry DHPC, there may be no equivalent message to consumers.

Finally, healthcare professionals are less likely to trust communications disseminated by industry.[63,92,135]

Legislation does not bind the TGA to consult or collaborate with industry for the development or dissemination of safety warnings, nor does it provide the TGA with any authority over DHPCs issued by companies. There is some evidence that TGA informally negotiates with and advises industry in a collaborative manner on preparing and disseminating DHPCs.[74] Australian DHPCs fall within a gray area, as they are neither subject to regulation nor placed in the public domain by TGA because of their commercial ownership. Further, the TGA operates in a model of "responsive regulation," which relies on cooperation and responsible compliance from industry.[136]

While risk communication is intended to support patient safety, paradoxically it also enables medicines with serious adverse effects to remain on the market. While this may be justified when the perceived benefits exceed the risks, there are situations when a warning may not be adequate to mitigate harm. Decisions about whether to warn or withdraw may be directly or indirectly influenced by industry, and depend on the strength of regulation and regulatory decision making.[108,137] In Europe, the ongoing marketing of benfluorex in France after it had been withdrawn in other EU member states led to both the company and the French regulator facing criminal charges.[138] The benfluorex case led to stronger regulation for EU-wide consideration of serious risks. In Australia, attempts to withdraw dextropropoxyphene because of cardiotoxicity were hampered by the legislated process for appealing TGA decisions, providing the company with multiple opportunities to appeal and the TGA appearing to compromise rather than prolong the appeal process in the hope of achieving a favorable decision.[139] The drug was withdrawn in Canada, the United States and the United Kingdom due to the same adverse effects.

Risk communication capability and monitoring effectiveness

When considering risk communication capability, we noted a continuum of policy development among regulators progressing from the acquisition of knowledge, skills, expertise (for example staff or expert advice), guidance, and communication standards, to mechanisms to ensure the effectiveness of risk communication.

The EMA is the only regulator to explicitly state that behavior change, rather than the provision of information alone, is a goal for risk communication,[50] and the EMA is required by legislation to ensure that its strategies are effective in achieving this outcome. Regulators should consistently evaluate and continually improve regulatory and industry safety communications to ensure patient safety. This is essential when drugs are approved with an expectation that new safety issues will emerge.[11] Only the FDA and the EMA require industry to demonstrate the effectiveness of risk mitigation measures including communications. Despite this, standards of measurement and acceptable thresholds for effectiveness have not been established, and a 2013 Office of Audit report found that the FDA lacked the ability to determine the effectiveness of REMS.[21] FDA and EMA research undertaken to date has highlighted the complexity of communicating risks of medicines to both healthcare professionals and the lay public and the appropriate methods to evaluate risk communication outcomes remains unclear.[42,75,77]

To educate the public on the evolving nature of safety issues, regulators should not shy away from mentioning uncertainties over safety when new drugs are approved. Such uncertainties are identified as part of the approval process, yet are rarely highlighted in public arenas or media releases about new drug approvals.[89] The media plays a key role in disseminating regulatory messages to both consumers and healthcare professionals, but often fail to provide important information,[84,87,89] potentially leading to unintended consequences such as cessation of treatment by patients not affected by a warning.[35] Regulators could ensure that media releases accompany safety advisories and include key information such as quantified information about risk and benefit.[89]

Smaller regulatory bodies like Health Canada and the TGA do not have the same regulatory systems for postmarket risk management or authorities over industry as the FDA or the EMA. These regulators may rely to some extent on the EMA and the FDA to identify emerging concerns and on companies to report foreign regulators' actions.[67,140] This lack of capacity may put their citizens at risk of delayed action. Smaller regulators may still be effective communicators but need adequate networks and systems in place.[141]

In addition, some regulators have begun using structured benefit–risk decision templates and tools to quantify and systematize decision making. While their initial exploration and assessment have been for the capture of regulatory approval decisions, these tools may also have an application in documenting postmarket changes in benefit–risk assessments and identifying thresholds for safety advisories. [142]

Transparency

Regulators have privileged access to new safety information and are uniquely responsible among public health agencies for determining its importance and communicating risks to healthcare professionals and patients. Yet this important task occurs in a context of restraint imposed by the industry-focused nature of the regulatory process, particularly in regard to transparency.

Public access to data underlying postmarket advisories—except for spontaneous report databases—is limited in all jurisdictions. For example, no jurisdiction provides periodic safety reports publicly, although EU citizens can obtain these on request.[121] Even the results of postmarket studies required as a condition of marketing approval are generally not available directly from regulators, although they may eventually be published in journals.[107,121] To ensure that postmarket studies provide benefit and value in the clarification of safety profiles, public access is essential.[143] EU legislation has enabled the establishment of a postmarket study registry on which EMA-required noninterventional studies must be registered with public protocols and abstracts of results.[50,122] While a significant step, complete final reports of mandated studies need not be made available, and registration of nonmandated studies is optional.[50]

The imperative for transparency comes from an ethical goal of public accountability and ensuring that decisions are made in the public interest. Given the commercial impacts of regulatory decisions, this remains critical. The transparency of postmarket data lags that of hard-won gains in the premarket arena. Beyond

this, improved public understanding of the risks, benefits, and uncertainties that inevitably surround drug safety data could support more rational drug use. When new medicines are approved, the average citizen expects this means that they are safe, and the dominant public concerns are of access and price. However, it is well known that serious safety issues often emerge in the early years of real-world use due to the limited data available at the time of approval.[19]

EMA decision making was overall the most transparent, with all decisions relevant to the market authorization of a drug available on a single web page that is regularly updated and contains comprehensive information on regulatory processes. A publicly available risk management plan summary is updated regularly with key risks and mitigation strategies. Both Health Canada and the FDA provide comparatively less information about postmarket safety decisions, while TGA transparency is far less.

Regulators' decisions to make information public may be disputed and contested by industry through legal mechanisms; hence regulatory transparency should be supported with adequate powers under legislation. At the same time, regulators' actions in themselves create precedents, and the decisions made by regulators in individual cases become the basis of future actions, guidance, and rules.[106,144] The influence of industry on these individual decisions and thus on rulemaking may be substantial, highlighting the need for transparency.[112,144] Even without legislation, regulators can improve transparency. A Blueprint for FDA Transparency listed actions the regulator could take to improve transparency without legislative change, including greater disclosure of its own decisions and release of data from required postmarket studies.[107] Independent bodies with a legislated role (e.g., ombudsmen's offices) can play an important role in interpreting and enforcing public rights to information. Ultimately, transparency measures should be adequate to allow public confidence that conflicts of interest are being dealt with appropriately.

While not on par with EU transparency legislation, FDA,[107] TGA, and more recently Health Canada legislation[113] allow for the possibility of much greater transparency than is currently routine.

CONCLUSION

All regulators recognize a need for postmarket safety communication and aim to support the safe use of medicines. However, we found important differences in governance, legislated authority, communication capability, transparency, and the role of industry.

European pharmacovigilance legislation appears to be most unified in its focus on safety within a life cycle paradigm, with a supporting governance structure and greater commitment to transparency. The extent to which regulators perceive postmarket communication to be their own public health role, rather than perceiving themselves as the overseers of industry communications, requires further consideration. Regulators' authority to issue safety advice independent of industry involvement and their transparency of decision making should be key pillars on which their policy is assessed, regardless of the speed of drug approval.

