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Dissertação orientada pela Professora Doutora
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Resumo

O incompleto perfil de segurança dos novos medicamentos e o insuficiente conhecimento da relação benefício-risco no momento uma autorização de introdução no mercado (AIM) é concedida são premisas estabelecidas em farmacovigilânica. Na verdade, elas mesmas justificam a contínua monitorização do perfil de segurança dos medicamentos com AIM aprovada e identificação de riscos associados à sua utilização – actividades essenciais à manutenção da própria AIM.

Ora, a deteção e avaliação de reacções adversas aos medicamentos, seguida do estabelecimento de medidas de prevenção e minimização de risco, não só fazem parte da missão da farmacovigilância, como também integram os objectivos e responsabilidades das agências reguladoras e da indústria farmacêutica.

Algumas publicações científicas procuraram, ao longo dos anos, versar sobre estas mesmas medidas de prevenção e minimização de risco, mediante o estudo do conjunto de acções regulamentares face a questões de segurança. Na sua maioria, a análise foi efectuada em contextos singulares, como o caso de produtos biológicos, medicamentos órfãos, medicamentos com AIM concedida em circunstâncias excecionais, ou considerando as acções regulamentares no contexto de um determinado país ou pequeno grupo de países, como é o caso de exemplos publicados no Reino Unido, Espanha, Estados Unidos da América e Holanda.

Os resultados obtidos sugerem que tais acções regulamentares foram desencadeadas pelas autoridades reguladoras em cerca de 9 a 25% dos medicamentos com AIM aprovada em análise. Dois outros estudos denotam que, entre 1975 e 1999, pelo menos uma acção regulamentar foi tomada em função de problemas de segurança para 10% dos medicamentos com AIM aprovada nos Estados Unidos da América. Mais recentemente, um conjunto de productos biológicos foi associado a uma probabilidade de 14% de necessitar de uma primeira acção regulamentar derivada de questões de segurança nos primeiros 3 anos após a aprovação da AIM. Sendo que, para a mesma classe de medicamentos, os produtos biológicos com a primeira aprovação de AIM possuiam um risco acrescido de requerer tais acções de segurança.

No entanto, e apesar das várias agências reguladoras dos medicamentos e productos de saúde possuírem, objectivos e responsabilidades semelhantes no que tangue à necessidade de garantir a qualidade, eficácia e segurança dos medicamentos nos mercados em que actuam, nem sempre partilham da mesma interpretação e tomada de decisão face a um determinado conjunto de informações de segurança e eficácia para

um mesmo medicamento. As diferenças nos enquadramentos regulamentares, nas estruturas organizacionais e no modo de funcionamento das agências dos Estados Unidos da América (FDA) e da União Europeia (EMA) encontram-se descritas em detalhe na literatura publicada, tendo sido extensamente analizadas e comparadas.

Ao longo das últimas decadas, estas desemelhanças têm conduzindo a avaliações e recommendações divergentes. No âmbito da aprovação de medicamentos e produtos de saúde, a literatura analisada denota que, entre 1995 e 2008, 20% dos medicamentos oncológicos em estudo possuiam uma AIM aprovada pela FDA ou pela EMA, mas não por ambas. De igual modo, o conteúdo do resumo das caracteristicas possuía importantes diferenças em 28% do conjunto de medicamentos com AIM aprovada nos dois territórios. Finalmente, existem vários exemplos de decisões distintas no que se refere a acções regulamentares derivadas de questões de segurança num contexto pós-AIM, alguns dos quais particulamente mediáticos, como é o caso da rosiglitazona.

Por outro lado, importantes desenvolvimentos regulamentares tiveram lugar no contexto da farmacovigilância, quer no território dos Estados Unidos da América, em 2007, quer na União Europeia, em 2012. Estas alterações legislativas pretendiam, entre outros objectivos, dotar as referidas agências de mais recursos e de um maior poder de decisão, implementando, ao mesmo tempo, um conjunto mais rigoroso de requerimentos e obrigações para a indústria farmacêutica/para os detentores de AIM.

Perante este cenário de alterações legislativas e na ausência de uma recente análise das acções regulamentares derivadas de questões de segurança para um conjunto mais abrangente de medicamentos, este estudo foi proposto.

A elaboração desta tese possui como objectivo o estudo, análise e discussão das acções regulamentares derivadas de questões de segurança entre 2010 e 2015, nos Estados Unidos da América e na União Europeia. Paralelamente, propõe-se a considerar a frequência, o *timing* após a AIM ter sido concedida e a natureza destas mesmas acções regulamentares, bem como a analisar quais as áreas/classes terapêuticas com maior número de acções regulamentares derivadas de questões de segurança. As actividades regulamentares da EMA e da FDA, bem como as decisões em estudo, serão comparadas e analisadas, visando reflectir-se sobre a aparente reduzida harmonização na avaliação de medicamentos e produtos de saúde entre estas duas autoridades. Por fim, de modo a ilustrar as diferenças descritas, é apresentado um caso de estudo de um medicamento associado a uma recente discussão de segurança, e do conjunto de acções regulamentares tomadas em ambos os territórios.

Um estudo/descrição abrangente da história, estrutura organizacional, processos e missão das autoridades reguladoras em questão foi efectuado. As diferenças substânciais entre a FDA e a EMA no que se refere às atividades de farmacovigilância e acções regulamentares em função de questões de segurança foram igualmente analisadas. Simultaneamente, procurou-se estabelecer pontos de convergência no que respeita às responsabilidades e objectivos propostos, e ilustrar as múltiplas iniciativas de importante colaboração entre as agências destas duas regiões.

Para a análise das acções regulamentares foram consideradas (i) as comunicações dirigidas aos profissionais de saúde (Direct Heathcare Professional Communication - DHPC) publicadas em Portugal, no Reino Unido e as Dear Health Care Professional (DHCP) Letter nos Estados Unidos da América e (ii) as revogações de AIM em medicamentos comercializados na União Europeia em associação aos medicamentos retirados do mercado nos Estados Unidos da América por questões de segurança.

Os resultados obtidos indicam um maior recurso às comunicações dirigidas aos profissionais de saúde nos países da União Europeia que nos Estados Unidos da América, no período entre 2010 e 2015. A disseminação dos riscos de segurança associados aos produtos comercializados nos Estados Unidos da América decorre, de acordo com dos dados disponíveis, através de outras ferramentas de informação comunicação de risco, actualmente disponíveis para a FDA.

Dentro da globalidade dos dados analisadas, as pequenas moléculas apresentaram quer um maior número de comunicações de segurança, quer uma maior frequência de revogação/suspensão de AIM por razões de segurança. Por outro lado, os eventos adversos relacionados com os distúrbios cardíacos surgem como um dos principais impulsionadores das acções de segurança para as pequenas moléculas. Os dados obtidos demonstram ainda uma necessidade crescente de enfoque no que concerne a questões de segurança devido a erros de medicação. Resultados estes suportados pelas conclusões presentes na literatura actualmente publicada.

De igual modo, as notificações espontâneas de reacções adversas a medicamentos continuam a representar a maior fonte de informação de segurança desencadeadora de de comunicações dirigidas aos profissionais de saúde como acção regulamentar em todos os países analisados. Todavia, verifica-se uma crescente utilização de dados de ensaios clínicos e estudos epidemiológicos tanto na identificação, como na avaliação de problemas de segurança, o que sugere um real incremento da importância dos mesmos no universo da farmacovigilância.

Finalmente, no que diz respeito ao *timing* das acções regulamentares, 66,6% das revogações de AIM por questões de segurança tiveram lugar até 5 anos após a aprovação da AIM, enquanto que 50,4% das comunicações dirigidas aos profissionais de saúde foram emitidas até 6 anos após a aprovação da AIM.

O caso de estudo escolhido versou sobre as recentes discussões de segurança relativamente ao ácido valpróico (e derivados) e sua utilização em crianças, mulheres de idade fértil e grávidas, nomeadamente face aos riscos de malformações congénitas, alterações estruturais graves e importantes efeitos neurológicos adversos nestas sub-populações. O contexto da utlização destes medicamentos foi descrito e as recomendações/acções regulamentares da FDA e EMA, bem como de algumas autoridades nacionais de estados membros da União Europeia, apresentadas. Os diferentes mecanismos e estruturas nos processos de farmacovigilância implementados e os instrumentos/medidas de minimização de risco disponíveis para cada uma das entidades reguladoras parecem justificar as diferentes recomendações e decisões observadas. Por outro lado, observam-se importantes dissemelhanças na estrutura e no conteúdo do resumo das características do medicaments/folheto informativo nestas duas regiões.

Pela observação dos aspectos em estudo conclui-se que a análise e contextualização do quadro legislativo e do conjunto de processos e procedimentos actualmente disponíveis para a FDA e para a EMA é fundamentar no entendimento das decisões regulamentares e nas recomendações face a questões de segurança de medicamentos. A familiardidade com estes conceitos poderá promover uma maior sensibilização e entendimento, não só dos profissionais de saúde, mas também dos doentes e da população em geral, quer no que tange às avalições de medicamentos aquando do pedido de AIM, quer no que se refere às análise de dados de eficácia, qualidade ou segurança, que suportam a gestão de sinais, as alterações no conteúdo do resumo das característica do medicamento/folheto informativo, a implementação de medidas adicionais de minimização de risco e as decisões de revogação/suspensão de uma AIM.

Verificou-se ainda que a natureza dinâmica dos processos regulamentares no âmbito da farmacovigilância permanece bastante atual, pelo que a necessidade de colaboração permanente entre os múltiplos intervenientes é fundamental na redução da duplicação de esforços e no suporte dos processos de avaliação, concessão e manutenção das AIM, em benefício dos reguladores, indústria farmacêutica e particularmente dos doentes.

Summary

The natural history of approved drugs comprehends the discovery of new and important safety information in the post-marketing setting. In fact, studies show that for 9 to 25% of the drugs analysed, national or regional regulatory authorities required a safety-related regulatory action after their approval. Over the years, these publications have analysed safety-related regulatory actions, mostly on specific settings, such as for particular drug groups (e.g. biologicals, orphan medicines and exceptional circumstances/ conditional (accelerated) approval procedures) or individual countries.

On the other hand, although current FDA and EMA guidance are driven by similar objectives regarding the identification, monitoring and minimization of risks, commonly leading to generation of similar data needs, there are cases where the two regulatory agencies have recommended distinct regulatory actions in response to the same safety issues identified. Substantial differences have also been identified with regards to risk communication and in monitoring implementation of risk minimization measures.

Therefore, this study proposes to discuss and characterize the regulatory framework of pharmacovigilance activities within the European Union region and the United States of America, and analyse and compare the safety-driven regulatory actions for medicinal products, both small molecules and biologics, between the years of 2010 and 2015, following updates in applicable regulations in 2007 (for the US) and in 2012 (for the EU). The frequency, timing and nature of such regulatory actions evaluated, as well as the most impacted therapeutic groups. The direct communications to healthcare providers disseminated in Portugal, United Kingdom and US and the requests of withdrawal of medicinal products in the EU and the US territories were considered when analysing safety-related regulatory actions. Such recommendations provided by the EMA and the FDA were used to discuss the apparent lack of consistency in the assessment of medicinal products by these regulatory bodies. Finally, a case-study of a drug whose safety profile has been recently under evaluation in both territories is presented, and the recommendations/safety-related regulatory actions taken described.

The results suggest that direct communications to healthcare providers are more frequently distributed in the EU than the US, with the majority of the safety risks associated to marketed products in the US territory having been announced to HCP and the general public by other risk communication tools currently available to the FDA. Both safety driven direct communications to healthcare providers and withdrawals were more frequent for small molecule medicinal products. Additionally, the data retrieved supports

previous findings on differences having been shown to exist in the nature of the safety-related regulatory actions for biologicals compared with small molecules. Cardiac disorders related AE appear as a leading trigger for safety-driven regulatory actions for small molecules. Evidence also suggests more efforts still need to be allocated for tackling medication error-related adverse events. Spontaneous reports continue to account for the majority of the source data for triggering safety driven direct communications to healthcare providers in all regions, but relevant findings originating from clinical trials and epidemiological studies were observed, supporting the increasing importance of these sources in identifying and evaluating safety issues. With regards to timing of regulatory action, 66.6% of the safety-related withdrawals were issued within 5 years after approval, while 50.4% of the safety driven direct communications to healthcare providers were issued within 6 years after approval.

The use of valproic acid in children, women of childbearing potential ~~and potential~~ and during pregnancy given the associated risks of congenital malformations, major structural abnormalities and serious neurodevelopmental effects was chosen as case study. The distinct set of regulatory actions taken might be justified by the structurally different pharmacovigilance implemented mechanisms and instruments available to regulators in each territory but also given the inconsistencies in both structure and content of the labelling information between EU and US territories and to some extent within in EU territories.

Given the study performed, it is possible to conclude that the analysis and contextualization of the on legislative framework and processes of the FDA and the EMA is essential to understand the agencies regulatory decisions and recommendations. Dissemination of these may help improve overall awareness and allow for a better insight and understanding on matters of divergent drug approvals and post-marketing safety recommendations, either it being signal management activities, label updates, additional risk minimization measures and withdrawals/suspensions. The dynamic nature of regulatory processes for pharmaceuticals risk management is still present on today's exciting pharmacovigilance landscape and future regulatory standardization and increased collaboration is necessary to further help in reducing redundancy and support the review/assessment processes for the benefit of regulators, pharmaceutical industries and the patients.

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ADR	Adverse Drug Reaction
AE	Adverse Events
ATC	Anatomical Therapeutic Chemical
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
DHCP	Dear Health Care Provider
DHPC	Direct Healthcare Professional Communication
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration

FDAAA	Food and Drug Administration Amendments Act
GVP	Good Pharmacovigilance practice Guidelines
HCP	Health Care Practitioner
HIV/AIDS	Human immunodeficiency virus infection and acquired immune deficiency syndrome
ICH	International Conference on Harmonisation
ICMRA	International Coalition of Medicines Regulatory Authorities
IND	Investigational New Drug
INN	International Non-proprietary Name
MA	Marketing Authorisation
MAH	Marketing authorisation holders
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Competent Authority
PADER	Periodic Adverse Drug Experience Reports
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
REMS	Risk Evaluation and Mitigation Strategies
RMM	Risk Minimisation Measures
SCOUT	Sibutramine Cardiovascular Outcomes
SmPC	Summary of Product Characteristics
SOC	System Organ Class
US	United States of America
WHO	World Health Organization

1. Introduction

1.1 Pharmacovigilance: the basics

The origins of pharmacovigilance are traced back to a series of drug induced tragedies, such as sulphanilamide, thalidomide, practolol, benoxaprofen and oral contraceptives, which themselves (re)defined the purpose and scope of pharmacovigilance(1). In the past, the process of pharmacovigilance was often considered to begin only after a drug was authorised for use in every day clinical practice. Nowadays, however, it encompasses all safety-related activities beyond the point at which humans are first exposed to a new medicinal lproduct .

The World Health Organization (WHO) defines pharmacovigilance as *the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug related problem*(2). Such science is therefore, in its essence, a risk management process, a system used to monitor the safety of medicines, playing a substantial role in both public health and in ensuring protection of patients' safety.

The decision to approve a drug is based on it having a satisfactory balance of benefits and risks within the conditions specified in the product labelling(3), which is based on the information available at the time of approval. Nonetheless, due to the limitations of pre-marketing studies/data, drug safety can only be regarded as provisional when a new medicine is first marketed as there is a need to collect more evidence arising from 'real world' use(1,3). Systematic medicine safety monitoring is therefore necessary to identify previously recognized and unrecognized adverse drug reactions (ADR) and to evaluate the safety and efficacy of medicinal products during clinical trials and in the post-marketing period.

In fact, the knowledge related to the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed. In particular, during the early post-marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe(2). Serious hazards are seldom identified during pre-marketing clinical trials because sample sizes are almost invariably too small to detect them. In addition, the prevailing conditions of clinical trials – selected patients, short durations of treatment, close monitoring and specialist supervision – almost invariably

mean that they will underestimate the frequency of ADR relative to what will really occur in ordinary practice(1).

Warnings or restrictions will therefore be added to the product label, or a drug may be removed from the market, because unexpected or greater than expected morbidity or mortality is identified only after a drug enters widespread use. The discovery of new adverse events in the post-marketing setting is part of the normal, natural history of approved drugs(4). And thus, timely identification of and response to drug-related risks become central to the mission of pharmacovigilance and the health authorities.

As a matter of fact, the newly generated information for marketed medicinal products can have an impact on its benefit risk ratio, meaning that a detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance that can enable information feedback to the users of medicines in a timely manner(1). Generally speaking, the process starts with identification of a possible hazard, which is then evaluated and investigated and, if necessary, a set of actions is then taken with a view to minimising the risk. Pregnancy prevention in users of thalidomide is an example of such a safeguard; monitoring white blood cell counts to detect agranulocytosis in users of the antipsychotic drug clozapine is another(5–7). Implementation of such risk minimization measures also requires tools for communicating with health care providers (HCP), patients and caregivers and a periodic assessment of effectiveness should be made as a final step.