The greatest challenge may be one that only larger regulators have begun grappling with—how to assess the effectiveness of advisories and other risk mitigation strategies and, more importantly, what level of effectiveness will be acceptable. Without evidence of impact, current regulatory paradigms for risk communication cannot be assured to be achieving their safety, effectiveness, and accountability goals.

The gap between risk communication science, regulatory requirements, and real-world health outcomes requires continued investigation by regulators and researchers alike.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

FUNDING

This study was partially supported by funding provided by the Australian Government National Health and Medical Research Council (grant ID #1122332) with cofinancing by the Canadian Institutes of Health Research (grant ID #153275). A.L.B. received funding from a University of Sydney PhD Scholarship and a Harvard University Mobility Grant. A.S.'s work is funded by Arnold Ventures and the Harvard-MIT Center for Regulatory Science.

CONFLICT OF INTEREST

A.S. serves as the principal investigator on a grant from the US Food and Drug Administration on Risk Evaluation and Mitigation Strategy (REMS) Programs to Promote Appropriate Medication Use and Knowledge (75F40120C00044). M.L.D.B. is appointed as professor in Regulatory Science, for which the Chair is funded by the University of Copenhagen. In addition, she is director of the Copenhagen Center for Regulatory Science (CORS), based at the same university. CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, and LEO pharma) as well as patient organizations (Rare Diseases Denmark). The center is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and its research is not company-specific product or directly company related. Apart from the position at the University of Copenhagen, M.L.D.B. is employed part-time by Utrecht University as a senior researcher conducting research under the umbrella of the Utrecht-WHO Collaborating Center for Pharmaceutical Policy and Regulation. This center receives no direct funding or donations from private parties, including pharmaceutical industry. Research funding from public-private partnerships, e.g., IMI, The Escher Project (http://escher.lygature.org/) is accepted under the condition that no company-specific product or company related study is conducted. The Center has received unrestricted research funding from public sources, e.g., World Health Organization (WHO), Netherlands Organization for Health Research and Development (ZonMW), the Dutch National Health Care Institute (ZIN), EC Horizon 2020, the Dutch Medicines Evaluation Board (MEB), and the Dutch Ministry of Health. In 2017–2020, J.L. received payment for being on a panel at the American Diabetes Association, for talks at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, lawyer and a second brief on the role of promotion in generating prescriptions for Goodmans LLP and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives royalties from University of Toronto Press and James Lorimer & Co. Ltd. for books he has written. B.J.M. is a member of Health Action International (HAI-Europe Association), a nonprofit organization that supports public interests in pharmaceutical policy. She was a member of Health Canada's Expert Advisory Group on the Marketing of Opioids in 2018 and 2019, and acted as an expert witness for Health Canada in 2020 in a legal case related to marketing of an unregistered product. She has no other interests to declare and receives no funding from pharmaceutical companies. All other authors declared no competing interests for this work.

DISCLAIMER

P.B. is an employee of the European Medicines Agency. The views expressed in this article are her personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

1. Institute of Medicine of the National Academies. Committee on the Assessment of the US Drug Safety System. The future of drug safety — promoting and protecting the health of the public. In *Committee on the Assessment of the US Drug Safety System, Board on Population Health and Public Health Practice* (eds. Baciu, A., Stratton, K. & Burke, S.P.) (The National Academies Press, Washington DC, 2006).
2. European Commission. Commission staff working document: Accompanying document to the Proposal for a regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency and the Proposal for a directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. (Commission of the European Communities, Brussels, 2008).
3. European Commission. 50 years of EU pharma legislation: Achievements and future perspectives [conference report]. (2015).
4. Avorn, J., Kesselheim, A. & Sarpatwari, A. The FDA Amendments Act of 2007—assessing its effects a decade later. *New Engl. J. Med.* **379**, 1097–1099 (2018).
5. European Parliament and Council of Ministers. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of the European Union Vol. Directive 2010/84/EU (2010).
6. European Parliament and Council of Ministers. Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance. Official Journal of the European Union (2010).
7. Food and Drug Administration Amendments Act of 2007, 21 USC § 301 (2016).
8. European Commission. Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Official Journal of the European Union, 1–33 (2004).
9. Wiktorowicz, M., Moscou, K. & Lexchin, J. Transnational pharmacogovernance: emergent patterns in the jazz of pharmaceutical policy convergence. *Globalization Health* **14**, 86 (2018).
10. Demortain, D. The tools of globalization: ways of regulating and the structure of the international regime for pharmaceuticals. *Rev. Int. Polit. Econ.* **22**, 1249–1275 (2015).
11. Eichler, H.-G. *et al*. The risks of risk aversion in drug regulation. *Nat. Rev. Drug Discov.* **12**, 907–916 (2013).
12. Herder, M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. *Milbank Q.* **97**, 820–857 (2019).
13. Frank, C. *et al*. Era of faster FDA drug approval has also seen increased black-box warnings and market withdrawals. *Health Aff. (Millwood)* **33**, 1453–1459 (2014).
14. Lexchin, J. Post-market safety warnings for drugs approved in Canada under the Notice of Compliance with conditions policy. *Brit. J. Clin. Pharmacol.* **79**, 847–859 (2015).
15. Darrow, J.J., Avorn, J. & Kesselheim, A.S. Speed, safety, and industry funding—from PDUFA I to PDUFA VI. *New Engl J. Med.* **377**, 2278–2286 (2017).
16. Davis, C. & Abraham, J. Desperately seeking cancer drugs: explaining the emergence and outcomes of accelerated pharmaceutical regulation. *Sociol. Health Illn.* **33**, 731–747 (2011).
17. Pease, A.M., Krumholz, H.M., Downing, N.S., Aminawung, J.A., Shah, N.D. & Ross, J.S. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *BMJ* **357**, j1680 (2017).
18. Hoekman, J. & Boon, W. Changing standards for drug approval: A longitudinal analysis of conditional marketing authorisation in the European Union. *Soc. Sci. Med.* **222**, 76–83 (2019).
19. Downing, N.S. *et al*. Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *JAMA* **317**, 1854–1863 (2017).
20. Arnardottir, A.H., Haaijer-Ruskamp, F.M., Straus, S.M.J., Eichler, H.-G., de Graeff, P.A. & Mol, P.G.M. Additional safety risk to exceptionally approved drugs in Europe? *Brit J. Clin. Pharmacol.* **72**, 490–499 (2011).
21. US Department of Health and Human Services, Office of Inspector General. *FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety* (US Department of Health and Human Services, Washington, 2013).
22. Frau, S., Font Pous, M., Luppino, M.R. & Conforti, A. Risk Management Plans: are they a tool for improving drug safety? *Eur J. Clin. Pharmacol.* **66**, 785–790 (2010).
23. Zeitoun, J.D., Lefèvre, J.H., Downing, N.S., Bergeron, H. & Ross, J.S. Regulatory anticipation of postmarket safety problems for novel medicines approved by the EMA between 2001 and 2010: a cross-sectional study. *Pharmacoepidemiol. Drug Saf.* **25**, 687–694 (2016).
24. Mol, P.G.M. *et al*. Post-approval safety issues with innovative drugs: a European cohort study. *Drug Safety* **36**, 1105–1115 (2013).
25. Lexchin, J. New drugs and safety: what happened to new active substances approved in Canada between 1995 and 2010? *Arch. Intern. Med.* **172**, 1680–1681 (2012).
26. Perry, L.T. *et al*. Comparative analysis of medicines safety advisories released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern. Med.* **179**, 982–984 (2019).
27. Zeitoun, J.-D., Lefèvre, J.H., Downing, N., Bergeron, H. & Ross, J.S. Inconsistencies among European Union Pharmaceutical Regulator Safety Communications: a cross-country comparison. *PLoS One* **9**, e109100 (2014).
28. Pfistermeister, B., Saß, A., Criegee-Rieck, M., Bürkle, T., Fromm, M.F. & Maas, R. Inconsistencies and misleading information in officially approved prescribing information from three major drug markets. *Clin. Pharmacol. Ther.* **96**, 616–624 (2014).
29. European Medicines Agency. *Guideline on Good Pharmacovigilance Practices (GVP). Module XVI – Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators (Rev 2)*. EMA/204715/2012 Rev 2* (European Medicines Agency, Amsterdam, 2017).
30. US Food and Drug Administration. Draft guidance for industry: *FDA's Application of Statutory Factors in Determining when a REMS is Necessary*. (2016).
31. Lexchin, J. *Public Profits Versus Private Policy*. (University of Toronto Press, Toronto, 2016).
32. Herder, M. Denaturalizing transparency in drug regulation. *McGill J. Law Health* **8**, S57–S143 (2015).
33. Davis, C. & Abraham, J. *Unhealthy Pharmaceutical Regulation: Innovation, Politics and Promissory Science*. (Palgrave MacMillan, London, 2013).
34. Carpenter, D. *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton University Press, Princeton, 2014).
35. Bahri, P. Public pharmacovigilance communication: A process calling for evidence-based, objective-driven strategies. *Drug Saf.* **33**, 1065–1079 (2010).