Moreover, the process is iterative itself as new evidence may emerge or the measures taken may turn out to be insufficient. In fact, several drugs, such as Bextra (valdecoxib for Stevens–Johnson syndrome), Rezulin (troglitazone for hepatotoxicity), Vioxx (rofecoxib for myocardial infarctions) and Lotronex (alosetron hydrochloride due to severe constipation and ischemic colitis) have ended up being withdrawn from the European Union (EU) and/or the United States of America (US) markets because of serious/emerging adverse events that were unknown or not fully characterized when the product was approved, changing the benefit-risk profile of these drugs(1,8–13).

With regards to the regulatory requirements, the requisite and place for pharmacovigilance within medicines regulation may have only been widely recognised in the 1960s as a consequence of the thalidomide tragedy, however the science of drug safety has grown to become an essential component of today’s pharmaceutical regulatory environment. And, although the role and tasks of regulatory authorities include

public health protection and promotion of safe and effective use of medicines, both regulatory authorities and manufacturers/pharmaceutical companies are equally responsible for the safety of medicinal products they approve/produce and sell(1).

The major emphasis on patient safety and safety monitoring are also reflected in current driving policies of all regulatory authorities worldwide, such as the US Food and Drug Administration (FDA) Strategic Priorities for 2014-2018 and the European Medicines Agency (EMA) Network Strategy to 2020 draft, bearing witness to the intimate relationship between regulatory science and safety(14,15).

With no disregards to the safety monitoring during clinical trials and its importance within the legislative framework, the below regulatory analysis will essentially focus on the regulatory aspects of post-marketing safety surveillance for two the territories in discussion.

1.2 Legislative framework: EU versus US

Regulations and guidance concerning the development, production, marketing and sales of medicinal products involve paradoxical goals. Overall they must ensure that new and effective medical treatments reach the public rapidly while simultaneously providing protection from ineffective or even unsafe therapies and from predatory marketing practices that often tout unproven products to vulnerable patients(16).

While in the EU these responsibilities are shared between the national competent authorities and the European Medicines Agency (EMA), in the US, these regulatory functions fall within the competences of the US Food and Drug Administration (FDA).

1.2.1 Origins of the FDA

The FDA is the oldest comprehensive consumer protection agency in the US Federal Government. Its origins can be traced back to the Patent Office around 1848, carring out chemical analyses of agricultural products, a function that the newly created Department of Agriculture inherited in 1862(17).

Its modern regulatory functions began with the passage of the 1906 Pure Food and Drugs Act, which was endorsed in a law prohibiting interstate commerce in adulterated and misbranded food and drugs(17–19). The basis of this legislation rested on the requirements of product labelling rather than pre-market approval. Drugs, defined in accordance with the standards of strength, quality, and purity in the *United States Pharmacopoeia* and the *National Formulary,* could not be sold in any other condition

unless the specific variations from the applicable standards were plainly stated on the label(20). Following the therapeutic disaster of sulphanilamide elixir, the *Food, Drug, and Cosmetic Act* was signed on 1938. This new law brought cosmetics and medical devices under control, and it required that drugs were to be labelled with adequate directions for safe use. Moreover, it mandated pre-market approval of all new drugs, such that a manufacturer would have to prove to FDA that a drug was safe before it could be sold. It irrefutably prohibited false therapeutic claims for drugs, although a separate law granted the Federal Trade Commission jurisdiction over drug advertising(21).

Later in 1962, the FDA's mission was expanded by the Kefauver-Harris amendments that added the requirement that drugs be proven "effective" as well as safe, and placed strict controls on the use of investigational drugs(22). Regulations regarding drug safety oversight developed furthermore, in 1976, to include medical devices, once again following a therapeutic disaster in which thousands of women were injured by the Dalkon Shield intrauterine device (23,24).

Changes in the role of the FDA have come rapidly in the past decades, shaped in part by political pressure and expanding federal regulations, consumer activism, and industry involvement, with regards to the increasing complexity of drugs and devices, but also given the growth of the pharmaceutical industry into a major economic force within the US territory. Moreover, patient advocacy groups have shown to have influenced lawmakers, such is the case of creating incentives to stimulate industry interests in developing orphan drugs, and have played an instrumental role in the agency's development of accelerated techniques for drug approval, for example for the management of HIV/AIDS (16,24).

Other important amendments to Federal Food, Drug, and Cosmetic Act include the Orphan Drug Act (1983), with the objective to f facilitate and promote the development of medicines and biological products in the treatment of rare diseases; the Drug Price Competition and Patent Term Restoration Act, known as the Hatch-Waxman Act (1984), guiding the development of generic medicines through the implementation of an Abbreviated New Drug Application and a period of commercial exclusivity for generic medicines as well as patent extension for innovative medicines, and the Prescription Drug User Fee Act, dated to 1992, introducing a royalty system to speed up the FDA's evaluation times(25).

The FDA Modernization Act, adopted by the Congress in 1997, also represents a major strengthening of the FDA's mission, aiming to improve the efficiency of the FDA without

compromising patient safety. It covers several aspects of FDA operations, including the development of a better cooperation with the main international regulatory bodies, mainly the EU and Japan; the introduction of an additional market exclusivity of 6 months for medicines studied in paediatrics; the implementation of the Fast Track procedure to accelerate access to the market for drugs that treat serious diseases; the creation of a public data bank for clinical trials; and the implementation of new standards in the demonstration of drug efficacy(26,27).

Such developments were followed by the FDA's publication of *Innovation or Stagnation? - Challenge and Opportunity on the Critical Path to New Medical Products* in 2004, which examines the critical path needed to bring therapeutic products to fruition, and how the FDA can collaborate in and facilitate the overall pharmaceutical industry process (laboratory – production – end use) to make medical breakthroughs available to those in need as quickly as possible(26).

Nonetheless, it is the Food and Drug Administration Amendments Act (FDAAA), endorsed in 2007, which has had a pivotal role regarding the safety of medicines in the post-marketing setting and in the need for the FDA to develop an active safety surveillance system. In fact, this piece of legislation empowered the FDA with the authority to require labelling changes with respect to new safety information, as well as to request post-marketing epidemiology studies and risk evaluation and mitigation strategies (REMS) and clinical trials for new drugs approved under the Federal Food, Drug, and Cosmetic Act and for biological products. In addition, the FDAAA increased the requirements for registering clinical trials, the FDA's resources for risk management activities for pre and post-marketing and its authority over the contents of direct-to-consumer advertising, but also required the FDA to become more transparent on its processes, decisions and knowledge on drug related information and to improve its tools for risk communication to healthcare practitioners and the general public (4,28). Additionally, a consolidated website to provide post-market safety information to patients and HCP was to be established by the FDA(29).

During these years, the Medicare Prescription Drug Improvement and Modernization Act, introducing an entitlement benefit for prescription drugs, through tax breaks and subsidies and the Paediatric Research Equity Act, allowing FDA requiring that sponsors conduct clinical research into paediatric applications for new drugs and biological products, were also passed(26).

Further in 2012, FDA's authority and ability to protect and promote public health was expanded with the Food and Drug Administration Safety and Innovation Act. FDA was allowed to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products and to increase stakeholder involvement within their processes, particularly by connecting to and recognizing the value of patient input to the drug development enterprise, the 'Breakthrough Therapy' designation was created, to help promote innovation and speed patient access to safe and effective products. Companies could now expedite the development and review of new drugs in case of preliminary clinical evidence which indicated the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases. And finally, focus was given to enhancing the safety of the medicinal products supply chain(26,30).

1.2.2 Status quo

Currently the FDA's jurisdiction encompasses most food products, human and animal drugs, therapeutic agents of biological origin, medical devices, radiation-emitting products for consumer, medical, and occupational use, cosmetics and animal feed(31). Its core missions include 1) protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of US food supply, cosmetics, and products that emit radiation; 2) regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors; 3) advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health; and 4) safeguarding the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats(32).

As a whole, the United States Food and Drug Administration is the agency responsible for ensuring that prescription drugs marketed in the US territory are safe and effective, with both the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) monitoring and reviewing the safety information throughout life cycle of the medicinal products, under the Office of Medical Products and Tobacco.

CDER's mission is to protect and promote public health by helping to ensure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients. As part of the FDA, CDER performs an essential public health task regulating over-the-counter and prescription drugs, including biological therapeutics and generic drugs(33).

On the other hand CBER aims to ensure the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues, and gene therapies for both the prevention/diagnosis and treatment of human diseases, conditions, or injuries. This centre envisions to facilitate the development, approval of, and access to safe and effective products and promising new technologies, but also help to defend the public against the threats of emerging infectious diseases and bioterrorism(34).

1.2.3 US laws and regulations

The laws of the United States are adopted by congress and organized by subject into the United States Code. The Federal Food, Drug, and Cosmetic Act and subsequent amending statutes are codified into Title 21 Chapter 9. However, new laws cannot be enforced until new regulations ('administrative law') are issued, which are reordered in The Code of Federal Regulations (CFR). The CFR therefore is a systematisation of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government, which has the force and effect of a law. Title 21 of the CFR is reserved for rules of the Food and Drug Administration and contains all regulations pertaining to food and drugs, including those which apply to orphan drugs (21 CFR, Part 316), investigational new drugs (IND) (21 CFR, Part 312) and adverse drug event reporting(4,35).

Within pharmacovigilance, post-marketing reporting of adverse drug experiences are comprised in part 314.80, while section 312.32 addresses Investigational New Drug Safety Reports, and part 310.305 refers to records and reports concerning adverse drug experiences of marketed prescription drugs for human use without approved new drug application. Safety requirements and practices for biological products, on the other hand, are included in part 600.

In addition to the regulations published in the Federal Register, the FDA is also equipped with a set of documents representing its current thinking on a particular subject. These guidance documents provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing,

and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Most current available guidance on drug safety are depicted in the table below (Table *1*):

Table 1 - Current (April 2017) available Drug Safety FDA Guidance

Title	Status	Publishing date
Drug Safety Information - FDA's Communication to the Public	Final Guidance	02-03-2007
Medication Guides - Adding a Toll-Free Number for Reporting Adverse Events	Final Guidance	08-06-2009
Drug-Induced Liver Injury: Premarketing Clinical Evaluation	Final Guidance	29-07-2009
Format and Content of Proposed REMS, REMS Assessments, and Proposed REMS Modifications	Draft Guidance	01-10-2009
Post-marketing Studies and Clinical Trials - Implementation of Section 505(O)(3) of the Federal Food, Drug, and Cosmetic Act	Final Guidance	31-03-2011
Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies	Final Guidance	17-11-2011
Post-marketing Adverse Event Reporting for Medical Products and Dietary Supplements During an Influenza Pandemic	Final Guidance	23-02-2012
Classifying Significant Post-marketing Drug Safety Issues	Draft Guidance	08-03-2012
Drug Safety Information - FDA's Communication to the Public	Draft Guidance	08-03-2012
Safety Reporting Requirements for INDs and BA/BE Studies - Small Entity Compliance Guide	Final Guidance	19-12-2012
Safety Reporting Requirements for INDs and Bioavailability/Bioequivalence Studies	Final Guidance	19-12-2012
Safety Considerations for Container Labels and Carton Labelling Design to Minimize Medication Errors	Draft Guidance	23-04-2013
Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets	Final Guidance	14-05-2013

Title	Status	Publishing date
Safety Labelling Changes - Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act	Final Guidance	30-07-2013
Best Practices in Developing Proprietary Names for Drugs	Draft Guidance	28-05-2014
Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry	Draft Guidance	06-04-2015
Over-the-Counter Paediatric Oral Liquid Drug Products Containing Acetaminophen	Final Guidance	04-08-2015
Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act	Final Guidance	07-10-2015
Safety Assessment for IND Safety Reporting Guidance for Industry	Draft Guidance	16-12-2015
Safety Considerations for Product Design to Minimize Medication Errors Guidance for Industry	Final Guidance	11-04-2016
FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry	Draft Guidance	20-09-2016
Providing Post-market Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)	Final Guidance	28-11-2016

1.2.4 The novelty of the European Medicines Agency

The evolution of European regulation of medicinal products (and medical devices) is, by contrast, much more recent, with significant changes after the formation of the EU in 1993. Clinical trial applications are generally handled in the member state, whereas marketing applications are approved by state and/or central agencies in accordance with regulations set forth by the European Commission (EC). Formed in 1995, the EMA was created to harmonize processes in the member state regulatory agencies to reduce annual costs to drug companies as well as to eliminate competition-restricting regulation in sovereign states. However, the EMA does not oversee all drug approvals the way the FDA does in the United States, as there are different routes a drug can be approved (national, decentralised or centralised procedures), depending on multiple factors, which include its class and manufacturer preferences(36).

EU medicines legislation entails both the protection of public health and the creation of a single market for medicinal products. It is initially proposed by the European Commission, after which goes through consultative and political processes, and emerges via the European Parliament to be put into force by the Commission. In principle, in cases ofapparent conflict with any national legislation, EU law takes precedence, which does not necessarily mean that national authorities cannot enforce additional requirements in their own territory(37).

1.2.5 Legal requirements in the EU

Historically, the legislation underpinning the centralised system of authorisation exists in the form of a Regulation – number 2309/93, articles 19–26. However, most of the other EU legislation of medicines is fact contained in a single Directive – 2001/83, Title IX, articles 101–108. Aside from these, Directive 2001/20 covering clinical trials– is also relevant in relation to pharmacovigilance for investigational drugs(37).

On the other hand, the legal framework of pharmacovigilance for marketed medicines is provided for in Regulation (EC) No 726/2004 for centrally authorised medicinal products and in Directive 2001/83/EC with respect to nationally authorised medicinal products (including those authorised through the mutual recognition and decentralised procedures)(38). In addition, Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities stipulates operational details in relation to certain aspects of pharmacovigilance to be respected by marketing authorisation holders, national competent authorities and the EMA. Additionally, the EMA has released good pharmacovigilance practice guidelines (GVP) in order to facilitate the performance of pharmacovigilance activities(38,39), which include modules covering major pharmacovigilance processes (GVP modules I to XVI) and product- or population-specific considerations, such as the ones developed for vaccines and biological medicinal products.

Table 2 - Current (November 2017) GVP modules provided by the EMA

Title	Status	Effective Date
Module I – Pharmacovigilance systems and their quality systems	Adopted	02/07/2012
Module II – Pharmacovigilance system master file (Rev. 2)	Adopted	31/03/2017
Module III – Pharmacovigilance inspections	Adopted	16/09/2014

Title	Status	Effective Date
Module IV –Pharmacovigilance audits (Rev. 1)	Adopted	
Module V – Risk management systems (Rev. 2)	Adopted	31/03/2017
Module VI – Management and reporting of adverse events to medicinal products (Rev. 1)	Adopted	16/09/2014
Module VI – Collection, management and submission of reports of suspected adverse events to medicinal products (Rev. 2)	Adopted	22/11/2017
Module VI Addendum I – Duplicate management of suspected adverse event reports	Adopted	22/11/2017
Module VII – Periodic safety update report	Adopted	13/12/2013
Module VIII – Post-authorisation safety studies (Rev. 3)	Adopted	13/10/2017
Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev. 2)	Adopted	09/08/2016
Module IX – Signal management	Adopted	02/07/2012
Module IX – Signal management (Rev. 1)	Adopted	22/11/2017
Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse events	Adopted	22/11/2017
Module X – Additional monitoring	Adopted	25/04/2013
Module XV – Safety communication (Rev. 1)	Adopted	13/10/2017
Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev. 2)	Adopted	31/03/2017
Module XVI Addendum I – Educational materials	Adopted	16/12/2015

Legislation passed in 2010, accompanied by an implementing regulation in 2012, and further amended later that year, strengthened and rationalised the pharmacovigilance system. This was achieved, on one hand, by providing a clear legal basis for different roles and responsibilities of the principal actors within the EU (notably the pharmaceutical industry and regulators), by directing the EMA to develop a more robust, harmonised and rapid decision making process, and by increasing the engagement of patients and

health care practitioners. It also allowed patients to report ADR directly to the competent authorities.

The regulation called for a science-based integration of benefit and risk, ensuring that requirements are proportionate to risk and increasingly focused on proactive and planned solutions, but also aimed for a reduction on systems duplication, with greater efficiency and improved transparency. Overall, this new legal framework aimed to improve patient safety and public health through better prevention, detection and assessment of adverse events to medicines, for which the newly created scientific committee, the Pharmacovigilance and Risk Assessment Committee (PRAC) was fundamental(29,38–41).

Other changes included a strengthened coordination at the EMA, particularly on pharmacovigilance inspections and audits across the EU, better funding via fees, and reinforced authorization requirements with increased efforts on pharmacovigilance. Examples of these are the need of risk management plans for all new medicines, with measurements of the effectiveness of risk minimization as applicable, and stronger requirements for safety and efficacy studies in the post-authorization phase. Marketing authorisation holders (MAH) were then also requested to submit post-market benefit–risk reports (29,38–41).