36. Council of Canadian Academies. *Health Product Risk Communication: Is the Message Getting Through? The Expert Panel on the Effectiveness of Health Product Risk Communication* (Council of Canadian Academies, Ottawa, 2015).
37. Auditor General of Canada. Chapter 4—Regulating Pharmaceutical Drugs—Health Canada. In: 2011 Fall Report of the Auditor General of Canada (Office of the Auditor General of Canada, Ottawa, 2011).
38. Dal Pan, G.J. & Arlett, P.R. The US Food and Drug Administration–European medicines agency collaboration in pharmacovigilance: common objectives and common challenges. *Drug Saf.* **38**, 13–15 (2015).
39. Dal Pan, G.J. Gauging the effectiveness of medicines safety communications from global regulatory agencies. *JAMA Intern. Med.* **179**, 984–985 (2019).
40. US Food and Drug Administration, Center for Drug Evaluation and Research. Advances in FDA's safety program for marketed drugs: establishing premarket safety review and marketed drug safety as equal priorities at FDA's Center For Drug Evaluation And Research (US Food and Drug Administration, Maryland, 2012).
41. Carpenter, D. Reputation, gatekeeping, and the politics of post-marketing drug regulation. *Virtual Mentor* **8**, 403–406 (2006).
42. Kesselheim, A.S. *et al*. Methodological approaches to evaluate the impact of FDA drug safety communications. *Drug Saf.* **38**, 565–575 (2015).
43. Wiktorowicz, M., Lexchin, J. & Moscou, K. Pharmacovigilance in Europe and North America: divergent approaches. *Soc. Sci. Med.* **75**, 165–170 (2012).
44. The Federal Advisory Committee Act, 5 USC app. (as amended) (U.S General Services Administration, Washington).
45. European Medicines Agency. European Medicines Agency bids farewell to CHMP Pharmacovigilance Working Party <https://www.ema.europa.eu/en/news/european-medicines-agency-bids-farewell-chmp-pharmacovigilance-working-party> (2012). Accessed March 6, 2020.
46. Kaeding, M., Schmälter, J. & Klika, C. *Pharmacovigilance in the European Union. Practical Implementation across Member States* (Springer, Germany, 2017).
47. European Medicines Agency. *Summary of the EMA Public Hearing on Quinolone and Fluoroquinolone Antibiotics* (European Medicines Agency, London, 2018).
48. European Medicines Agency. *Summary of the EMA Public Hearing on Valproate in Pregnancy* (European Medicines Agency, London, 2017).
49. Santoro, A., Genov, G., Spooner, A., Raine, J. & Arlett, P. Promoting and protecting Public Health: how the European Union Pharmacovigilance system works. *Drug Saf.* **40**, 855–869 (2017).
50. European Medicines Agency. *Guideline on Good Pharmacovigilance Practices (GVP).* Module XV – Safety communication (Rev 1). EMA/118465/2012 Rev 1 edn. (2017).
51. Health Canada and the Public Health Agency of Canada. Evaluation of the Human Drugs Program 1999-2000 to 2011-2012 (2014).
52. Health Canada. An overview of the Marketed Health Products Directorate <http://publications.gc.ca/collections/collection_2011/sc-hc/H164-2-2008-eng.pdf> (2008). Accessed September 12, 2019.
53. Health Canada. *Health Product Vigilance Framework*. (Health Canada, Ottawa, 2012).
54. Health Canada. Scientific/Expert Advisory Panels <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/scientific-expert-advisory-panels/scientific-advisory-bodies.html> (2012). Accessed January 10, 2020.
55. Australian Government Department of Health Therapeutic Goods Administration. Advisory Committee on Medicines (ACM) <https://www.tga.gov.au/committee/advisory-committee-medicines-acm> (2019). Accessed December 2019.
56. Australian Government Department of Health Therapeutic Goods Administration. Scheduling delegate's final decision: codeine, December 2016 <https://www.tga.gov.au/scheduling-decision-final/scheduling-delegates-final-decision-codeine-december-2016> (2016). Accessed December 2019.
57. Commonwealth of Australia. Therapeutic Goods Regulations 1990. In: F2019C00844 (Australia, 2017).
58. US Food and Drug Administration. CDER's Drug Safety Communications: Ensuring postmarket safety <https://www.fda.gov/drugs/news-events-human-drugs/cders-drug-safety-communications-ensuring-postmarket-safety> (2015). Accessed June 13, 2020.
59. US Food and Drug Administration, Center for Drug Evaluation and Research, & Center for Biologics Evaluation and Research. Guidance – Drug Safety Information – FDA's Communication to the Public. DRAFT GUIDANCE (withdrawn) (US Food and Drug Administration, Maryland, 2012).
60. US Food and Drug Administration, Center for Drug Evaluation and Research, & Center for Biologics Evaluation and Research. Guidance for industry and FDA staff: Dear Health Care Provider Letters: improving communication of important safety information. (US Food and Drug Administration, Maryland, 2012).
61. US Food and Drug Administration, Center for Drug Evaluation and Research, & Center for Biologics Evaluation and Research. Guidance for industry and FDA staff: Dear Health Care Provider Letters: improving communication of important safety information (US Food and Drug Administration, Maryland, 2014).
62. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal of the European Communities. L 311/67 (2001).
63. de Vries, S.T. *et al*. Communication on safety of medicines in Europe: current practices and general practitioners' awareness and preferences. *Drug Saf.* **40**, 729–742 (2017).
64. Government of Canada. Food and Drug Act. In: RSC, 1985, c F-27 Act current to 2017-12-05 and last amended on 2017-06-22 edn. (Government of Canada).
65. Government of Canada. Food and Drug Regulations. In: CRC, c 870 Last amended on June 17, 2019 edn. (Government of Canada, 2019).
66. Risk Sciences International. *Review of Health Canada's Actions in the Recall of Alysena* (Health Canada, Ottawa, 2013).
67. Health Canada. Regulations Amending the Food and Drug Regulations (Vanessa's Law). Regulatory impact analysis statement. Canada Gazette (2017).
68. Health Canada. Risk Communication – protecting Canadians through information (2011).
69. Health Canada. Guidance document: description of current risk communication documents for marketed health products for human use (Health Canada, Ottawa, 2008).
70. Janssen Inc.Invokana (canagliflozin) and Invokamet (canagliflozin and metformin) — Risk of Lower Limb Amputation (2017).
71. Health Canada MedEffect Canada. Guidance document for industry – issuance of health professional communications and public communications by market authorization holders. Guide and template(Minister of Health, Ottawa, 2010).
72. Commonwealth of Australia. *Therapeutic Goods Information Specification* (Federal Register of Legislation, 2009).
73. Australian Government Department of Health Therapeutic Goods Administration. Pharmacovigilance responsibilities of medicine sponsors. Australian recommendations and requirements. Version 2.0 September 2017 (TGA, ACT, 2017).
74. Torka, M., Mintzes, B., Bhasale, A., Fabbri, A., Perry, L. & Lexchin, J. Secret safety warnings on medicines: a case study of information access requests. *Pharmacoepidemiol. Drug Saf.* **28**, 551–555 (2019).
75. Briesacher, B.A. *et al*. A critical review of methods to evaluate the impact of FDA regulatory actions. *Pharmacoepidemiol. Drug Saf.* **22**, 986–994 (2013).
76. Dusetzina, S.B. *et al*. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med. Care* **50**, 466–478 (2012).
77. Goedecke, T., Morales, D.R., Pacurariu, A. & Kurz, X. Measuring the impact of medicines regulatory interventions – Systematic

review and methodological considerations. *Br. J. Clin. Pharmacol.* **84**, 419–433 (2018).
78. Weatherburn, C.J., Guthrie, B., Dreischulte, T. & Morales, D.R. Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: Systematic review, time series analysis and meta-analysis. *Br. J. Clin. Pharmacol.* (2019).
79. Dal Pan, G.J. Communicating the risks of medicines: time to move forward. *Med. Care* **50**, 463–465 (2012).
80. Piening, S., Haaijer-Ruskamp, F.M., de Graeff, P.A., Straus, S.M.J.M. & Mol, P.G.M. Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. *Drug Saf.* **35**, 1061–1072 (2012).
81. Artime, E. *et al*. Are risk minimization measures for approved drugs in Europe effective? A systematic review. *Expert Opin. Drug Saf.* **18**, 443–454 (2019).
82. Bell, S.G., Matsumoto, M., Shaw, S.J., Brandt, J. & Krauss, G.L. New antiepileptic drug safety information is not transmitted systematically and accepted by U.S. neurologists. *Epilepsy & Behav.* **29**, 36–40 (2013).
83. Piening, S., De Graeff, P.A., Straus, S.M.J.M., Haaijer-Ruskamp, F.M. & Mol, P.G.M. The additional value of an e-mail to inform healthcare professionals of a drug safety issue: A randomized controlled trial in the Netherlands. *Drug Saf.* **36**, 723–731 (2013).
84. Woloshin, S. *et al*. Media coverage of FDA drug safety communications about zolpidem: a quantitative and qualitative analysis. *J. Health Commun.* **22**, 365–372 (2017).
85. Way, D., Blazsin, H., Löfstedt, R. & Bouder, F. Pharmaceutical benefit-risk communication tools: a review of the literature. *Drug Saf.* **40**, 15–36 (2017).
86. Cohen, D. Rosiglitazone: what went wrong? *BMJ* **341**, c4848 (2010).
87. Hernandez, J.F., Mantel-Teeuwisse, A.K., van Thiel, G.J.M.W., Belitser, S.V., Raaijmakers, J.A.M. & Pieters, T. Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study. *BMJ Open* **1**, e000290 (2011).
88. Riddle, M.A. Paroxetine and the FDA. *J. Am. Acad. Child Adolesc. Psychiatry* **43**, 128–130 (2004).
89. Schwartz, L. & Woloshin, S. *FDA and the Media: Lessons from Tysabri about Communicating Uncertainty.* (National Academy of Medicine, Washington, 2015).
90. Lofstedt, R. Risk communication: the Avandia case, a pilot study. *Expert Rev. Clin. Pharmacol.* **3**, 31–41 (2010).
91. US Food and Drug Administration. The future of drug safety—promoting and protecting the health of the public. FDA's response to the Institute of Medicine's 2006 report (US Food and Drug Administration, Maryland, 2007).
92. Møllebaek, M., Kaae, S., De Bruin, M.L., Callréus, T., Jossan, S. & Hallgreen, C.E. The effectiveness of direct to healthcare professional communication – a systematic review of communication factor studies. *Res. Social Adm. Pharm.* **15**, 475–482 (2019).
93. Kesselheim, A.S. *et al*. Changes in prescribing and healthcare resource utilization after FDA Drug Safety Communications involving zolpidem-containing medications. *Pharmacoepidemiol. Drug Saf.* **26**, 712–721 (2017).
94. Duckhorn, J., Lappin, B., Weinberg, J. & Zwanziger, L.L. The FDA's Message Testing: Putting health literacy advice into practice. *Information Services & Use* **39**, 59–67 (2019).
95. US Food and Drug Administration, Center for Drug Evaluation and Research. Drug safety priorities: initiatives and innovation. 2015–2016 (US Food and Drug Administration, Maryland, 2016).
96. US Food and Drug Administration. *Communicating risks and benefits: An evidence-based user's guide* (US Food and Drug Adminstration, Maryland, 2011).
97. US Food and Drug Administration. Draft guidance for industry: REMS assessment: planning and reporting. (US Food and Drug Administration, Maryland, 2019).
98. Kesselheim, A.S. *et al*. Multimodal analysis of FDA drug safety communications: lessons from Zolpidem. *Drug Saf.* **42**, 1287–1295 (2019).
99. Alqvist-Radstad, J.*et al*. SCOPE Work package 6. Healthcare professional survey. Medicines safety communications and their effectiveness. (SCOPE, London, 2016).
100. Bahri, P. & Castillon Melero, M. Listen to the public and fulfil their information interests – translating vaccine communication research findings into guidance for regulators. *Br. J. Clin. Pharmacol.* **84**, 1696–1705 (2018).
101. European Medicines Agency & Heads of Medicines Agencies (2013). *Guideline on Good Pharmacovigilance Practices – Product- or Population-specific Considerations I: Vaccines for Prophylaxis Against Infectious Diseases* (European Medicines Agency, London, 2013).
102. European Medicines Agency & Heads of Medicines Agencies. *Guideline on Good Pharmacovigilance Practices (GVP) – Product- or Population-Specific Considerations IV: Paediatric Population* (European Medicines Agency, London, 2018).
103. Health Canada. *Guidance Document – Submission of Risk Management Plans and Follow-up Commitments* (Minister of Health, Ottawa, 2015).
104. European Medicines Agency & Heads of Medicines Agencies. *Guideline on Good Pharmacovigilance Practices (GVP)*. Module V – Risk management systems (Rev 2) (European Medicines Agency with Heads of Medicines Agencies, London, 2013).
105. Australian Government Department of Health Therapeutic Goods Administration. Risk management plans for medicines and biologicals Australian requirements and recommendations. Version 3.1, November 2017 edn. (Commonwealth of Australia, Woden, ACT, 2017).
106. Herder, M. Toward a jurisprudence of drug regulation. *J. Law Med. Ethics* **42**, 244–262 (2014).
107. Sharfstein, J.M. *et al*. Blueprint for transparency at the U.S. Food and Drug Administration: recommendations to advance the development of safe and effective medical products. *J. Law Med. Ethics* **45**, 7–23 (2017).
108. Light, D.W., Lexchin, J. & Darrow, J.J. Institutional corruption of pharmaceuticals and the myth of safe and effective drugs. *J. Law Med. Ethics* **41**, 590–600 (2013).
109. Carpenter, D. Corrosive capture? The dueling forces of autonomy and industry influence in FDA pharmaceutical regulation. In: *Preventing Regulatory Capture: Special Interest Influence and How to Limit it* (eds. Carpenter, D. and Moss, D.A.) 152–72. (Cambridge University Press, Cambridge, 2013).
110. Carpenter, D. Reputation and regulatory power. In: *Reputation and Power, Organizational Image and Pharmaceutical Regulation at the FDA*. (Princeton University Press, Princeton, 2014).
111. Lexchin, J. The pharmaceutical industry and the Canadian Government: Folie à Deux. *Healthc Policy* **13**, 10–16 (2017).
112. Hwang, T.J., Avorn, J., Carpenter, D. & Kesselheim, A.S. Quantifying the food and drug administration's rulemaking delays highlights the need for transparency. *Health Aff.* **33**, 309–315 (2014).
113. Lexchin, J., Herder, M. & Doshi, P. Canada finally opens up data on new drugs and devices. *BMJ* **365**, l1825 (2019).
114. Herder, M. Reviving the FDA's Authority to Publicly Explain Why New Drug Applications Are Approved or Rejected. *JAMA Intern. Med.* **178**, 1013–1014 (2018).
115. Fralick, M. & Kesselheim, A.S. Periodic benefit-risk evaluation reports have substantial promise to guide patient care and should be made publicly available. *Pharmacoepidemiol. Drug Saf.* **26**, 597–599 (2017).
116. Kesselheim, A.S. & Mello, M.M. Confidentiality laws and secrecy in medical research: improving public access to data on drug safety. *Health Aff.* **26**, 483–491 (2007).
117. McCoy, M.S., Pagán, O., Donohoe, G., Kanter, G.P. & Litman, R.S. Conflicts of interest of public speakers at meetings of the anesthetic and analgesic drug products advisory committee. *JAMA Internal Med.* **178**, 996–997 (2018).
118. Abola, M.V. & Prasad, V. Characteristics and conflicts of public speakers at meetings of the Oncologic Drugs Advisory Committee to the US Food And Drug Administration. *JAMA Int. Med.* **176**, 389–391 (2016).
119. Pham-Kanter, G. Revisiting financial conflicts of interest in FDA advisory committees. *Milbank Q* **92**, 446–470 (2014).