Later on, in 2013, the EC adopted an Implementing Regulation introducing a black symbol to identify medicinal products which are subject to additional monitoring, followed by aa Delegated Regulation on post-authorisation efficacy studies, in2014. Generally speaking, such additional studies could be required to address certain well-reasoned scientific concerns, which may have a direct impact on the maintenance of the marketing authorisation (MA) (38,39).

Further developments comprise of Addendum I to Module XVI on educational materials published on December 2015 and the revision of the Safety Communication GVP module, in 2017, particularly with amendments to the template Direct Healthcare Professional Communication (DHPC) and DHPC Communication Plans(42).

More recently, the final Module IX on signal management and its addendum and the revision 2 of Module VI were published and will both come into effect on November 2017, together with the new EudraVigilance functionalities and the requirements of application of the ICH-E2B (R3) guideline. New Product- or Population-Specific Considerations, namely on the paediatric population are also currently available for public consultation(42).

1.2.6 Common grounds

Despite the organizational and processual differences here depicted, similarities can be easily drawn for these two major regulatory authorities, particularly in terms of aims and responsibilities: ensuring that high-quality, safe and effective medicines are made available to patients in a timely manner.

The formal path of harmonization was initially lead by the International Conference on Harmonisation (ICH) in 1990, bringing together the regulatory authorities and pharmaceutical industry of the US, Europe and Japan to discuss scientific and technical aspects of drug registration. Today, the ICH continues to issue guidelines for the standardization of clinical practices and technical requirements for human drugs, including the establishment and management of quality control laboratories and the prompt dissemination of new information on serious adverse drug effects(43). Thanks to the communication platform/forum provided by the ICH, regulatory agencies have agreed to key changes in practice and regulations far faster than it would ever be possible otherwise, and pharmaceutical development within organisations is now possible on an increasingly global basis rather than regionally, to benefit of patients.

Different projects within several international bodies have also been under development specifically for pharmacovigilance. In addition to ICH, collaborations have been forged within the WHO, the Council of International Organisation of Medical Sciences and the Drug Information Association. These organisations promote the global importance of post-marketing drug safety and provide a global platform for adverse event data collection, propose broad frameworks for post-approval safety activities, develop technical specifications for industry submissions to regulatory bodies around the world, and offer a forum for education and exchange of ideas(44).

More recently, a relatively new International Coalition of Medicines Regulatory Authorities (ICMRA) is bringing together regulators from 22 countries, and the WHO as an observer, spanning across North America, South America, Europe, Asia and Africa. Unlike the more operational ICH, ICMRA is designed to construct strategic orientations, providing high-level advocacy and leadership. Currently, the group is focused on the pharmaceutical supply chain, international crisis management (e.g. Ebola, Zika outbreaks), mutual recognition of good manufacturing practices (GMP), pharmaceutical inspections and other more comprehensive topics on the use of generic medicines and pharmacovigilance activities(45–47).

In parallel to the described harmonization developments, there seems to be an increasing tendency towards collaborative efforts on patient safety between the FDA and the EMA, provided their similar objectives on the identification, monitoring and minimization of risks (48). Recently approved legislation and regulation by both parties has focused on increased transparency, a higher level of accountability, a rigorous scientific basis for post-marketing decision making, improved processes, and better funding for these activities(29). Such shared values provide another motivation for close collaboration.

In fact, since 2003, the EMA and the FDA have been holding regular meetings in multiple cluster areas, focusednot only on biosimilars, oncological therapeutics, orphan medicines and paediatric drugs, but also on safety of medicines (44). Designed to complement, rather than replace each other international undertakings in pharmacovigilance, these initiatives aim to promote exchange of information on safety related issues and to provide advance notice of anticipated regulatory action, public information and communication prior to decision-making. Product-related risk assessments with a special emphasis on emerging safety concerns, policies, guidance documents and regulations are also typically exchanged during these meetings(49).

Another practical example of proactive aligned approaches for drug safety surveillance are the requirements for REMS and Risk Management Plans (RMP). Over the last few years, regulatory authorities have been changing the emphasis from the reactive collection of safety data to a more proactive safety surveillance approach. Public scrutiny of regulatory bodies, on the other hand, has also increased the focus on pharmacovigilance with the downstream impact of increased regulatory requirements for the post-marketing use. A comparison study of FDA and EMA guidance for pharmaceutical risk management indicates a similarity in overall objectives with respect to identifying, monitoring and minimizing a risk and a good degree of synergy in respective tool kits. Both agencies allow flexibility in the determination of product-specific actions required, recognizing the dependency on differing adverse effects of potential concern. However, they do differ on elements such as monitoring of implementation of risk minimization activities and reporting time requirements(50).

With regards to post-approval periodic reports reviewing cumulative safety information, FDA usually requests Periodic Adverse Drug Experience Reports (PADER), while EMA and other agencies adopted the periodic benefit-risk evaluation report (PBRER). The PBRER is based on the 2013 ICH guideline E2C (R2) and intends to promote a consistent approach to periodic post-marketing safety reporting among the ICH regions,

enhancing efficiency by reducing the number of reports generated for submission to regulatory authorities. Both report types share a similar philosophy, presenting (i) a comprehensive, concise and critical analysis of any new and/or emerging information on the risks and (ii) the benefit in the approved indications, to enable an appraisal of the product's overall benefit-risk profile. This evaluation is designed to help ascertain whether further investigations are necessary and whether changes should be made to the approval or to the medicinal product's labelling, particularly for serious, unexpected adverse events. As a matter of fact, the FDA accepts all three formats - the PADER/Periodic Adverse Experience Report, Periodic Safety Update Report (PSUR "old format") and PBRER - to fulfil the post-marketing periodic safety reporting requirements as per applicable legislation and has recently published a guideline describing the procedures applicants should follow for different scenarios. However, the reporting intervals and regulatory environment in which these periodic safety report updates occur is not uniform worldwide, allowing considerable differences in terms of content(51–53).

On what it concerns signal management activities, both agencies are essentially responsible for the frequent monitoring and evaluation of data accumulated within specific databases: the EudraVigilance (EMA) and FDA Adverse Event Reporting System (FAERS)/US Vaccine Adverse Event Reporting System, in addition to submitting reports of suspected adverse effects associated with medicinal products to VigiBase, the WHO global database of individual case safety reports. Moreover, both agencies maintain tracking tools for validated safety signals: the European Pharmacovigilance Issues Tracking Tool, CDER's Document Archiving, Reporting, and Regulatory Tracking System and CBER's Therapeutics and Blood Safety Branch's Safety Signal Tracking. Similar processes and working groups for analysing safety information are maintained, marketing authorisation holders are often requested supplementary records and recommendations for regulatory action, such as labelling changes, risk management programs and enhanced public communication are issued as necessary, following in depth analysis of each safety topic. Transparency and public record keeping on potential safety signals are currently a key value for both agencies: each month EMA publishes an overview listing all safety signals discussed during the latest Pharmacovigilance Risk Assessment Committee (PRAC) meeting and the recommendations given for each of them, while FDA conducts regular, bi-weekly screening of the FAERS database, making available a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last monitoring(54–62). Besides these, several other methods for communication of drug safety information, e.g. 'MedWatch Alerts', 'DHCP

letters', 'Drug Safety Communications' and 'Safety & Availability (Biologics) Communications' are easily retrieved from the FDA website(63).

Innovative strategies on proactive safety surveillance programs also exist on both sides of the Atlantic, such as the US Mini-Sentinel/Sentinel Initiative, designed to improve active surveillance by better understanding and more accurately estimating the incidence of a given safety risk in a relevant population. In fact, regulatory impact of Mini-Sentinel pilot includes improved signal refinement and support to FDA actions, on labelling changes (or decisions not take action in case where existing labels and communications adequately describe benefits and safety risks) and on safety communications; by characterizing the distribution (e.g. age and sex) of health outcomes of interest and ongoing drug surveillance; and by identifying and characterising drug-use patterns across the United States(64). Examples of important actions taken include review of dabigatran(65), Rotavirus vaccine(66,67), olmesartan(68), influenza vaccine(69), and human papillomavirus quadrivalent(70).

Within EU, the EU-ADR project aimed at computerized system detecting adverse drug reactions and thus supplementing spontaneous reporting systems, by exploiting clinical data from electronic healthcare records of over 30 million patients from several European countries (The Netherlands, Denmark, United Kingdom and Italy). In this project, a variety of text mining, epidemiological and other computational techniques was used to analyse the medical records in order to detect 'signals'. Based on this system, the EU-ADR Alliance was created - a collaboration framework for running drug safety studies in a federated manned, using extracted data from multiples European electronic healthcare record databases. The EMA has commissioned three studies so far regarding the use of oral contraceptives, the risk of cardiac valve disorders associated with the use of bisphosphonates, and the monitoring of the effectiveness of risk minimization in patients treated with pioglitazone-containing products(71–73).

1.2.7 Points of departure

However, significant divergences within drug safety review and benefit-risk balance assessment of medicinal products remain. Despite ongoing attempts at international harmonisation described above, legislative requirements for the regulation of medicines, including for safety related topics, differ considerably around the world, resulting in multiple cases which are indeed well known for divergent regulatory decisions (28,74–78).

With regards to pre-approval, contrasts between FDA's and EMA's processes and regulations are plenty, with the most frequently addressed in published literature being time required for drug approvals and transparency of nonpublished drug trials data(16,79). In a recent article looking at the decision-making process for anticancer drugs at both EMA and FDA through a comparative qualitative study reporting directly the views, opinions, and experiences of regulators themselves, respondents provided various explanations for divergent regulatory opinions between EMA and FDA, particularly emphasising the different interpretation of the end points such as the progression-free survival as a measure of the clinical benefit. (80).

In this same article, FDA respondents thought that their agency tended to approve broader therapeutic indications than the EMA, whereas EMA respondents thought to be more restrictive, limiting the indication to very specific patient populations. In fact, EMA respondents agreed that in EU, the more frequent use of therapeutic indications tailored on very specific patient populations could be related to country-specific reimbursement policies with only the selected patient population reported in the label being covered by the national health system(80).

Still within oncology therapies, studies comparing the approaches of the EMA and the FDA in the evaluation and approval of new anticancer indications, found there were clinically relevant differences in therapeutic indications approved by the two agencies. An overall trend suggesting that the agency that was second in approving was usually more restrictive in the wording of the indication compared with the agency that provided first approval was also discussed(81). Comparisons have also been drawn for weight management therapies and anti-diabetic medicinal products(78,82).

Several publications also address the possible relationship between delays in approval and a more refined assessment of safety, efficacy and risk/benefit(80,81,83–87). Potential risks of products that had a special review designation (fast track, accelerated approval and orphan designation) for both adverse efficacy (gefitinib) and safety (lapatinib) given the data emerged during their post-marketing periods are also extensively studied to date (84,86)

Overall, disparities in drug approvals among regulatory agencies are attributed to differences in legislation and approval procedures, efficacy endpoints, disease activity indices, benefit/risk assessment, decision-making approaches and post-marketing requirements(74,78,80,83,84,86–96).

In the matter of post-approval safety surveillance, differences are also easily identifiable. For instance, pharmacovigilance planning is emphasized in the EU system, while a similar approach has not been formally adopted in the US. The detailed framework of post-approval safety studies and efficacy studies is different from that of post-marketing requirements for studies or clinical trials of a safety issue in the US. Additionally, there are also fundamental operational differences between the two agencies. In the EU system, scientific review is performed by experts within a decentralized network of national agencies, whose work is referred to a centralized committee, the Pharmacovigilance and Risk Assessment Committee. In the US, scientific review work is conducted within a single centralized agency, though there is no single body within the FDA that reviews each and every recommendation.

Different interaction modalities with both industry and patients represent an additional source of divergence between the two agencies, with a potential impact on decision making(81). And finally, strategies of communicating risks to patients/healthcare providers and monitoring effectiveness of risk minimization measures implemented are unique for each system, as are reporting time requirements(81).

1.3 Sources of information

Accurately assessing the potential benefits and risks posed by a drug in the post-marketing context requires the use of a wide variety of scientific data, including findings from clinical trials, epidemiologic and outcomes research, such as observational studies and meta-analyses, and post-marketing surveillance systems which detect and help to characterize adverse events. All sources of data - not only or primarily those obtained from clinical trials - have therefore the potential to contribute to sound regulatory decision-making(4).

Monitoring product safety in the real word has been traditionally done by passive surveillance or the collection of spontaneously reported adverse events from healthcare providers and consumers following the administration of a medicinal product. Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions(97). Several databases systems containing information on adverse events submitted to the health authorities are now available to support the agencies' drug post-marketing safety surveillance programs

(VigiBase, Adverse Event Reporting System and Vaccine Adverse Event Reporting System and EudraVigilance)(12).

Active surveillance, in contrast to passive surveillance, seeks to determine the complete number of adverse events via a continuous pre-organized process. Examples of active surveillance include sentinel sites, drug event monitoring and registries, such as follow-up of patients treated with a medicinal product with a risk management programme. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system(97).

On another hand, traditional epidemiologic methods are also a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series, namely cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective). Moreover, descriptive studies can too constitute an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations(97).

Finally, when significant risks are identified from pre-approval clinical trials, further clinical studies might be called for, either to evaluate the mechanism of action for the adverse event, to determine whether a particular dosing instruction can put patients at an increased risk of adverse events or even which group of patients might be at an increased risk of adverse events, through genetic testing(97).

1.4 Safety driven regulatory changes

Approval of a marketing authorization signals the start of on-going evaluation of both benefits and risks during entire market life cycle of a drug. Regardless of the efforts to ensure drug safety before launch, it is the use of drugs in ‘real world’ setting which leads to the identification of new and important safety topics, often resulting in relevant safety driven regulatory actions.

Early US studies suggested that 10% of drugs registered in the US between 1975 and 1999 required a safety-related action(98,99). Another survey on drug safety discontinuations in the United Kingdom, the US and Spain, determined that 3 to 4% of all the drugs introduced in these countries were subsequently discontinued for safety reasons in at least one of the three countries. Therapeutic classes most commonly

associated with safety discontinuations were the nonsteroidal anti-inflammatory drugs, vasodilators and antidepressants(100).

More recent data suggests that for about 10% of all marketed drugs, safety-related regulatory actions are required for new and serious safety issues leading to hospitalization, disability or even death(101). Research on Direct Healthcare Professional Communications in the Netherlands also concluded that 9% of all drugs on the market required a safety-related action(102).

These safety issues may emerge both shortly after market entry and/or at a later stage in the drug's life cycle(98,102,103), with half of all new black-box warnings appearing only after a drug has been under commercialization for around 12 years. In the US, half of the medicinal products with safety-driven withdrawals had remained on the market for 5 years or more, while newly approved drugs have a one-in-three chance of acquiring a new black-box warning or being withdrawn for safety reasons within 25 years of approval(104).

Studies have also been conducted for specific sub-groups of medicinal products. Orphan drugs granted marketing authorizations by accelerated approval, oncological products and products belonging to the anatomical main group of 'Alimentary track and metabolism' appear to have a higher risk for a safety-related regulatory action(103).

With regards to biologics, literature suggests that approximately one out of four biologics approved in the US and/or the EU has required a safety-related regulatory action, defined as written communications to healthcare professionals and 'black-box' warnings, after granting of marketing authorization(105). Studies also show that biopharmaceutical products have a 14% probability of having an initial safety-related regulatory action within the first 3 years following market approval, with a higher risk of a safety-driven recommendations for the first biological products in each class(105).

On the whole, above published figures illustrate the need for safety data to be gathered throughout the life cycle of a medicine due to the known limitations of clinical trials in predicting safety in 'real-world' use. By continuously collecting information once a medicine is available to the general public and taking action in response, regulators can ensure better public protection from emerging safety issues throughout a medicine's life cycle. Post-marketing research offers therefore a valuable and necessary complement to pre-registration studies in continuously evaluating the benefit-risk balance of marketed drugs.

Following identification of a new or important safety information, it is necessary to divulge such findings. Regulatory authorities and the pharmaceutical industry are, therefore, equipped with several different tools and strategies for if and when a safety issue emerges. Being able to communicate to both the public and healthcare practitioners about the safe use of medicinal products and about the risks associated to their use is key.

On the one hand, labelling requirements are an essential part of the marketing authorisations both in the US and the EU, emerging as the basis of information for healthcare professionals and patients on how to use a medicine safely and effectively. It is hence crucial that labelling documents are kept updated throughout the lifecycle of a medicinal product, as new efficacy or safety data arise(106–108).

Particular visual tools are available in each region. For instance, a warning is displayed in the US label and patient package as a framed box named 'Black Box Warning' which highlights particular serious or life-threatening potential safety issues of a prescription drug(109,110). In the EU, medicines under additional monitoring present a black inverted triangle displayed in their package leaflet and summary of product characteristics, helping to identify medicines, which are being monitored more intensively by the EU regulators.