120. Bhasale, A., Mintzes, B. & Sarpatwari, A. Communicating emerging risks of SGLT2 inhibitors—timeliness and transparency of medicine regulators. *BMJ* **369**, m1107 (2020).
121. European Medicines Agency. *European Medicines Agency Policy on Access to Documents*. POLICY/0043 (European Medicines Agency, London, 2018).
122. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. *ENCEPP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance*, 2019 edn. (European Medicines Agency, 2019).
123. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3). EMA/118465/2012 Rev 1 edn. <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xv-safety-communication-rev-1_en.pdf> (EMA, Amsterdam, 2017).
124. Health Canada. Regulatory Transparency and Openness – 2017–2018 Activities <https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/2017-2018-activities.html> (2019). Accessed August 12, 2019.
125. Health Canada. Amendments to the Food and Drugs Act: Guide to New Authorities (power to require and disclose information, power to order a label change and power to order a recall) <https://www.canada.ca/en/health-canada/services/drugs-health-products/legislation-guidelines/amendments-food-drugs-act-guide-new-authorities-power-require-disclose-information-power-order-label-change-power-order-recall.html> (2017). Accessed August 1, 2019.
126. Health Canada. Guidance document – disclosure of confidential business information under paragraph 21.1(3)(c) of the Food and Drugs Act <https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/request-disclosure-confidential-business-information/disclosure-confidential-business-information/guidance.html#a1.1> (2019). Accessed September 10, 2019.
127. Australian Government Department of Health Therapeutic Goods Administration. ACM meeting statements <https://www.tga.gov.au/acm-meeting-statements> (2019). Accessed December 2019.
128. Commission of the European Communities. Proposal for a Directive of the European Parliament and of the Council amending, as regards information to the general public on medicinal products subject to medical prescription, Directive 2001/83/EC on the Community code relating to medicinal products for human use. (Commission of the European Communities, Brussels, 2008).
129. Brown, P. & Bahri, P. 'Engagement' of patients and healthcare professionals in regulatory pharmacovigilance: establishing a conceptual and methodological framework. *Eur. J. Clin. Pharmacol.* **75**, 1181–1192 (2019).
130. Fabbri, A. *et al*. Industry funding of patient and health consumer organisations: systematic review with meta-analysis. *BMJ* **368**, l6925 (2020).
131. Lexchin, J. Association between commercial funding of Canadian patient groups and their views about funding of medicines: An observational study. *PLoS One* **14**, e0212399 (2019).
132. National Institute for Health and Care Excellence. Citizens Council <https://www.nice.org.uk/get-involved/citizens-council> (2019). Accessed January 10, 2020.
133. Sansom, L., DeLaat, W. & Horvath, J.Review of Medicines and Medical Devices Regulation. Report on the regulatory framework for medicines and medical devices (2015).
134. Mol, P.G.M., Straus, S.M.J.M., Piening, S., de Vries, J.T.N., de Graeff, P.A. & Haaijer-Ruskamp, F.M. A decade of safety-related regulatory action in the Netherlands. *Drug Saf.* **33**, 463–474 (2010).
135. Thompson, C.A. 'Dear Healthcare Professional' letters may not be effective REMS communication tool. *Am. J. Health Syst. Pharm.* **71**, 177–178 (2014).
136. Australian Government Department of Health Therapeutic Goods Administration. *The Therapeutic Goods Administration's Risk Management Approach to the Regulation of Therapeutic Goods*. Version 4.0 edn. (ed. TGA) (Commonwealth of Australia, ACT, 2011).
137. Davis, C. & Abraham, J. A comparative analysis of risk management strategies in European Union and United States pharmaceutical regulation. *Health Risk Soc.* **13**, 413–431 (2011).
138. Dyer, O. France to prosecute its drug regulator and Servier in scandal over diabetes drug. *BMJ* **358**, j4231 (2017).
139. Buckley, N.A. & Faunce, T.A. Trials and tribulations in the removal of dextropropoxyphene from the Australian register of therapeutic goods. *Med. J. Aust.* **199**, 257–260 (2013).
140. Commonwealth of Australia. *Therapeutic Goods Act 1989*. (Commonwealth of Australia, Australia, 2017).
141. Maor, M. Organizational reputations and the observability of public warnings in 10 pharmaceutical markets. *Governance* **24**, 557–582 (2011).
142. Pignatti, F. *et al*. Structured frameworks to increase the transparency of the assessment of benefits and risks of medicines: current status and possible future directions. *Clin. Pharmacol. Ther.* **98**, 522–533 (2015).
143. Doshi, P. & Jefferson, T. Disclose data publicly, without restriction. *J. Law Med. Ethics* **45**, 42–45 (2017).
144. Carpenter, D. FDA transparency in an inescapably political world. *J. Law Med Ethics* **45**, 29–32 (2017).
145. Australian Government Department of Health and Ageing Therapeutic Goods Administration. Trans-Tasman early warning system. Processes in Australia and New Zealand. Version 1.0 edn. (TGA, ACT, 2013).
146. CFR – Code of Federal Regulations Title 21 <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=20.61> (2019). Accessed October 20, 2019.
147. US Food and Drug Administration. Draft guidance: *Classifying Significant Postmarketing Drug Safety Issues*. (US Food and Drug Administration, Maryland, 2012).
148. Skerrit, J.Therapeutic Goods Information (Early Warning System) Specification 2013. Instrument and Explanatory statement (2013).
149. Health Canada. Guide for using the Standardized Health Product Risk Communication Template. 2015-11-23 (2015).
150. Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. SCOPE Work package 6. Risk communication. National strategy for implementation of recommendations on risk communication: Key actions. (SCOPE, London, 2016).
151. Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. (SCOPE, London, 2016).
152. US Food and Drug Administration. *FDA Strategic Plan for Risk Communication and Health Literacy 2017–2019* (US Food and Drug Administration, Maryland, 2017).
153. European Medicines Agency. PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Rev 1). In: EMA/165407/2017 Pharmacovigilance Risk Assessment Committee (European Medicines Agency, London, 2017).
154. Kesselheim, A. S. *et al*. Patient and physician perceptions of drug safety information for sleep aids: a qualitative study. *Drug Saf.* **40**, 531–542 (2017).
155. European Medicines Agency. What we publish on medicines and when <https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-when> (2020). Accessed March 14, 2020.
156. European Medicines Agency. List of all signals assessed and discussed by the PRAC and resulting changes to product information listed by meeting <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management/prac-recommendations-safety-signals> (2020). Accessed March 14, 2020.
157. European Commission. Public Health – Union Register of medicinal products <https://ec.europa.eu/health/documents/community-register/html/reg_hum_act.htm?sort=a> (2020). Accessed June 26, 2020.

Appendix 3: Supplemental file for Section 4.4 – Coding instrument

SAFER Content Extraction Form

Alice Bhasale, Lucy Perry, Ashleigh Hooimeyer, Annim Mohammad, Eliza McEwin, Barbara Mintzes
2019

Advisory ID_Drug risk issue

_____
(auto-generated from advisory ID and drug risk issue)

ADVISORY IDENTIFICATION AND CODING DETAILS

Dataset being coded

☐
☐
☐
☐

Coder

◯
◯
◯
◯
◯
◯
◯
◯

Drug risk issue

_____

Advisory ID

_____

Country

◯ United States
◯ Canada
◯ United Kingdom
◯ Australia
◯ Denmark

Date of advisory (imported)

_____

ABOUT THE ADVISORY

Type of advisory

◯ DHPC
◯ Alert
◯ Investigation
◯ Bulletin
◯ Public
◯ DHPC - REMS

Weblink

_____

1. Does the advisory mention any of the following
- starting to investigate/is early in investigation
- has not yet determined what the safety data mean
- start of safety review (HC) or referral procedure (EMA), or emerging safety concern (FDA), or labelled a 'monitoring communication' (TGA)

◯ Yes
◯ No

2. In the advisory, is another advisory mentioned for this safety issue (from the same regulator)?

Look for:
-mention of another advisory
- links to another advisory
-EMA and MHRA are treated as same regulator

◯ Yes
◯ No
◯ Unclear

2a. Is the current advisory providing:

◯ New information/advice
◯ Reminder about previous advice
◯ Neither of the above/unclear

2b. Provide the date and details (e.g. URL) of the OTHER advisory, if available

_____

REASONS FOR THE ADVISORY

3. Does this advisory appear to have been triggered by evidence of a safety concern ?

(including literature or studies or ADR reports)

◯ Yes
◯ No

3a. Please provide the details of the trigger, including study citations and dates if provided.

_____

4. Which of the following are mentioned as other reasons for the advisory?

Note: For UK advisories, the EMA is not considered an other country regulator, but other individual countries are

☐ Previous risk mitigation was unsuccessful
☐ Actions of other country regulators
☐ Media reports
☐ Other
☐ None

Please provide details for OTHER:

_____

TYPE OF SAFETY CONCERN

5. Is the advisory:

ALL CLEAR - use only if refers to previous history/discussion about possible risk, or reverses a previous warning.

RISK MITIGATION - use if the focus is on communicating a mitigation strategy as opposed to the safety issue

OTHER can be used if advisories are providing reassurance after media reports or routine monitoring updates (eg vaccines AEs) where no harm is found.

- ◯ Warning about a potential or actual harm
- ◯ Providing an 'all clear' for a previous issue
- ◯ Warning about reduced efficacy or lack of effect
- ◯ Risk Mitigation Strategy for a safety concern
- ◯ Other

NOTE - You have selected ALL CLEAR

ALL CLEAR should be chosen only if the advisory mentions previous concern about of risk or describes data suggesting harm. For advisories providing reassurance (e.g. about unfounded media reports) or providing routine monitoring updates (e.g. vaccines AEs), choose OTHER.

Please specify

_____

6. Does the advisory indicate that the safety concern is:

- ◯ Known adverse effect/change to known adverse effect
- ◯ New/emerging safety problem/adverse effect
- ◯ Other
- ◯ Unclear

Please specify OTHER or UNCLEAR

_____

6a. What indicates this safety concern was already known?

Note: a review to investigate the concern does not mean it was known already

- ☐ Advisory says it was already in the product information
- ☐ The advisory states it was known
- ☐ Refers to a previous advisory
- ☐ Other

Please specify 'other'

_____

6b. Do any of the following apply to the 'known' safety concern?

- ☐ More serious or more frequent than expected
- ☐ Risks for a specific and/or vulnerable population have been found
- ☐ Differences between drugs in the class
- ☐ Other new information has emerged about the safety concern
- ☐ None of the above

Please specify 'other new information'

_____

INFORMATION ABOUT FREQUENCY OF HARMS

7. Is information provided about numbers of events?

words or numerals (e.g. three or 3)

- ◯ Yes
- ◯ No
- ◯ States that the number affected/frequency is unknown

7a. How is the numeric information about harm described (tick all that apply)

If multiple, code all that are about the harm or risk that is the subject of the advisory

- ☐ Natural frequency (e.g. 1 in 10 people)
- ☐ Rate (e.g. 0.1 per 1000 patient-years)
- ☐ Percentage (%)
- ☐ Number with no denominator (e.g. 3 ADR reports)
- ☐ Other

7b. Please cut and paste the numeric information about the adverse effect

_____

Please specify 'other'

_____

8. Is the risk described in comparative terms?

- ◯ Yes
- ◯ No

8a. How is the comparative risk of harm described?