Additionally, agencies may wish to directly communicate a new important safety information to health care practitioners. A Dear Healthcare Professional letter (in the US) is a paper-based personalized mailing to healthcare professionals, the content of which should be agreed by the manufacturer of the drug and by the agency prior to their dissemination. In the EU, Direct Healthcare Professional Communications can be used to quickly disseminate key information to healthcare professionals. In the UK, for example, the national competent authority (NCA) additionally issues alerts, warnings and 'Drug Safety Updates' to inform healthcare providers on new found risk, updates to practices and minimize patient harm(111).

Finally, regulators also retain the authority to revoke marketing authorisation due to safety concerns. A medicinal product within the EU region can therefore be suspended and/or withdrawn from the market when the benefits of a drug no longer outweigh its risks(101). Similarly, the FDA can either revert to recalls or market withdrawals for the products under its supervision(112).

1.4.1 Labelling updates

As previously mentioned, labelling is a crucial communication source to provide important safety information to both patients and healthcare professionals, and an integral part of the patients' disease treatment/prevention.

Within the EU territory, labelling requirements have been harmonized and are described in the applicable legislations(113,114). The summary of product characteristics (SmPC) is the basis of information for healthcare professional on how to use the medicine and needs to be included in the marketing authorization application for all EU medicinal products, thus being an intrinsic and integral part of the marketing authorization. The Package Leaflet (PL) is to be drawn up in accordance with the SmPC and contains all the information which is necessary and useful for the patient.

In the US, the labelling constitutes a summary of essential scientific information needed for safe and effective use of the drug. It should be informative, accurate, and neither promotional in tone nor false or misleading, and should be based on data derived from human experience whenever possible. Medicinal product applicants are made aware of the requirements for the content and format of labelling for human prescription drug and biological products in both the Physician Labeling Rule (PLR) and Patient Counselling Guidance(107,108).

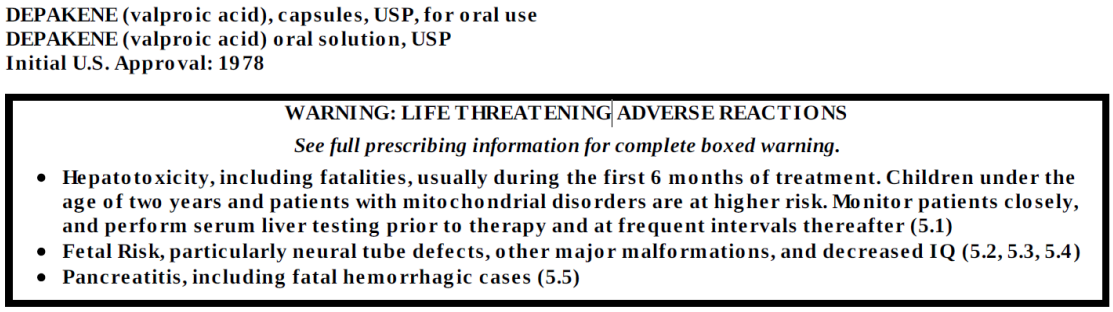
One would expect that labels would not differ significantly among countries given that, at the time of granting marketing authorizations, regulatory authorities evaluate the same scientific data submitted by pharmaceutical companies. Additionally, labelling documents are kept updated throughout the lifecycle of a medicine as new efficacy or safety data emerge, which is again to be submitted to all necessary national competent authorities. However regulatory decisions impacting labelling documents also seem to be affected by the different local regulations and cultures(115).

In fact, inconsistencies in doses, indications and overall safety profiles are known to exist among regions(88,105,116–122). These differences may arise from biological factors, such as pharmacokinetics and ADR incidence, which often show racial and gender differences(123–125). Nonetheless, more often than not, divergences in regulatory requirements, evaluation processes, healthcare systems and the general public's risk perception emerge as factors that differentially impact the information included within labelling documents. Moreover, although package inserts contain information for the safe use of drugs, its format is not internationally standardized, and the structure and contents differ across countries.

One particular study on antineoplastic tyrosine kinase inhibitors found evidence that labelling for accelerated approval and priority review products was revised significantly more frequently than labels for traditional products. It was however unclear whether these updates were driven by new safety issues or for safety concerns already identified in the pre-approval phase. Given that these drugs are intended for the most serious of oncology settings with the highest unmet need, there may have been greater tolerance for any safety issues initially(84).

1.4.2 Territory specific considerations: Box Warning and Black triangle list

For medicinal products marketed in the US, a particular serious form of risk communication is available for when the FDA mandates that a set of clear warnings be highlighted at the beginning of the labelling material with a black box:



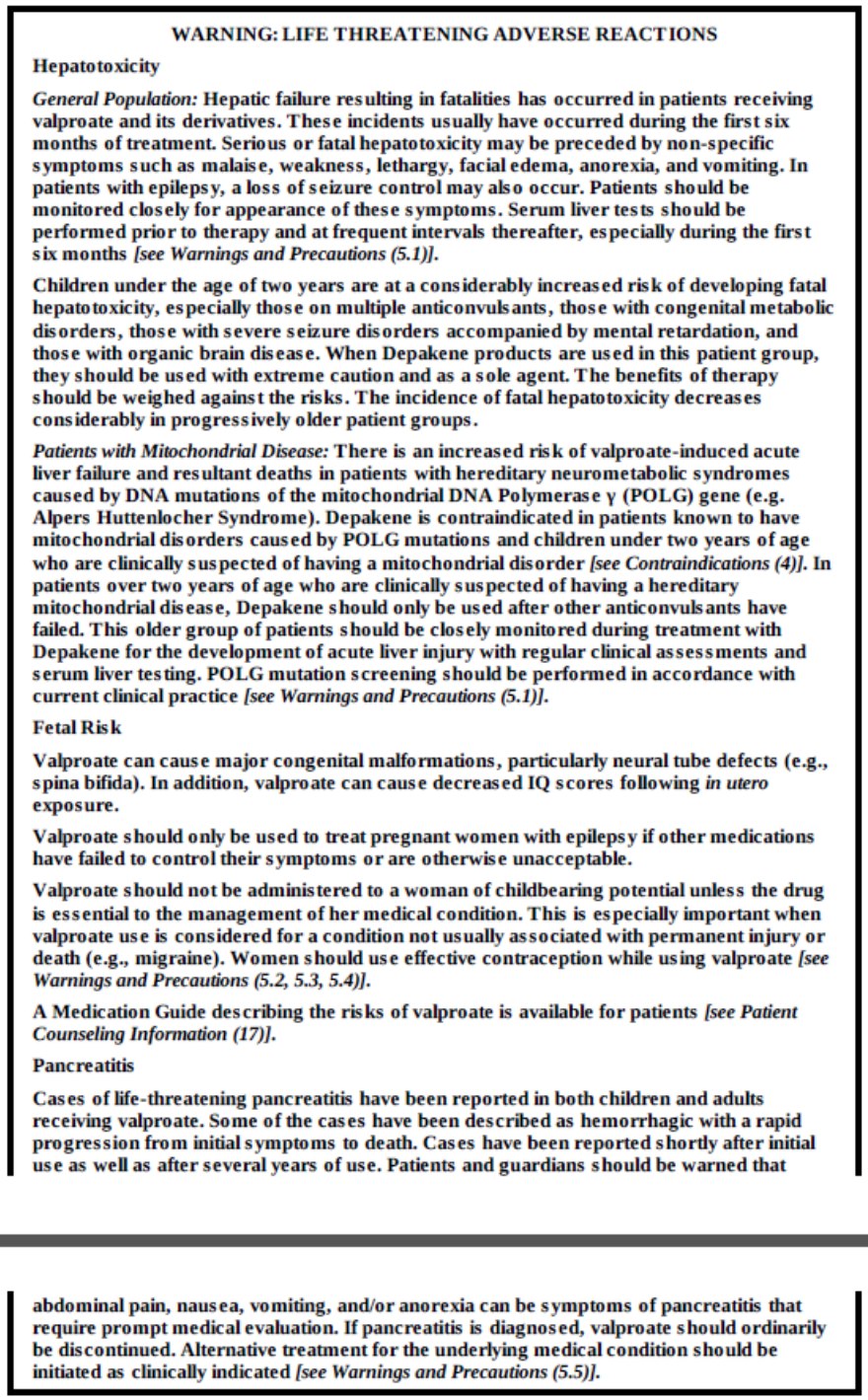
DEPAKENE (valproic acid), capsules, USP, for oral use
DEPAKENE (valproic acid) oral solution, USP
Initial U.S. Approval: 1978

WARNING: LIFE THREATENING ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

- **Hepatotoxicity, including fatalities, usually during the first 6 months of treatment. Children under the age of two years and patients with mitochondrial disorders are at higher risk. Monitor patients closely, and perform serum liver testing prior to therapy and at frequent intervals thereafter (5.1)**
- **Fetal Risk, particularly neural tube defects, other major malformations, and decreased IQ (5.2, 5.3, 5.4)**
- **Pancreatitis, including fatal hemorrhagic cases (5.5)**

Figure 1 – Black box warning from the Package Insert (Highlights of Prescribing Information) for DEPAKENE (valproic acid), AbbVie Inc. last updated on October 2017, available on https://dailymed.nlm.nih.gov/dailymed/



WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity

General Population: **Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months *[see Warnings and Precautions (5.1)]*.**

Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When Depakene products are used in this patient group, they should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Patients with Mitochondrial Disease: **There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g. Alpers Huttenlocher Syndrome). Depakene is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder *[see Contraindications (4)]*. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakene should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakene for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice *[see Warnings and Precautions (5.1)]*.**

Fetal Risk

Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores following *in utero* exposure.

Valproate should only be used to treat pregnant women with epilepsy if other medications have failed to control their symptoms or are otherwise unacceptable.

Valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using valproate *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

A Medication Guide describing the risks of valproate is available for patients *[see Patient Counseling Information (17)]*.

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated *[see Warnings and Precautions (5.5)]*.

Figure 2 – Black box warning from the Package Insert (Full Prescribing Information) for DEPAKENE (valproic acid), AbbVie Inc. last updated on October 2017, available on https://dailymed.nlm.nih.gov/dailymed/

This provision to be applicable to certain contraindications or serious warnings, particularly those that may lead to death or serious injury. On the other hand, these 'boxed warnings' or 'black box warnings' (BBW) can be intended to highlight the dangers associated either with the use of individual drugs or with specific drug classes(110).

Clear guidance is provided by the FDA to the pharmaceutical industry for the boxed warning section of prescription drug labelling to be used to highlight one of the following situations(126):

1) There is an adverse event so serious in proportion to the potential benefit from the drug (e.g. a fatal, life-threatening or permanently disabling adverse event) that it is essential that it be considered in assessing the risks and benefits of using the drug;
2) There is a serious adverse event that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g. patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation);
3) The FDA approved the drug with restrictions to distribution/use to ensure safe usage (e.g. Approval with restrictions or REMS elements to assure safe use).

Boxed warnings are ordinarily based on clinical data, but serious animal toxicity may also ~~be~~ give rise to a boxed warning(127). The BBW must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" sections, accompanied by the identifying number for the section or subsection containing the detailed information "WARNING" and other words that are appropriate to identify the risk in question(35,127).

Published literature suggests boxed warnings are associated with more than one third of FDA-approved human prescription drugs, through a variety of therapeutic classes and commonly used across both inpatient and outpatient settings(128). Currently, there are 934 marketed drugs with a boxed warning in place[1].

Analysis of safety labelling changes between 2005 and 2008 gathered BBW additions or revisions accounted for approximately 14% of these changes(129). Another set of data suggested that about 20% of approved chemical entities either acquire a BBW or are withdrawn from the market due to safety concerns up to 25 years from approval(98). Furthermore, because serious drug-related adverse events are more often a function of the pharmacologic class, most BBWs seem to be typically applied to all members of a given class(98,130,131).

[1] Micromedex export on 11-May-2017.

Other investigators reported a higher likelihood of post-approval black box warnings to labels for oncology drugs having received accelerated approvals compared with those which had regular approval (17% *versus* 9%). Additionally, of the four black box warnings added to the labels of oncology products with accelerated approval, three were only added more than 2 years after approval (84,85).

Another study reported that BBW could be divided into 4 major categories of information: interactions (drug-drug, drug-disease), testing (baseline, ongoing), informational notifications (prescriber, dispenser, administrator, patient, third-party/registry), and ‘‘nonactionable.’’ In such analysis, 37% of boxed warnings were classified as nonactionable and difficult to implement into health information systems, such as warnings included the risk of suicide associated with antidepressants and the risk of tendon rupture and tendinitis associated with systemic fluoroquinolones(132).

Overall, the presence of a boxed warning on a prescription drug label currently presents multiple important regulatory and commercial implications. For example, administrative penalties are in place for facilities lacking safeguards against the inappropriate use of drugs with BBW and the addition of a new boxed warning could potentially be grounds for which the Centers for Medicare and Medicaid Services may institute new authorization criteria or even withdrawal of the drug from Medicare Part D formularies(128,132,133). Therefore, Simultaneously, BBW may influence if and how a medicinal product is prescribed, particularly when alternatives without BBWs exist. Such was the case of decline in sales for atypical antipsychotics following the labelling updates for increased mortality in dementia-affected elderly, but similar patterns are reported for other medicinal products (134–140).

Alternatively, within the EU territory, a new concept of risk communication was introduced with the list of medicines under additional monitoring, following the updates to the pharmacovigilance legislation in 2012 (113,114).

Such concept originates from the need to enhance the ADR reporting rates for newly authorised products for which the safety profile might not be fully characterised or for products with newly emerging safety concerns which also require to be better characterised. Its main goals are therefore to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and thereby informing the safe and effective use of medicinal products(141). An inverted equilateral black triangle as stipulated in the Implementing Regulation (EU) No 198/2013,

followed by an explanatory statement in the summary of product characteristics, makes these medicinal products readily identifiable.

This list includes centrally and nationally authorised medicines in the following categories:

- Medicines that contain a new active substance that was not contained in any authorised medicine in the EU on 1 January 2011;
- Biological medicines authorised after 1 January 2011, including biosimilars;
- Medicines for which the marketing-authorisation holder is required to carry out a post-authorisation safety study;
- Medicines given conditional approval or authorised under exceptional circumstances and medicines authorised with specific obligations on the recording or monitoring of suspected adverse drug reactions.

Medicinal products can be included on this list at the time of first time approval or at any time during its life cycle and shall remain under additional monitoring for five years or until the PRAC agrees such additional monitoring is no longer required.

1.4.3 Communicating with Heath Care Professionals

As already recognized, new or updated information about drug products emerges throughout a product's life cycle. For marketed products, there are occasions when it is important to communicate this information promptly to HCP involved in prescribing or dispensing a drug or in caring for patients who receive a drug. Such direct safety communications concern important new information on an authorised medicinal product, which may have an impact on its risk-benefit balance and its conditions of use(142).

As per the EU regulatory framework, a direct healthcare professional communication (DHPC) refers to a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorisation holder or a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. The preparation of DHPC involves cooperation between the marketing authorisation holder and the competent authority and an agreement between these two parties regarding to the content of the DHPC and the communication plans, including the intended recipients, the timetable and the channels for disseminating the DHPC. Additionally, where there are several marketing authorisation holders of the same active substance and/or a class of products for which a DHPC is to be issued, a single consistent message should be delivered.

GVP module XV also describes the specific situations when a DHPC should be disseminated given the need to take immediate action or change current practice in relation to a medicinal product:

- Suspension, withdrawal or revocation of a marketing authorisation for safety reasons;
- An important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;
- A restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care.

Other situations where dissemination of a DHPC should be considered are also stated:

- New major warnings or precautions for use in the product information;
- New data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
- New evidence that the medicinal product is not as effective as previously considered;
- New recommendations for preventing or treating adverse events or to avoid misuse or medication errors with the medicinal product;
- Ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action.

Further provisions on the principles and means of safety communication as well as guidance on the coordination and dissemination of safety communication within the EU network are described in the newly amended GVP Module XV – Safety communication, including annexes for the revised Direct Healthcare Professional Communication (DHPC) and DHPC Communication Plan templates.

Finally, a competent authority in EU may disseminate or request the marketing authorisation holder to disseminate a DHPC in any situation where the competent authority considers it necessary for the continued safe and effective use of a medicinal product.

A recent study reported that EMA does not currently display a publicly available list of safety driven DHPC issued. Furthermore, among the top 10 highest prescribing EU countries, only four (France, Netherlands, Spain and the United-Kingdom) currently make such DHPC publicly available since 2001, while some other countries (e.g.

Germany, Belgium or Sweden) have only recently begun to display on their website information regarding DHPC(143). With regards to Portugal, the national competent authority maintains available in its website the list of DHPC distributed since 2009.

The same study also concluded there were substantial inconsistencies in the safety communications made available for newly authorized medicines, between the studied countries. Although the impact of these differences could not be assessed, authors suggested it raised questions about safety policies and regulatory efficiency and could possibly confuse patients and physicians(143).