If multiple descriptions, code all that are about the harm or risk that is the subject of the advisory

- ☐ Relative terms (e.g doubling of risk, 50% higher)
- ☐ Absolute terms (6 vs 12 per 100 people on treatment)
- ☐ Other
- ☐ Unclear

Please specify 'unclear' or 'other'

_____

9. Does the advisory use words to describe how likely the safety concern is?

- look for words that describe how likely or often this concern is
- e.g. rare, common, uncommon, frequent

Does not apply to numbers spelt out as words only

- ◯ Yes
- ◯ No

9a. Is the frequency described as:

- ◯ Very rare
- ◯ Rare
- ◯ Uncommon
- ◯ Infrequent
- ◯ Common
- ◯ Very common
- ◯ None of the above/Other

Please specify how the risk was described in words

_____

OUTCOMES

10. What outcomes are described?

- ☐ Clinical/patient outcomes (e.g. liver failure)
- ☐ Outcomes of test or investigation results (e.g. raised liver enzymes)
- ☐ Neither of the above

Please specify the other described outcomes

_____

11. Does the advisory mention serious outcomes or adverse events?

e.g. resulting in, or potentially leading to:
- long term outcomes or require ongoing treatment
- hospitalisation or prolonged hospital stay
- disability or permanent damage
- a congenital anomaly

Please answer based on your knowledge of the outcomes described - if you are unsure about the significance of the outcome, check.

- ◯ Yes
- ◯ No
- ◯ Unclear

11a. What serious adverse outcomes/events are described?

_____

12. Does the advisory specifically mention risk of death or fatal outcomes?

Note: words such as death/fatal/Life-threatening/mortality etc are mentioned in the advisory. This should NOT be inferred from the condition/adverse effect

- ◯ Yes
- ◯ No

12a. Please cut and paste the text describing death/fatal outcome/mortality risk

_____

EVIDENCE OF HARMS

13. Which data in the advisory suggest that the drug IS associated with the adverse event?

(Enter as many as apply)

- ☐ Systematic review
- ☐ Randomised controlled trials (RCT)
- ☐ Clinical trials or clinical studies (unspecified)
- ☐ Observational/epidemiological studies
- ☐ Case reports (including ADR reports)
- ☐ Literature (published)- general/unspecified
- ☐ Post-market data - unspecified
- ☐ Not reported
- ☐ Other

(for advisories about harm)

Please specify what other types of data are provided.

_____

13a. What data in the advisory suggested that the drug WAS associated with the adverse event? (Enter as many as apply)

- ☐ Systematic review
- ☐ Randomised controlled trials (RCT)
- ☐ Clinical trials or clinical studies (unspecified)
- ☐ Observational/epidemiological studies
- ☐ Case reports (including ADR reports)
- ☐ Literature (published)- general/unspecified
- ☐ Post-market data - unspecified
- ☐ Not reported
- ☐ Other

(for advisories that are 'all clears')

Please specify what other types of data are provided.

_____
(all clear)

13b. Which data in the advisory suggest lack of efficacy (Enter as many as apply)

- ☐ Systematic review
- ☐ Randomised controlled trials (RCT)
- ☐ Clinical trials or clinical studies (unspecified)
- ☐ Observational/epidemiological studies
- ☐ Case reports (including ADR reports)
- ☐ Literature (published)- general/unspecified
- ☐ Post-market data - unspecified
- ☐ Not reported
- ☐ Other

(for advisories that are 'lack of efficacy')

Please specify what other types of data are provided.

_____
(lack of efficacy)

OTHER INFORMATION ABOUT CAUSALITY

14. Are data provided suggesting that the drug does NOT cause the adverse effect?

- ◯ Yes
- ◯ No

14a. Which data suggest that the drug IS NOT associated with the adverse event? (Tick as many as apply)

- ☐ Systematic review
- ☐ Randomised controlled trials (RCT)
- ☐ Clinical trials or clinical studies (unspecified)
- ☐ Observational/epidemiological studies
- ☐ Case reports (including ADR reports)
- ☐ Literature general/unspecified
- ☐ Not reported
- ☐ Other

14b. Please specify the other data which suggest the drug is NOT associated with the adverse event

_____

15. Is there anything else in the advisory that suggests the drug is NOT associated with the adverse effect, or raises doubt about the association?

- ◯ Yes
- ◯ No

Please describe the information

_____

15a. Is there anything else you would like to comment on regarding the way information about risk or the recommended action is presented?

BACKGROUND INFORMATION

16. What background about the drug and treatment of the condition are described?

- ☐ Other adverse effects of the drug/class, which are not the subject of the advisory
- ☐ Indication of the drug
- ☐ Specific beneficial health effects
- ☐ Other drugs to treat the condition
- ☐ Other

Please specify 'other'

_____

HEALTH PROFESSIONAL ADVICE

17. Is the information targeted to health professionals?

- ◯ Yes
- ◯ No
- ◯ Unclear

18. Which best describes the advice or recommendations to health professionals?

NOTE: If more than one category applies, choose one option, ranked in the order shown (1 to 3) , where '1' is the highest rank

- ◯ They should do something (specific action) when prescribing or treating patients - 1
- ◯ They should be aware of this safety information (awareness) - 2
- ◯ No advice or recommendations to health professionals are provided - 3

18a. AWARENESS ONLY ADVICE

Overall, are the recommendations for prescribers non-specific in nature, including statements like: .
- prescribe with caution
- consider the risks and benefits before prescribing
- follow the recommendations in the product information (which are not given in the advisory)

- ◯ Yes
- ◯ No

19. GENERAL ACTIONS

What general advice is specified for health professionals in the advisory?

- ☐ Do not take any specific action (explicitly stated)
- ☐ Educate/counsel/advise patient
- ☐ Follow the existing product information/label (stated)
- ☐ Follow the new/changed product information/label (stated)
- ☐ Prescriber should be aware of the safety concern (e.g. as a possible diagnosis)
- ☐ None of the above

20. Is advice given about testing or monitoring?

Includes general monitoring advice and any objective measurement/assessment

- ◯ Yes
- ◯ No

20a. Is the testing/monitoring advice about a pre-treatment test only, with no ongoing monitoring advice?

An example would be testing of kidney function before a single dose of contrast agent is given, but with no follow-up testing - choose YES.

If the advice includes both pre-treatment and ongoing assessment, choose NO.
(For example testing kidney function before treatment and while on treatment).

◯ Yes
◯ No

21. What testing and/or monitoring is described?

☐ signs and symptoms, clinical assessment
☐ lab tests (e.g. blood, urine)
☐ other clinical investigations (e.g. ECG)
☐ imaging (X-ray, MRI, U/S, CT etc)

22a. WHAT TO MONITOR
Is the test sufficiently specified?

'Test' may refer to any assessment or examination.