An equivalent term for safety communications is also present in the US regulations. As per the FDA Guidance, Dear Health Care Provider (DHCP) letters consist of correspondence — often in the form of a mass mailing from the manufacturer/distributor of a human drug or biologic or from the FDA. DHCP letters may also be distributed by email and are often made available on the Internet (e.g. on company web sites or through patient advocacy groups)(142).

Within US territory, information relates to an important safety concern that could affect the decision to use a drug or require some change in behaviour by HCP, patients or caregivers in order to reduce the potential for harm from a drug. Some DHCP letters are written as part of REMS communication programs to inform intended target audiences about the implementation of a new or modified REMS or to present additional safety information about the product(142). On the other hand, a DHCP letter can also provide information on how to improve the effectiveness of a drug or drug shortage issues updates, or may be even needed to correct misleading information in advertising or other types of prescription drug promotion.

Regardless of the purpose, the FDA encourages manufacturers to consult with the appropriate review division, in order to discuss and determine whether a DHCP letter should be used, the target audience and the time frame for its distribution. Additionally, recommendations on how to organize information to ensure effective and formatting techniques to improve accessibility are provided(142).

The US regulation describes three types of DHCP letters(144), providing examples of model letters:

- Important Drug Warning Letter - used to convey important new safety information that concerns a significant hazard to health and therefore could affect the decision to use a drug or require a change in behaviour concerning use of the

drug. This type of DHCP letter is used to convey information that is being incorporated into one or more of the following sections of the prescribing information: Boxed warnings, contraindications or warnings and precautions.

- Important Prescribing Information Letter - used to convey important changes to the prescribing information other than those changes that are described in an Important Drug Warning letter. These are usually used to convey important changes to both the 'Indications and use' and 'Dosage and administration' sections of the prescribing information.
- Important Correction of Drug Information Letter - intended to correct false or misleading information or other misinformation in prescription drug promotional labelling and advertising that is the subject of a *Warning Letter*[2] or other FDA action.

Despite of the different designations, regulation from both territories seem to aim towards the same goal of alerting physicians and other HCP about important new or updated information. An overview table is provided below for comparison purposes (Table 3).

[2] Defined by the FDA as correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations.

Table 3 - Characterization overview of direct communication strategies with Health Care Providers in EU and US territories.

	EU territory	US territory
How is it done?	Via Direct Healthcare Professional Communication (DHPC)	Via Dear Health Care Provider (DHCP) Letter
Why/when is it needed?	To inform HCPs of important safety information. This situation includes, but is not limited to: - Suspension, withdrawal or revocation of a marketing authorisation for safety reasons; - An important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons; - A restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care. - New major warnings or precautions for use in the product information; - New data identifying a previously unknown risk or a change in the frequency or severity of a known risk; - New evidence that the medicinal product is not as effective as previously considered; - New recommendations for preventing or treating adverse events or to avoid misuse or medication errors with the medicinal product; - Ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action	To inform HCPs of important safety information This situation includes, but is not limited to: - Information that could affect the decision to use a drug or require some change in behavior by HCP, patients or caregivers - As part of REMS communication programs to inform intended target audiences about the implementation of a new or modified REMS or to present additional safety information about the product - To improve the effectiveness of a drug - To update on drug shortage issues - To correct misleading information in advertising or other types of prescription drug promotion
How is it done?	Cooperation and agreement between EMA/local HA and MAH with regards to: - Content of DHPC	FDA encourages manufacturers to consult with the appropriate review division, in order to: - Discuss and determine whether a DHCP letter should be used

	EU territory	US territory
	- Communication plans, including the intended recipients, the timetable and the channels for disseminating the DHPC	- Determine target audience - Determine the time frame of distribution
Are there different types?	No	Yes - Important Drug Warning Letter – in case of important updates to 'Boxed warnings', 'Contraindications' or 'Warnings and precautions' sections of prescribing information - Important Prescribing Information Letter – used for important changes to both the 'Indications and use' and 'Dosage and administration' sections of the prescribing information - Important Correction of Drug Information Letter - intended to correct false or misleading information or other misinformation in prescription drug promotional labelling and advertising that is the subject of a Warning Letter or other FDA action
Who is responsible for dissemination?	MAHs	Manufacturers
Where can you access these?	DHPCs may be available in NCA websites, as applicable for local territory	DHCPs may be available on manufacturers/companies' websites and sometimes patient support groups, but are not systematically available through FDA website

1.4.4 Recalls, suspensions and withdrawals

Finally, regulators also retain the authority to revoke a marketing authorization due to post-marketing safety concerns, either through suspension and withdrawal from the market or resorting to recalls or market withdrawals.

As per the applicable legislation, a recall is the removal or correction of a marketed product that the US Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, which can be conducted on the firm's initiative, by FDA request or by FDA order under statutory authority. The following type of recalls are described under the CFR(112):

- Class I – when there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
- Class II – when the use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote;
- Class III – when the use of or exposure to a violative product is not likely to cause adverse health consequences.

On the other hand, a market withdrawal is described for when a product has a minor violation that would not be subject to FDA legal action. The firm removes the product from the market or corrects the violation. Additionally, medical device safety alerts can be issued in situations where a medical device may present an unreasonable risk of substantial harm(112). Industry guidance intended to assist those members of industry regulated by the FDA in handling all aspects of a product recall, including all corrections and removals, is available since 2011(145).

Similarly, as per the EU regulations, EMA and national competent authorities may recommend suspending or revoking an authorization if(113):

- The product proves to be harmful in the normal conditions of use;
- Its therapeutic efficacy is lacking;
- The risk-benefit balance is not favourable;
- Its qualitative and quantitative composition is not as declared;
- Certain conditions related to MA are not fulfilled.

Additionally, products will be withdrawn from the European market in case (i) the above listed reasons are present, (ii) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of manufacturing have not been

carried out, (iii) and/or other requirements or obligations relating to the granting of the manufacturing authorisation have not been fulfilled(113).

Since the 2012, marketing-authorisation holders of human medicines also have to notify EU regulators of any action to withdraw a product from the market, together with the reason for this action, when the decision is based on any of the above mentioned grounds (113,114,146,147), or when they intend to:

- Temporary or permanent cease marketing of a medicinal product;
- Suspend marketing of a medicinal product;
- Withdrawn a medicinal product from the market;
- Request for the withdrawal of a marketing authorisation;
- Non-apply for the renewal of a marketing authorisation.

Over the decades, drug regulatory agencies, pharmaceutical companies and various studies have reported drug withdrawals due to safety concerns. Initial publications suggested that drugs withdrawn or restricted represent a small proportion (about 1%) of marketed drugs, with 75 drugs/drug products having been removed from the market due to safety problems between 1969 and 2002(148). A more recent study reported that circa 95 drugs were documented to have been withdrawn due to death as the primary reason between 1950 and 2013(148). However, not all of these drugs were withdrawn world-wide.

As a matter of fact, disparities in regulatory decisions between the regulatory bodies are often described. A study concluded that out of the 22 cases of drugs withdrawn due to safety concerns, between 1997 and 2005, in the US and EU, 10 presented a discrepancy in regulatory decisions/recommendations(149). Controversial debates resulting from these conflicting assessments are also well described in the literature (e.g. cyclooxygenase-2 inhibitors and glitazones)(119,150).

2. Objectives

Over the years, multiple studies have analysed safety-related regulatory actions, mostly for particular settings, such as for specific drug groups (e.g. biologicals, orphan medicines and exceptional circumstances/ conditional (accelerated) approval procedures) or individual countries (102,103,105,151).

Data shows that between 9 to 25% of the drugs analysed required a safety related regulatory action by regulatory authorities after approval (102,152). An US study provided evidence that 10% of the drugs registered in the US between 1975 and 1999 required a safety-related regulatory action. More recently, biologics have been associated with a 14% probability of requiring a first safety-related regulatory action within the first 3 years of being approved, with a higher risk of a safety related action in 'first-in-class' biologics.

In parallel, differences between EU and US regulatory frameworks and bodies are known and have been described to have led to divergent assessments, resulting in distinct regulatory actions (50,153). In fact, in spite of similar objectives and responsibilities, agencies do not always share the same interpretation of a medicinal product's safety and efficacy data. Between 1995 and 2008, 20% of the oncological pharmaceuticals were approved by either the FDA or the EMA, but not by both, and 28% of approved drugs had significant variations in the label wording(154). Likewise, the safety review of approved drugs has also produced different safety-related regulatory actions(155).

Considering the lack of an overall recent picture of safety-driven regulatory actions for medicinal products, both small molecules and biologics, particularly following the significant implications for pharmacovigilance activities emerging from the new legal frameworks in the US (2007) and in the EU (2012) an analysis of the safety-driven regulatory actions between 2010 and 2015, in either of these two territories was proposed. The aim of this study was to:

- Determine the frequency, timing and nature of the safety related regulatory actions analysed;
- Ascertain the most prevent therapeutically areas and molecule classes of the safety related regulatory actions analysed;
- Compare regulatory activities and decisions between EMA and FDA;
- Assess the apparent lack of harmony in addressing specific safety issues;

- And discuss the case of a particular chemical or biological entity exemplifying distinct safety related regulatory actions, between EMA and FDA.

3. Safety Communication

This section aims to perform an analysis on the determinants and nature of safety-related regulatory actions in the EU and US territories, for which direct communications to healthcare providers (DHCP letters/DHPC) have been distributed between the years of 2010 and 2015.

3.1 Materials and Methods

Safety communications published in Portugal and the United Kingdom by the National Competent Authorities were used as direct communications to healthcare providers for the EU territory, given that no global list of DHPC is available for EU products. DHPC were identified from the websites of the National Authority of Medicines and Health Products, IP (INFARMED) in Portugal and the Medicines & Healthcare Products Regulatory Agency (MHRA) in the United Kingdom. All DHPC issued from 1 January 2010 to 31 December 2015 in the United Kingdom and Portugal and available on the websites were included in this study.

The FDA website was also searched for DHCP letters for the same period. Very few DHPC were available and the Division of Drug Information within the FDA's Center for Drug Evaluation and Research was contacted in order to retrieve a list of DHCP letters distributed for the covering period. A response was received stating that no comprehensive database containing all DHCP letters is available for or maintained by FDA's Center for Drug Evaluation and Research. An additional access to this data was submitted through the Freedom of Information Act. However, information was received that the FDA does not maintain a database with all Dear Health Care Provider Letters and that Companies are not required to provide FDA with such letters. Therefore the FDA website was screened to retrieve any other type of safety communication to HCP and/or the public containing safety-related regulatory actions for all the entries identified for the EU countries in study.

The data extracted from DHPC included date of publication, International Non-proprietary Names (INN) and safety issue described in the letter and the source triggering the safety publication (e.g. data originating from clinical trials, spontaneous ADR reports, epidemiological studies etc). Information on whether earlier DHPC had been distributed that same safety topic for a given drug or if the topic described concerned any special subset of patients (e.g. children, elderly, hepatic impaired or renal impaired patients) was also noted. The nature of the safety issue was classified

according to the Medical Dictionary for Regulatory Activities (MedDRA version 20.0) using System Organ Class (SOC). Furthermore, the time between the initial approval date (for the specific territory of DHPC publication) and DHPC was determined. Approval date was retrieved from EMA website for centralized approved products, and from Infomed - Base de dados de medicamentos (Medicine's database from the Portuguese national competent authority for Medicines and Health Products)[3] and electronic Medicines Compendium (eMC)[4] websites for the remaining products with DHPC issued for Portugal or the UK, respectively. For DHPC issued within the USA, date of approval was retrieved from FDA Drugs@FDA database for FDA Approved Drug Products and DailyMed website[5].

The extracted data was summarized in Excel and populated according to the following variables:

- Year (YY) and month (MM) of publication
- Brand name
- INN
- Drug type: biological or small molecule
- Anatomical Therapeutic Chemical (ATC) code and classification, both 1st level - anatomical main group (ATC I) and 4th level - chemical subgroup (ATC II)
- Reason for DHPC to be distributed: safety topic, supply issue, quality issue, efficacy information or other
- Safety topic description (by SOC)
- Source: main source of the safety topic presented as per the DHPC. These could have originated from spontaneous reports, clinical trials, MAHs/EMA/NCA database analysis, epidemiological studies, pharmacokinetic studies, literature article(s), pre-clinical studies and quality control analysis, etc.
- Type: US DHCP letters were further describer in terms of types as per US legislation, from 'Important Drug Warning Letter', 'Important Prescribing Information Letter' and 'Important Correction of Drug Information Letter'
- Date of approval
- Country of publication (PT, UK and/or US)
- Action for US: corresponds to FDA set of actions (Yes/No) taken for entries originating for PT/UK DHPC, and its description, such as FDA statements, safety

[3] http://app7.infarmed.pt/infomed/inicio.php, accessed between Jan 2016 and Sep 2017.
[4] https://www.medicines.org.uk/emc/, accessed between Jan 2016 and Sep 2017.
[5] https://dailymed.nlm.nih.gov, accessed between Jan 2016 and Sep 2017.

labelling changes, drug safety alerts, drug safety communications and inclusion of boxed warnings for the specific safety concern in analysis, withdrawal or recall of the product and initiation of FDA requested studies.

- Other: non-grouped information was also populated such us on whether previous DHPC had occurred for that same safety topic for a given drug or the topic described concerned any special subset of patients or a whole class of medicinal products.

Where applicable, chi-square tests were used to assess associations.

3.2 Results

3.2.1 Characterization overview

A total of 516 DHPC were identified from the data retrieved for the covering period studied. Of these, 223 DHPC were distributed in Portugal, 274 DHPC in the UK and 19 DHPC in the United States of America. Screening and analysis of these 516 DHPC for overlapping of safety issues per INN or class with similar issue dates between any of the three regions identified a total of 364 'single' DHPC.

Of the 364 DHPC identified, 18 related to efficacy matters, namely changes in indications or new strengths, 56 concerned supply issues, such as market shortages or manufacturing site closures, and 27 referred to quality related communications with no reported adverse events, such as possible presence visible particles in parenteral solutions, sterility concerns or batch recalls due to vial defects. The majority however concerned safety related issues, adding to a total of 260 DHPC (71.4%). The remaining three letters include a name change, an error correction present in a previous label and the introduction of peel-off tracking labels (Figure 3).

Similar safety distributions were found for DHPC issued in each of the studies countries: 71.9 % in the UK, 68.4% in the US and 76.2% in Portugal (Figure 4).

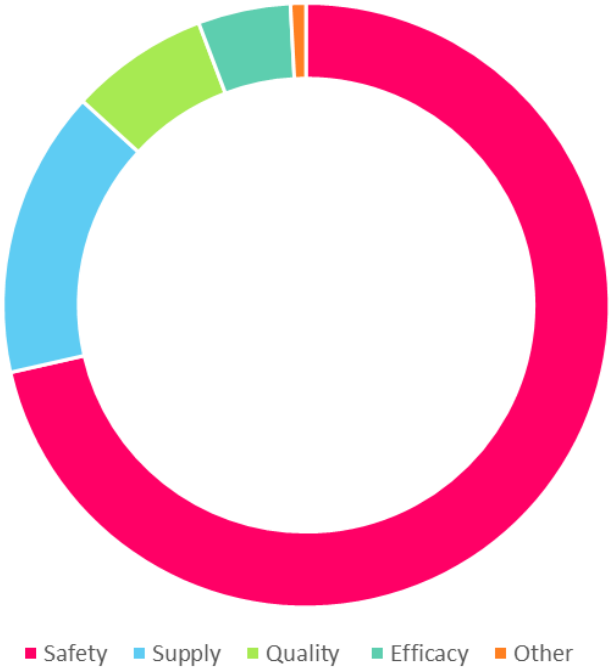


Figure 3 - Rational for distribution of Direct Healthcare Professional Communications issued between 2010 and 2015 in the UK, Portugal and the US

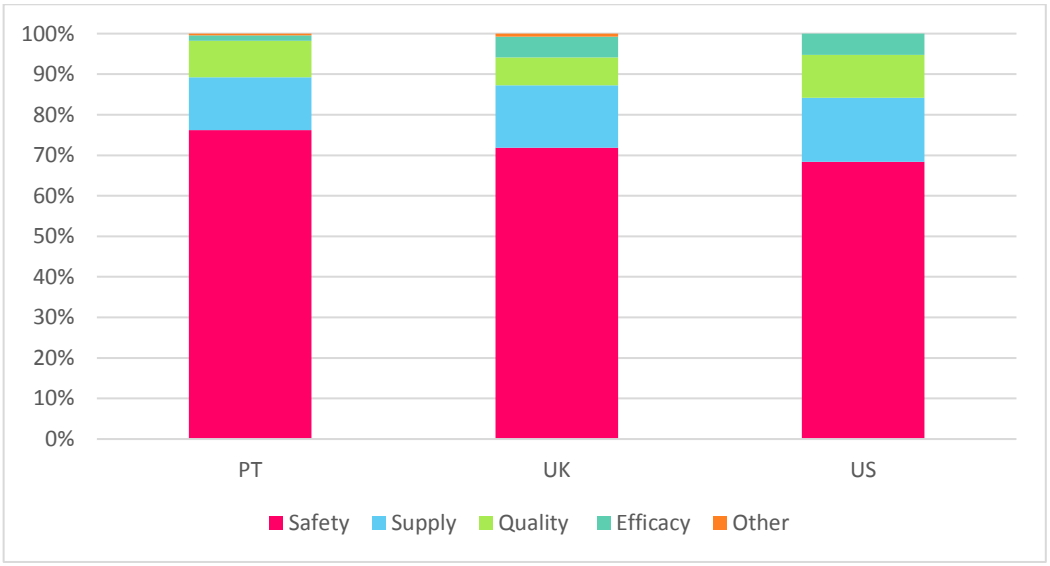


Figure 4 - Rational for distribution of Direct Healthcare Professional Communications issued between 2010 and 2015 per country studied

With regards to the Anatomical Therapeutic Chemical (ATC) Classification System distribution of medicinal products with a DHPC, a total of 182 different ATC codes were retrieved, with the majority of the DHPC analysed belonging to the anatomical main groups of 'Antineoplastic and immunomodulating agents' (25.8%), 'Antiinfectives for

systemic use' (14.6%), 'Blood and blood forming organs' (11.5%) and 'Nervous system' (11.5%) (Figure 5).

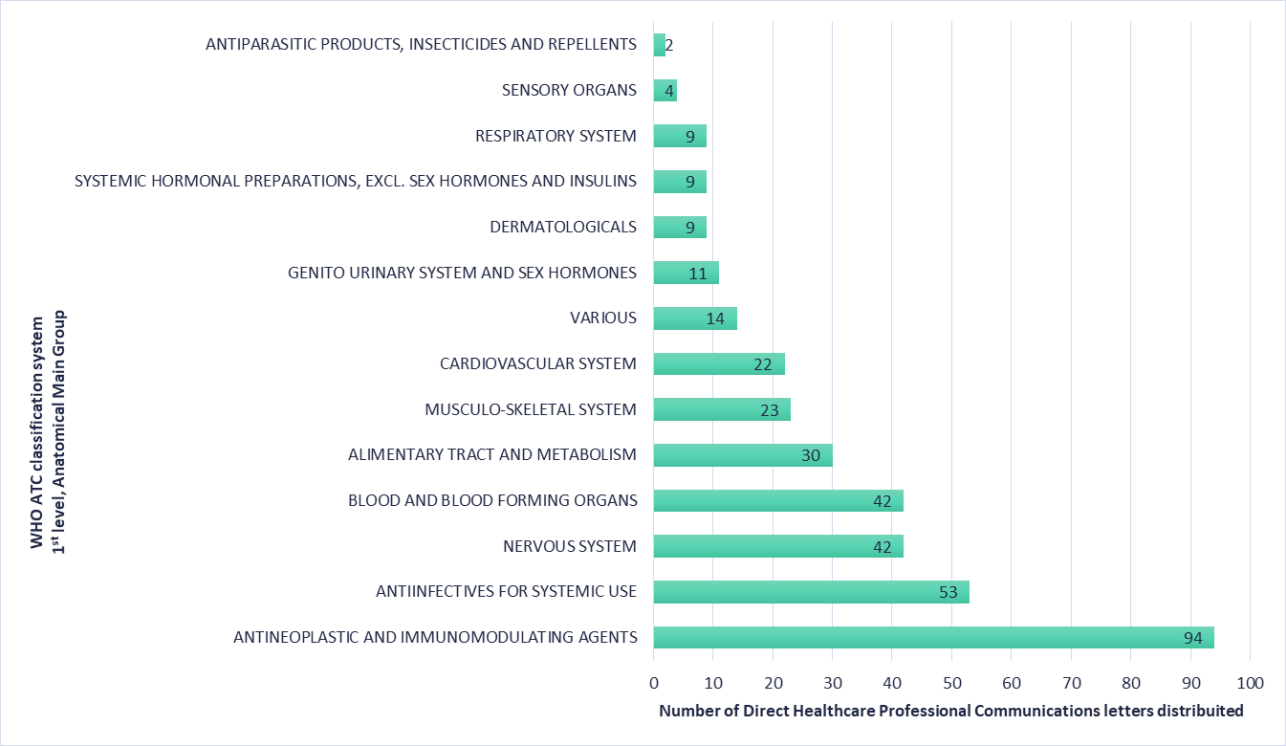


Figure 5 – Number of Direct Healthcare Professional Communications issued between 2010 and 2015 per anatomical main group (1st level of the WHO Anatomical Therapeutic Chemical (ATC) classification system)

When segmented for safety related communications (260), the distribution was analogous, with 24.6% of the letters belonging to the anatomical main groups of 'Antineoplastic and immunomodulating agents', 14.6% to 'Antiinfectives for systemic use', 12.7% to 'Nervous system' and 11.9% to 'Blood and blood forming organs' (Figure 6).

In respect of chemical subgroup for safety driven DHPC, the most recurrent classes included immunosuppressants (19), monoclonal antibodies (12), other drugs affecting bone structure and mineralization (08), protein kinase inhibitors (07), other immunosuppressants (06) and solutions for parenteral nutrition (06). Similar frequent chemical subgroups were identified when analysing the entire set of DHPC: immunosuppressants (20), monoclonal antibodies (14), other antineoplastic agents (09), other drugs affecting bone structure and mineralization (08), protein kinase inhibitors (07) and enzymes (08).

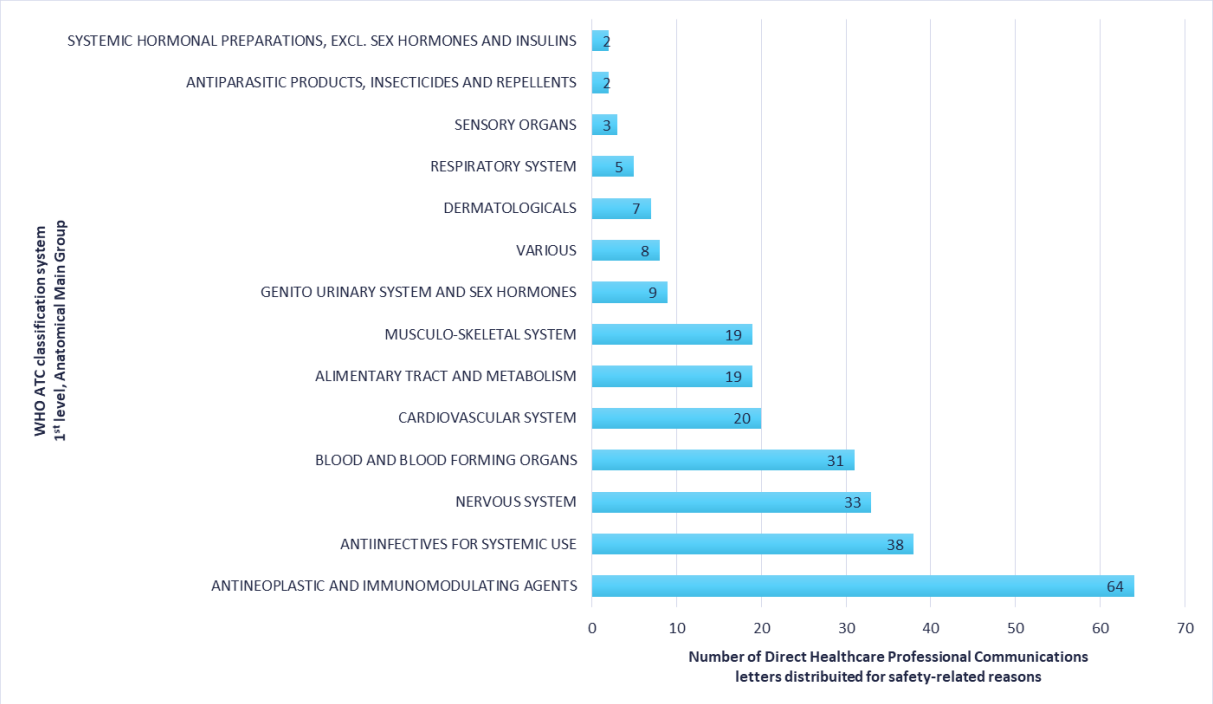


Figure 6 - Number of Direct Healthcare Professional Communications issued for safety-related reasons between 2010 and 2015 per anatomical main group (1st level of the WHO Anatomical Therapeutic Chemical (ATC) classification system)

3.2.2 Regional distribution and overlapping DHPC

From the published 516 DHPC, only one DHPC was issued in the three studied countries for the covering period.

This safety communication concerned medication errors associated with the use rivastigmine transdermal system (Exelon Patch) – Annex I to III. Distributed in April 2010 in both the UK and Portugal and later issued for the US as an 'Important drug warning' in September 2010, these communications describe the receipt of post-marketing reports of medication errors by the MAH associated with the use of rivastigmine patch some of which resulting in overdose. Exelon Patch was initially approved by the FDA in April 2000 and in May 1998 in the UK.

Other eight DHPC for safety topics addressed both in UK and PT could be retrieved from the FDA website but DHPC did not include publication date (one) or where outside the studied interval (seven) and were not included in above data. For comparison purposes a brief analysis of these was however performed. Out of these eight, four concerned small molecules and the remaining four biological medicinal products, involving the following anatomical main groups: Antineoplastic and immunomodulating agents (03), Blood and blood forming organs (02), Alimentary tract and metabolism (01),

Antiinfectives for systemic use (01) and Nervous system (01). Safety topics addressed varied between Injury, poisoning and procedural complications SOC (03), Infections and infestations SOC (02), Cardiac disorders SOC (01), Congenital, familial and genetic disorders SOC (01), Metabolism and nutrition disorders (01), Nervous system disorders (01) and Vascular disorders SOC (01).

A short description of the safety topics addressed in these six DHPC is presented below, with the exception of undated DHPC for rosiglitazone and cardiac events and DHPC for rituximab and the screening for hepatitis B virus before treatment. In fact, the DHPC issued for Portugal and UK (November 2013) concerned an update to the recommendation for hepatitis B virus screening, now recommended in all patients (not just those at risk of hepatitis B virus infection) before starting treatment with rituximab in all indications, while the US DHPC (July 2006) only referenced previous recommendations. Furthermore, despite DHPC for rosiglitazone pertained to its cardiovascular toxicity, safety communication for Portugal and UK (2010) concerned a clarification on the arrangements for the recall of rosiglitazone-containing medicines from these markets following the recommendation by the EMA to suspend the marketing authorisation across Europe, while DHPC published in the US only summarized the major changes to the labelling for rosiglitazone and cardiovascular events.

Risk of air embolism with the inappropriate use of spray devices administering fibrin sealant products

Safety communications were issued both in Portugal and in the UK in August 2011 and then again in January 2013 for above mentioned life threatening risk. Latest DHPC presented a total of nine cases of air embolism (including three fatal cases) reported in association with fibrin sealants administered by spray application using a gas pressure regulator device. These events seem to be related to the use of the spray device at a higher-than-recommended pressure, and/or in too-close proximity to the tissue surface. The same safety issue had been communicated to HCP in the US in October 2009 in an Important Drug Warning. This concerned a post-marketing fatality report in association with the use of fibrin sealant (human), using a spray device at higher than recommended pressure and in close proximity to the surface of the tissue, received by the FDA. All letters included instructions to be followed when using a spray device for fibrin sealant application to prevent air or gas embolism. Additionally, in April 2010 and given the life-threatening/potentially fatal consequences of air or gas embolism, the FDA recommended US prescribing information for fibrin sealant products to be updated to address this concern. No updates to PI were described in EU DHPC in either occasions

however the risk of life-threatening/fatal air or gas embolism with the use of spray devices employing a pressure regulator to administer fibrin sealants is adequately covered in the UK label(156). Fibrin sealant products were first approved in 1998 in the USA, later on in the UK in 2000 and in 2007 in Portugal.

Mycophenolate mofetil and serious risk of teratogenicity

A safety communication was sent out in November 2015 to HCP in both Portugal and the UK on strengthened advice for pregnancy prevention for both women and men when using mycophenolate mofetil. This DHPC described the new added to section 4.3 Contraindications of the SmPC, which were added following a cumulative review of birth defects, following mycophenolate being confirmed as a powerful human teratogen. Evidence showed of an increased rate of congenital malformations and spontaneous abortions associated with mycophenolate in comparison with other medicines. On the other hand, in July 2015 safety labelling changes were approved by FDA/CDER in regard to embryofetal toxicity in the Warnings section, to pregnancy in the Prevention section and to the inclusion of congenital disorders on Post-marketing Experience, Adverse events section(157). The increased risks of first trimester pregnancy loss and of congenital malformations plus the change to pregnancy category D based on positive evidence of fetal risk observed in post-marketing data and from the US National transplantation pregnancy register had already been communicated to US HCP in an Important Drug Warning back in October 2007. Similarly, in 2007 and 2008 UK SmP for CellCept 1g/5ml powder for oral suspension was updated to include changes to sections 4.6 Pregnancy and Lactation and 4.8 Undesirable Effects given the new data on congenital disorders and spontaneous abortions with mycophenolate mofetil(158). Mycophenolate mofetil was first approved in Portugal and the UK in 1996 and later on in 1997 in the US.

Natalizumab and Progressive Multifocal Leukoencephalopathy (PML)

DHPC were issued both in Portugal and in the UK in February 2010 informing HCP of both the 31 cases of PML from approximately 66,000 people exposed to natalizumab up to January 2010 and of the apparent increase in risk with the duration of treatment. On the other hand, the US DHPC retrieved from FDA website dated from July 2006 detailed only 2 cases of PML but addressed the addition of a Boxed Warning to the Prescribing Information for the increased risk of PML with natalizumab therapy. Natalizumab was first approved in 2004 in the USA, later on in the June 2006 in the EEA.

Stavudine and potentially severe side effects

In March 2011, DHPC were issued in Portugal and the UK concerning post-marketing safety reports and published literature on lactic acidosis, lipoatrophy and peripheral neuropathy. These resulted in a restriction of indications for stavudine and subsequent updates to the Product Information: sections 4.1 Therapeutic indications and 4.2 Posology and method of administration to limit the duration of stavudine therapy to the shortest time possible. On the other hand, Important Drug Warning retrieved dated from 2002 and described the potential for lactic acidosis as a complication of therapy with nucleoside analogues, including stavudine and its signs and symptoms. Current US Prescriber Information for ZERIT states *nucleoside reverse transcriptase inhibitor for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV)-1 infection* as indications for stavudine.

Only one safety topic was addressed in both the UK and US DHPC issued during the covering period. In May 2013, UK HCP were informed of the potential risk for liver injury for tolvaptan and necessary product label updates, based on the results from further clinical trials investigating a different potential indication with long-term use of tolvaptan at higher doses than for the approved indication. Earlier that year, in January, the same had been communicated to US HCP through an Important Drug Warning letter.

During the covering period, a total of three UK DHPC were found to be overlapping with one US DHCP letters, which had been distributed outside of the reporting period. These DHPC concerned leflunomide and the distribution of educational risk minimization materials in regard to risks of i) hepatotoxicity, including very rare cases of severe liver injury, which may be fatal, ii) hematotoxicity, including rare cases of pancytopenia, leukopenia, eosinophilia and very rare cases of agranulocytosis; iii) infections including rare cases of severe uncontrolled infections (sepsis), which may be fatal and iv) serious birth defects when administered during pregnancy, which were published in the UK on January 2011, May 2011 and June 2012. Within the US, an Important Prescribing Information letter had been distributed on October 2003 to inform HCP of the updates to the US labelling (Warnings - Hepatotoxicity and Immunosuppression Potential/Bone Marrow Suppression sections, Precautions - Laboratory Tests and Adverse events sections) based on the rare post-marketing reports of serious hepatic injuries and severe infections.

On the other hand, whithin the studied period, one DHPC was identified concerning a safety topic overlapping for both Portugal and US territories. These safety communications addressed gadolinium-based contrast agents and the risk developing nephrogenic systemic fibrosis. In January 2011 Portuguese HCP were reminded of this

risk and made aware both of the different classification (high, medium or low risk) of gadolinium-containing contrast agents established by Committee for Medicinal Products for Human Use (CHMP) based on the potential risk of developing nephrogenic systemic fibrosis but also on the changes to the prescribing information of these medicines, depending on the risk classification of the agents. In regard to the US, back in September 2007 an Important Drug Warning had been issued to inform HCP of the revisions to the prescribing information gadolinium-based contrast agents based on post-marketing reports showing an increased the risk of the development of nephrogenic systemic fibrosis, namely the inclusion of a Boxed Warning and an update to the Warnings section.

3.2.3 Drug type

From the total data studied, DHPC were found to be more frequently distributed for small molecules (72.0%) than for biological products. Similarly, for safety-related DHPC, communications concerning small molecules were more frequently observed (76.9%) than the ones published for biological products.