Scoring examples
Heart rate = yes
Cardiovascular examination = no

◯ Yes
◯ No

22b. WHEN TO START MONITORING
Is the time to start monitoring specified?

Scoring examples
Monitor potassium before start of treatment = Yes
Test renal function before starting and at least once a year after starting = Yes
Monitor potassium periodically = No

◯ Yes
◯ No

22c. WHEN TO STOP MONITORING
Is the time to stop monitoring specified?
e.g. When in reference range
After stopping treatment
After explicit period

Scoring examples
Monitor potassium for two days after initiation = Yes
Stop monitoring after the drug is stopped = Yes
Monitor potassium when initiating treatment = No

◯ Yes
◯ No

22d. HOW FREQUENTLY TO MONITOR-
Is the frequency of monitoring specified?

Scoring examples
Every three months = Yes
Periodically = No

◯ Yes
◯ No

22e. CRITICAL VALUE-
Is the critical value specified?

Scoring examples
Renal function (creatinine clearance < 45 mL/min) = Yes
Renal impairment = No

◯ Yes
◯ No

22f. ADJUSTMENT TO THERAPY
Is the therapy adjustment specified?

Scoring examples
If bradyarrhythmia is observed, a dose reduction or discontinuation should be considered = Yes
Adjust therapy if required = No

◯ Yes
◯ No

23. DOSING:

Is advice about dose or frequency specified for health professionals ?

◯ Yes
◯ No

23a. Is the DOSING advice - general advice such as to use 'as recommended' or the 'lowest effective dose' or similar

◯ Yes
◯ No

23b. Is the DOSING advice recommending a change to standard recommended dose/frequency?

◯ Yes
◯ No

23c. FORMULATION:

Is there advice to use a different formulation ?

◯ Yes
◯ No

Please specify the alternative formulation

_____

23d. DURATION:

Is advice about duration of use specified for health professionals ?

◯ Yes
◯ No

23e. Is the DURATION advice
- to use for recommended duration or as short as possible

◯ Yes
◯ No

23f. Is the DURATION advice
- advising a change to standard or recommended duration

◯ Yes
◯ No

24. CHOICE OF TREATMENT/PATIENT SELECTION

What action(s) are specified for health professionals in the advisory?

- ☐ Avoid medicine or food interactions
- ☐ Avoid/do not prescribe the drug to patients with certain characteristics (not interactions)
- ☐ Switch to an alternate medicine(s)
- ☐ Stop medicine in patients on therapy, in certain circumstances
- ☐ Do not start any new patients on therapy
- ☐ Discontinue and restart as required

24a. For "Avoid/do not prescribe to certain populations" - please specify who should not receive the drug according to the advisory

_____

24b. For "Switch to an alternative medicine/class" - Is an alternative medicine or class named?

- ◯ Yes
- ◯ No

Please specify the alternative medicine(s)

_____

24c. For "Stop medicine in patients on therapy" - please cut and paste the text about stopping the medicine

_____

25. Is it clear for the prescriber which patients the advice applies to?

- ◯ Yes
- ◯ No

26. Is any other action for health professionals specified?

- ◯ Yes
- ◯ No

Please specify the other actions for health professionals

_____

26a. How would you rate the usefulness of the advice given to health professionals?

not at all useful — moderately useful — Very useful

(Place a mark on the scale above)

CONSUMER ADVICE

27. Is there information targeted to consumers/public?

- ◯ Yes
- ◯ No

28. Which best describes the advice or recommendations to consumers/the public?

Note: Does not include information for prescribers to give patients

- ◯ They should do something (specific action) when when using the drug - 1
- ◯ They should be aware of this safety information (awareness) - 2
- ◯ No advice or recommendations directly to consumers are provided - 3

29. What action(s) are specified for the consumer/ public?
(Tick as many as apply)

- ☐ Do not stop medicine
- ☐ Stop use of medicine in certain circumstances
- ☐ Consult health professional
- ☐ Report any adverse experiences/symptoms
- ☐ Look at other educational materials (e.g. CMIs)
- ☐ Be aware of the signs or symptoms of the adverse effect
- ☐ Do not be alarmed/concerned
- ☐ Other advice for this medicine

Please specify (cut and paste) other specific advice.

_____

REGULATORY ACTION

30. Does the advisory refer to European regulatory actions - e.g. the European Medicines Agency, or EMA?

- ◯ Yes
- ◯ No

31. Is it clear how the regulator came to know about this safety concern and/or what triggered their interest?

Note:
Must be stated as the reason for the regulator becoming interested or concerned about the safety issue

- ◯ Yes
- ◯ No

If yes please specify

_____

32. Is it clear how the sponsor(s) came to know about this safety concern and/or what triggered their interest?

- ◯ Yes
- ◯ No

If yes please specify

_____

33. Does the advisory mention a change to the product information?

- or 'Label/Labelling', Product Monograph or Summary of Product Characteristics (SMPc)

- ◯ Yes
- ◯ No

33a. Have the changes already occurred?

- ◯ Yes
- ◯ No
- ◯ Unclear

33b. Which section of the product information/label has been changed?

NB The advisory will usually refer to the section.

If the section or type of change is not specifically mentioned, choose 'Other'.

- ☐ No details provided
- ☐ Indications
- ☐ Contraindications
- ☐ Dosing or administration
- ☐ Monitoring advice
- ☐ Adverse reactions/effects
- ☐ Warnings and/or precautions
- ☐ Boxed warning (or black box warning)
- ☐ Other

33c. Has an indication been removed ?

- ◯ Yes
- ◯ No

33d. Has a new contraindication been added?

- ◯ Yes
- ◯ No

33e. Has the maximum or recommended dose changed?

- ◯ Yes
- ◯ No

34e. Has a new warning been added?

- ◯ Yes
- ◯ No

34f. Please specify other ways the label/product information has been changed.

_____

35. Is the regulator doing anything else, according to the advisory? (Apart from changing the product information)

Note:
i) for MHRA advisories, the 'regulatory' or regulatory action refers to either EMA or MHRA

- ☐ Will continue monitoring
- ☐ Actively investigating further
- ☐ Requiring new or revised post market studies
- ☐ Restrictive prescribing programs eg pregnancy prevention programs
- ☐ Other communication to prescribers or professional bodies
- ☐ Other communication to consumers, patient organisations, public
- ☐ Change to CMI, Medication guide, patient summary or equivalent
- ☐ Suspension of marketing
- ☐ Other
- ☐ No other regulatory action

Please specify 'Other'

_____

36. How much information is provided about the decision making and process leading up to the advisory?

- ☐ No information
- ☐ Brief information (e.g. a 'a review was conducted' but no details are provided
- ☐ Detailed information (more substantive information, including links to more detail such as the full review includes steps taken by the regulator, who was involved, data considered and the rationale for the safety advice)

Please describe briefly

_____

37. What role(s) of the sponsor are mentioned in the advisory? (Tick as many as apply)

With or without the company name

- ☐ As the distributor/manufacturer
- ☐ Informing via this advisory
- ☐ Actively investigating/ providing data to regulators (including leading to advisory)
- ☐ Conducting educational programs
- ☐ Restrictive prescribing programs
- ☐ Other communication to prescribers or professional bodies
- ☐ Other communication to consumers, patient organisations, public
- ☐ Other
- ☐ No role specified

Please describe briefly