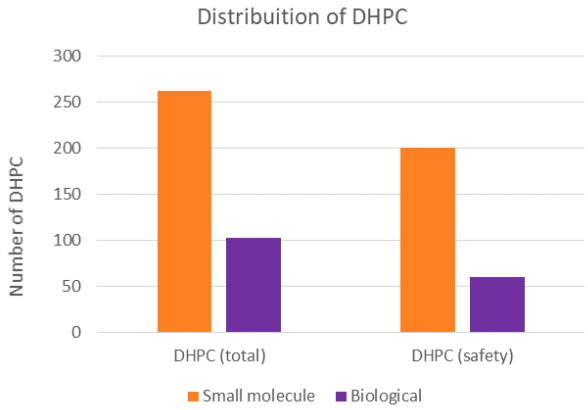


Figure 7 – Number of DHPC distributed by product type (biological vs small molecule) for the total set of DHPC retrieved and for safety-related DHPC only.

3.2.4 Nature of Adverse events (AE)

Safety-related DHPC published during the reporting period referred most often to adverse events under Injury, poisoning and procedural complications (16.2%), with 12 DHPC concerning medication error related AE, and Cardiac disorders (13.1%) SOCs. With regards to small molecules, above mentioned SOCs were also the ones with most retrieved adverse events (17.3% for Injury, poisoning and procedural complications and 16.1% for Cardiac disorders SOCs), while for biologicals they were most often classified under Immune system disorders (22.4%), Injury, poisoning and procedural complications (11.9%) and Vascular disorders (10.4%) SOCs.

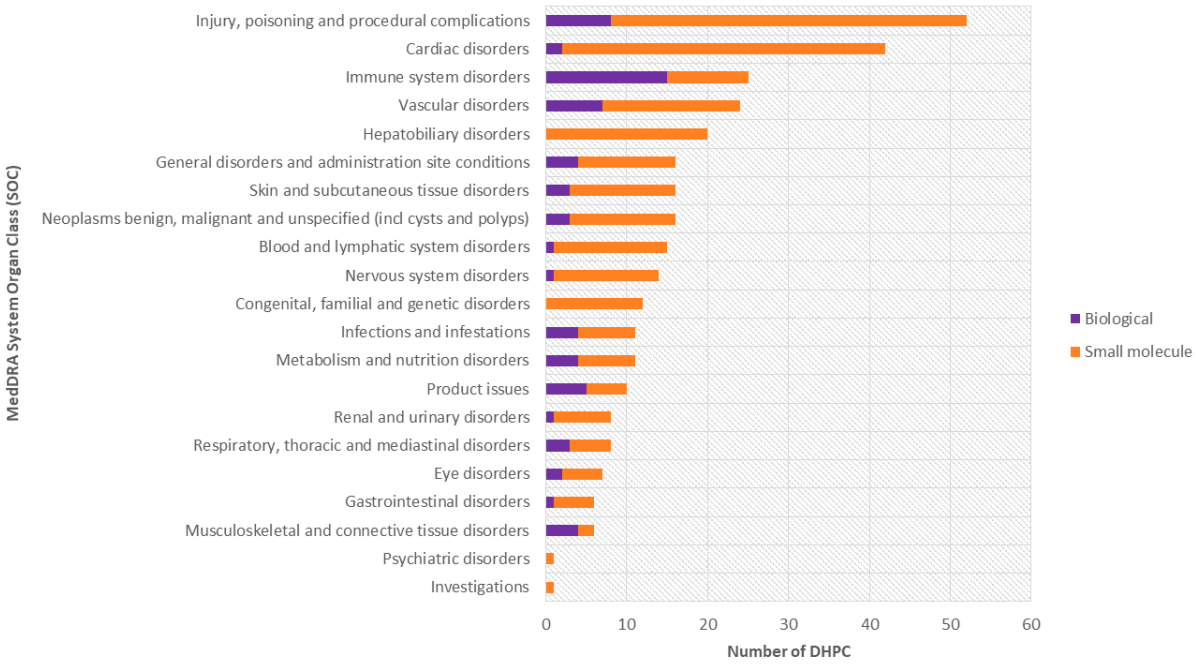


Figure 8 - Number of safety-related Direct Healthcare Professional Communications mapped to MedDRA SOC as per the adverse drug reactions presented, per drug type (biological vs small molecule).

DHPC published for small molecules were also significantly more frequent in most of the sub-grouped SOC analysis (Table 4), in comparison to the DHPC distributed for biologicals (chi-square=67.974 df=20, p<0.001). Cardiac disorders (chi-square=10.004, df=1, p=0.002) and Hepatobiliary disorders (chi-square=4.359, df=1, P=0.037) SOC-related AE were significantly more frequent for small molecules safety communications, while Immune system disorders (chi-square=22.628, df=1, p<0.001) and Musculoskeletal and connective tissue disorders (chi-square=5.195, df=1, p=0.023) SOC-related AE were significantly more observed in DHPC distributed for biological products. Finally, product issues (chi-square=3.638, df=1, p=0.056) SOC-related AE were equally frequent in both class of medicinal products.

Table 4 – Number of DHPC mapped by MedDRA SOC as per the adverse drug reactions present in the DHPC, per drug type (biological vs small molecule).

MedDRA SOC	Biological	Small molecule
Blood and lymphatic system disorders	1	14
Cardiac disorders[6]	1	41
Congenital, familial and genetic disorders	0	12
Eye disorders	2	5
Gastrointestinal disorders	1	5

[6] SOCs with a significant statistical difference between biological and small molecules medicinal products.

MedDRA SOC	Biological	Small molecule
General disorders and administration site conditions	4	12
Hepatobiliary disorders6	0	20
Immune system disorders6	15	10
Infections and infestations	4	7
Injury, poisoning and procedural complications	8	44
Investigations	0	1
Metabolism and nutrition disorders	4	7
Musculoskeletal and connective tissue disorders6	4	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	13
Nervous system disorders	1	13
Product issues	5	5
Psychiatric disorders	0	1
Renal and urinary disorders	1	7
Respiratory, thoracic and mediastinal disorders	3	5
Skin and subcutaneous tissue disorders	3	13
Vascular disorders	7	17
Grand Total	**67**	**254**

The majority of the safety communications identified for small molecules with AE reported under Cardiac disorders SOC was retrieved for medicinal products belonging to the main anatomical groups of alimentary tract and metabolism (24.4%), antiinfectives for systemic use (17.1%), cardiovascular system (17.1%) and antineoplastic and immunomodulating agent (14.6%) (Figure 9).

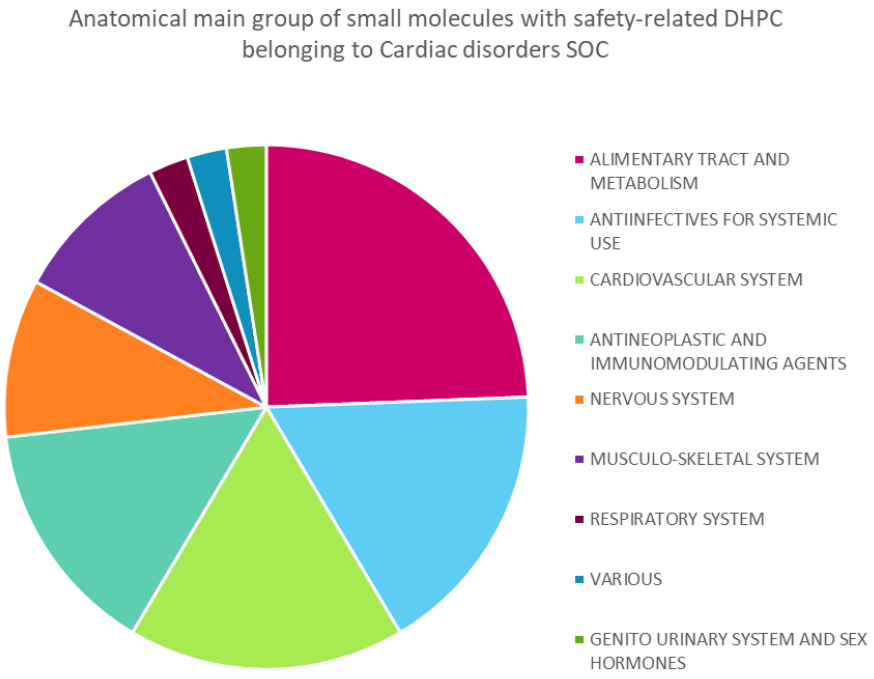


Figure 9 – Anatomical main group distribution (%) for small molecule with safety-related DHPC with adverse drug reactions mapped to the Cardiac disorders MedDRA SOC

On another hand, for safety communications for small molecules and reporting AE related to hepatobiliary disorders, DHPC retrieved belonged mostly to the main anatomical groups of antineoplastic and immunomodulating agents (35.0%) and antiinfectives for systemic use (25.0%) (Figure 10).

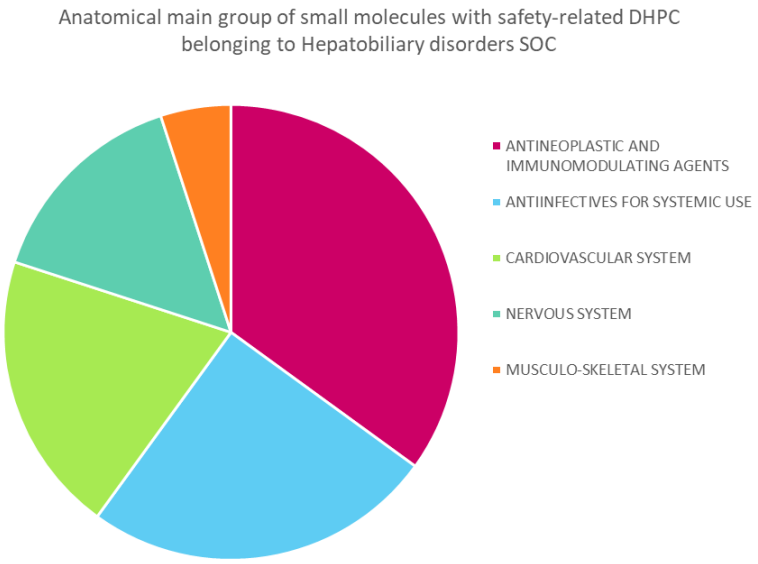


Figure 10 - Anatomical main group distribution (%) for small molecule with safety-related DHPC with adverse drug reactions mapped to the Hepatobiliary disorders MedDRA SOC

Out of the seven DHPC retrieved for small molecules reporting hepatobiliary disorders in products of the antineoplastic and immunomodulating ATC class, four of these related to selective immunosuppressants chemical subgroup. Of the five DHPC retrieved for small molecules reporting hepatobiliary disorders in products of the antiinfectives for systemic use ATC class, four of these related to imidazole (03) and triazole (01) derivatives (data not shown).

With regards to biological products and AE falling under the immune system disorders SOC, the vast majority of these safety concerns was retrieved for medicinal products belonging to either the main anatomical groups of antineoplastic and immunomodulating agents (46.7%), or antiinfectives for systemic use (40.0%) (Figure 11). Additionally, out of the seven DHPC retrieved for biological medicinal products reporting immune system disorders in products of the antineoplastic and immunomodulating anatomical main class, four of these referred to monoclonal antibodies chemical subgroup (Figure 12).

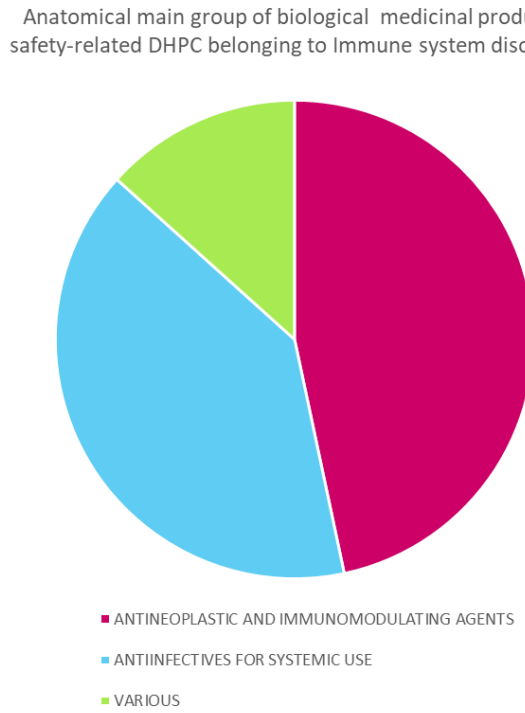


Figure 11 - Anatomical main group distribution (%) for biological medicinal products with safety-related DHPC with adverse drug reactions mapped to the Immune system disorders MedDRA SOC

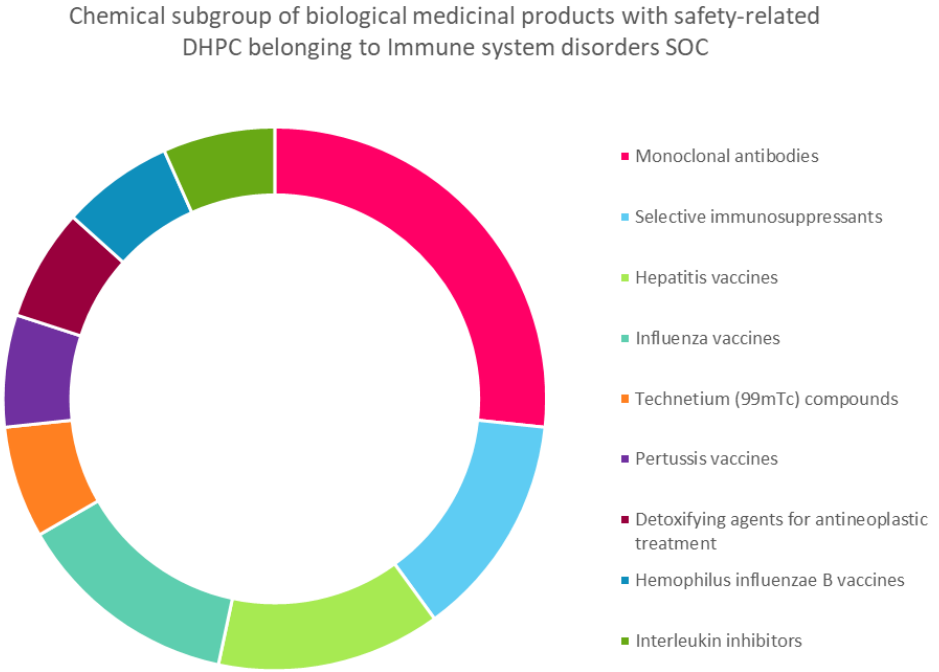


Figure 12 – Chemical group distribution (%) for biological medicinal products with safety-related DHPC with adverse drug reactions mapped to the Immune system disorders MedDRA SOC

Similarly, for biological medicinal products and safety communications describing AE related to musculoskeletal and connective tissue disorders, 80% of the DHPC retrieved

belonged to the anatomical main group of musculo-skeletal system itself, all of which referring to chemical group of 'Other drugs affecting bone structure and mineralization' (data not shown).

Finally, AE reported for product issues SOC were mostly prevalent for the following main anatomical groups: antiinfectives for systemic use (03), out of which two referred to biological medicinal products, cardiovascular system (02) and antineoplastic and immunomodulating agents (02).

Table 5 – Anatomical main group and chemical group distribution (counts) for biological medicinal products with safety-related DHPC with adverse drug reactions mapped to the Product Issues MedDRA SOC

ATC classification	Biological	Small molecule
Antiinfectives for systemic use	**2**	**1**
Encephalitis vaccines	1	
Triazole derivatives		1
Vaccines	1	
Cardiovascular system		**2**
Adrenergic and dopaminergic agents		2
Antineoplastic and immunomodulating agents	**2**	
Gonadotropin releasing hormone analogues	1	
Interferons	1	
Nervous system		**1**
Amides		1
Sensory organs	**1**	
Antineovascularisation agents	1	
Blood and blood forming organs		**1**
Solutions affecting the electrolyte balance		1
Grand total	5	5

3.2.5 Safety-related DHPC sources

For the subset of studies products, multiple sources of data were identified having triggered a safety evaluation and/or on which the safety evaluation was performed, either by the MAH or NCA/Agency, and resulted in the publication of the DHPC.

For DHPC pertaining to safety-related topics, the following sources were commonly mentioned in the DHPC or related source documents: Spontaneous Reports (63.8%), Clinical Trial (36.2%), Epidemiological study (9.6%), Literature (6.5%) and Pre-clinical (4.2%) (Figure 13). Some DHPC or source documents also presented safety information

originating from other sources, such as quality, name or packaging changes, updates to parental nutrition guideline, error corrections from the previous labelling and pharmacokinetic study. Such scenarios were captured as 'Other' (8.1%). Finally, for six DHPC, the absence of detailed data both in the letter itself and any associated documentation resulted in the grouping of source as 'Company database' (1.2%) and 'Health Authority database + Company database' (1.2%). One DHPC also mentioned electrophysiological data, in addition to studies and post-marketing reports. When data involved three or more complementary sources these were classified as 'Comprehensive'. A total of 5.7% DHPC were classified as having 'Comprehensive' search, the majority of which including data analysis at least from clinical trials, literature and spontaneous reports (71.4%, data not shown).

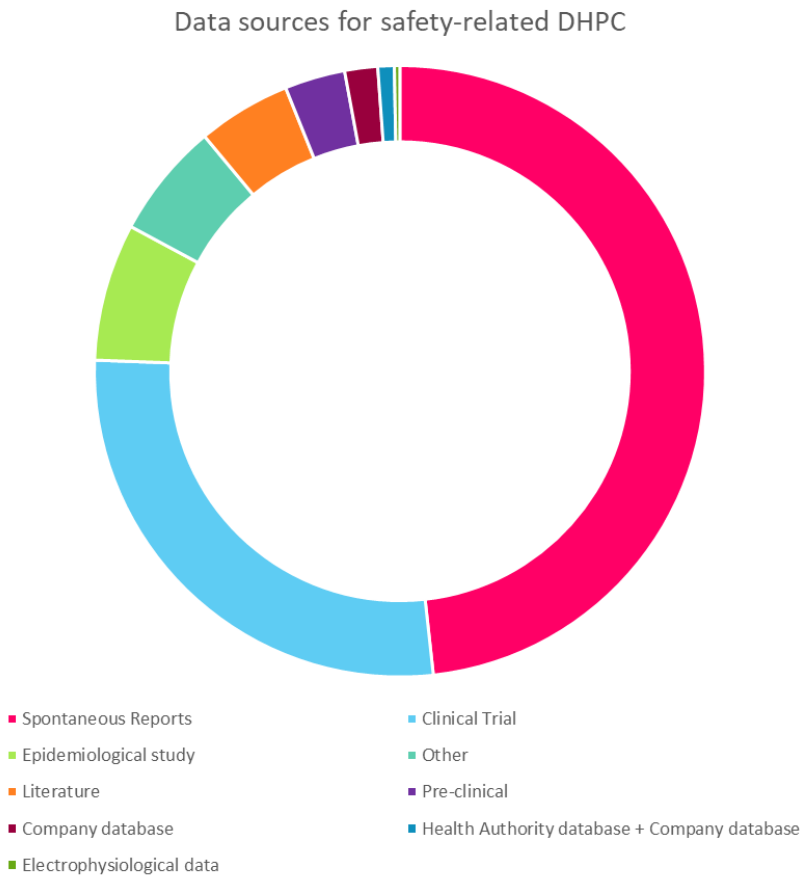


Figure 13 - Sources of data (%) for safety-related DHPC having triggered a safety evaluation and/or on which the safety evaluation was performed, either by the MAH or NCA/Agency

Regarding the region of origin, around half of the data sources for the safety communications retrieved from both the EU (50.8%) and the US (46.4%) referenced spontaneous reports. Supporting data from clinical trials and epidemiological studies were more prevalent in the set of DHPC originating from EU than the DHCP letters

retrieved the US territory. Literature references and grouping under 'Other' were, on the other hand, more common for the DHPC published in the US. References to MAH or Health Authority databases, pharmacokinetics studies and pre-clinical data were only present for DHPC published in EU territory. Finally, in case of multiples sources classified as 'Comprehensive' data, all of the safety-related DHPC were retrieved either for Portugal or the UK, originating from either a in depth review from the EMA or from the UK NCA (Figure 14).

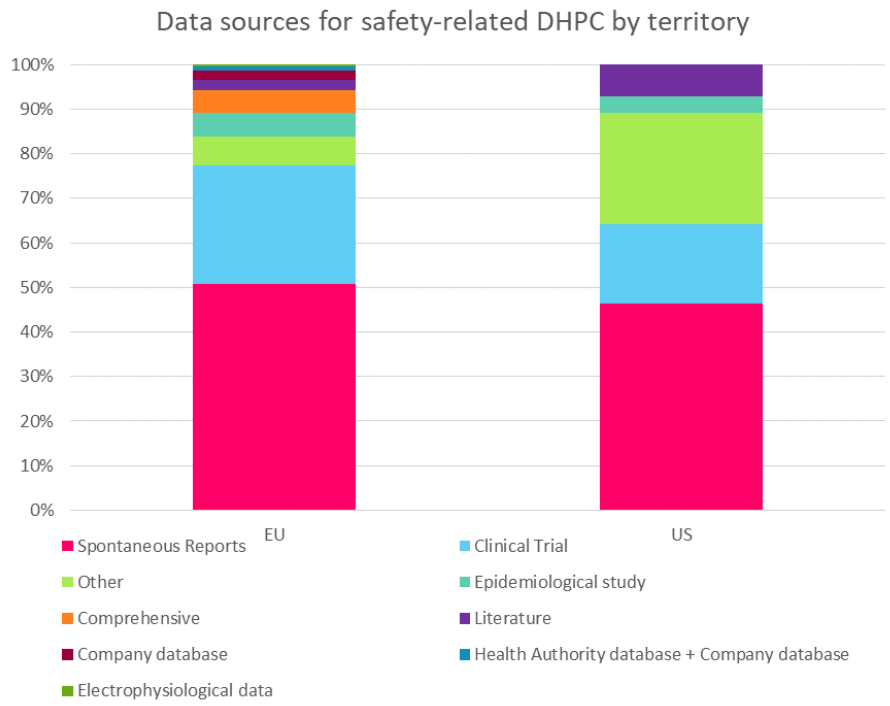


Figure 14 - Sources of data (%) for safety-related DHPC having triggered a safety evaluation and/or on which the safety evaluation was performed, either by the MAH or NCA/Agency, presented by territory

3.2.6 Non-overlapping DHPC

A total of 238 'single' safety communications were retrieved for topics for which DHPC were either published in Portugal and/or in the UK, but not in the US territory. Out of these, 53.4% could be linked to one or more of the following strategies used by the FDA for communication of safety risks or actions taken: Safety Labelling Changes (103), Drug Safety Communication (41), Drug Safety Alert (19), Safety Labelling Changes, including Black Box Warning (15), FDA Adverse Events Reporting System (02), FDA Statement (01), FDA Study (01) and Packaging Changes (01).

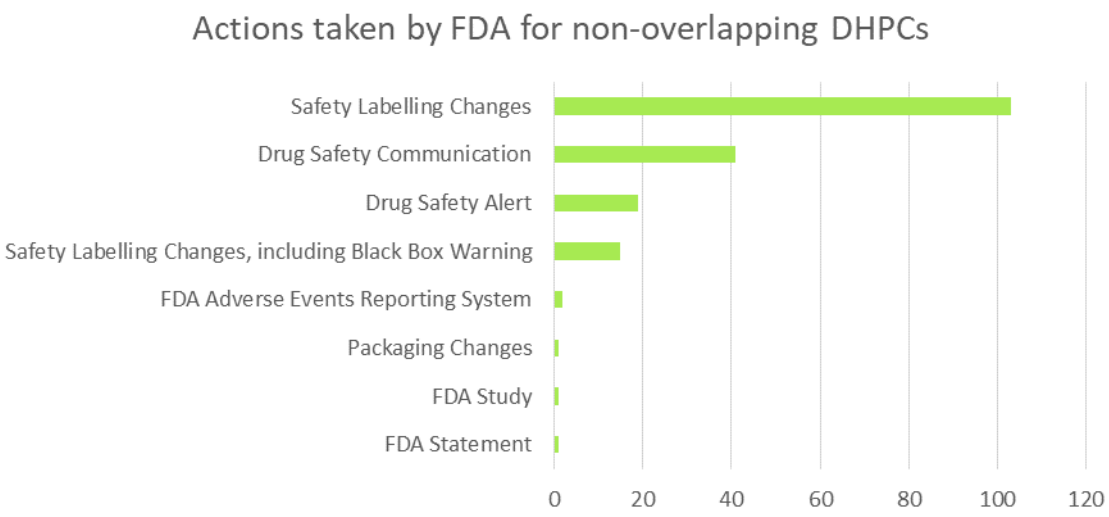


Figure 15 – Actions taken by the FDA (counts) for all the safety driven DHPC published either in Portugal and/or in the UK, but not in the US territory, for which another kind of safety communication/regulatory action was available from the FDA website.

For the 111 EU DHPC no communication to HCP and/or to the public or any further action could be retrieved from the analysis of the FDA website. Out of these, 29.7% corresponded to products and/or formulations not marketed in the US territory. The majority of this products were to small molecules (76.9%), mostly belonging to the Antineoplastic and immunomodulating agents (19), Nervous system (09), Antiinfectives for systemic use (09) and Cardiovascular system (09) anatomical main groups (data not shown).

For the remaining non-overlapping DHPC concerning medicinal products marketed in the US but with no identified safety communication/action, the safety topics more frequently reported belonged to Injury, poisoning and procedural complications SOC (08), Hepatobiliary disorders SOC (05), Cardiac disorders SOC (05) and Metabolism and nutrition disorders SOC (04) (Figure 16). Statistical significance was retrieved when comparing between EU DHPC with no identified US action (excluding EU DHPC for US non-marketed products) and EU DHPC with a indexed FDA action for Injury, poisoning and procedural complications SOC (Chi-square=6.846, df=1, $p<0.01$). The safety issues classified under this SOC concerned overdose (02), drug administration error (02), labelled drug-drug interaction medication error (01), product preparation error (01), new drug administration rate (01) and medication errors (01) (data not shown).

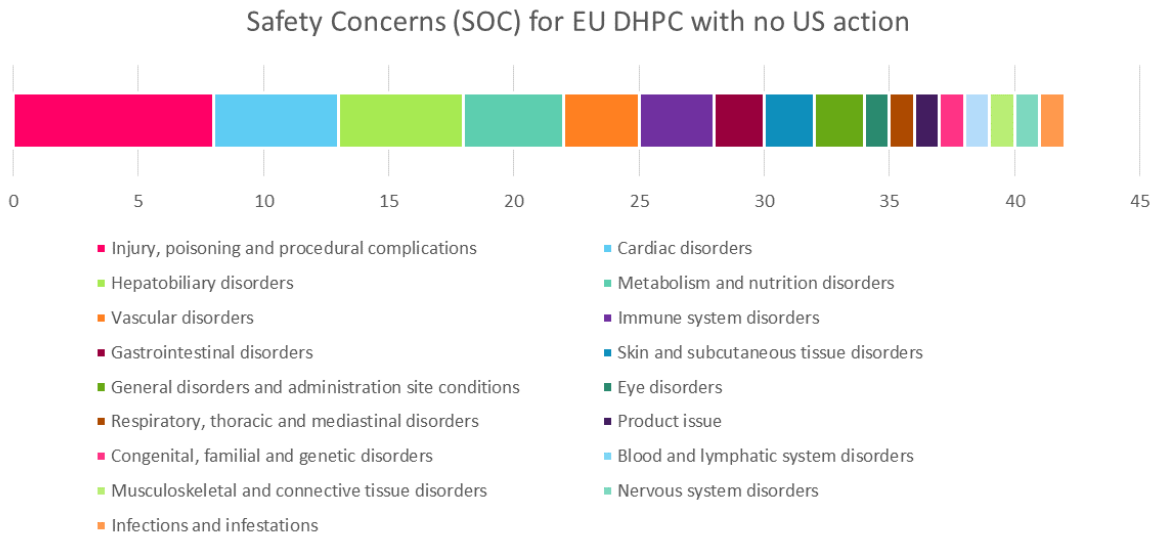


Figure 16 - Number of safety-related DHPC published in the EU region mapped to MedDRA SOC as per the adverse drug reactions presented for which there was no safety communication from the FDA.

3.2.7 Timing of regulatory action

For the subset of products studies, the median time between approval and the distribution of the DHPC was 13.7 years (globally), with an average of 11.0 years for biological medicinal products and of 14.7 years for small molecules. With regards to safety driven DHPC, the median time between approval and the safety communication was 11.7 (globally), with an average of 8.1 years for biological medicinal products and an average of 12.7 years for small molecules. Data shows 50.4% of the safety driven DHPC were issued within 6 years after approval.

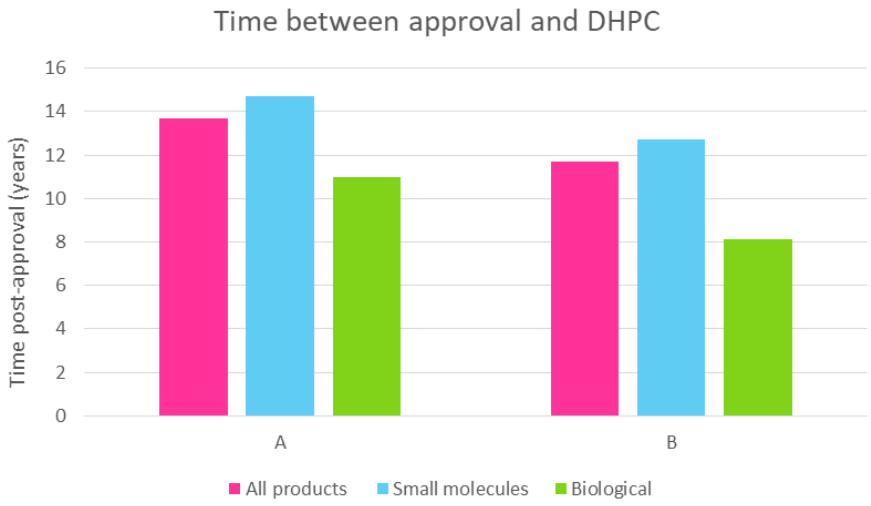


Figure 17 – Average time (years) between marketing authorization approval and distribution of DHPC regardless of reason (A) for all products types (pink), for small molecules (blue) and for biologicals (green); and distribution of safety-related DHPC (B) for all products types (pink), for small molecules (blue) and for biologicals (green).

3.3 Discussion

Results from DHPC analysis indicate a more prevalent distribution of safety communications for safety driven topics. Such results are in line with the scope of the use of direct communications to healthcare providers, as per the local regulations and guidance for both the EU and the US. In this study DHPC were predominantly disseminated for small molecules. Although serious safety issues have been suggested to be more common with biological agents(105), the fact that small molecules still dominate the market may be here reflected in both the total number of DHPC and for the safety-driven subset analysis.

Results also showed the majority of the safety driven DHPC belonged to the anatomical main groups of 'Antineoplastic and immunomodulating agents' (25.8%). Literature suggests that these drugs have been frequently associated with more safety driven regulatory actions(85,102). Additionally, the fact that these drugs are often used outside of their approved indication could also explain the higher frequency of safety related issues(85).

Only one overlapping DHPC could be found for the covering period between the US, Portugal and the UK. The fact that there very few DHPC available through the FDA website may greatly contribute for this fact, as 53.4% of the DHPC published in Portugal and/or in the UK could be linked to one of the strategies used by the FDA for communication of safety risks in the covering period. Additionally, the exclusion of safety communications published outside of the covering period given the different timelines for identification, assessment and regulatory action between US and UE should also be considered.

Safety-related DHPC referred most often to adverse events under Injury, poisoning and procedural complications (16.2%) and Cardiac disorders (13.1%) SOCs. Previous studies seem to support such distribution findings, at least in the Netherlands(102). The high frequency of Injury, poisoning and procedural complications SOC-related AE resulted from the 12 DHPC reporting medication error related AE. Medication errors are common around the globe(159) and responsible for considerable patient harm(160). In fact, the prevention of medication errors by healthcare professionals has gained particular interest in the last years, especially by the health authorities/regulators who have been developing strategies to minimise its potential risks (159,161,162).

Adverse events relating to the Cardiac and Hepatobiliary disorders SOCs were significantly more frequent for DHPC for small molecules, while Immune system and Musculoskeletal and connective tissue disorders SOC-related AE were significantly more frequently observed in DHPC distributed for biological products. Differences have been shown to exist in the nature of the safety-related regulatory actions for biologicals compared with small molecules(105). Published literature on DHPC and withdrawals for safety reasons reflect findings for small molecules(98,100,102,163), while research on biologicals approved in the United States and the European Union also retrieved comparable results for immune system disorders(103,105). The multiple safety communication on osteonecrosis of the jaw distributed for denosumab in 2014 and 2015 account for the increased frequency of Musculoskeletal and connective tissue disorders SOC-related AE.

Spontaneous reports accounted for around 50% of the source data for triggering safety driven DHPC in all regions. These findings seem to be in line not only with previous studies and the overall key role spontaneous reporting of adverse drug effects has had historically in the post-marketing surveillance(164,165), but also with recent data suggesting a positive correlation between spontaneous reports and different types of safety driven regulatory actions in Japan(166). On the other hand, clinical trials and epidemiological studies accounted for 45.8% of the data sources for safety-related DHPC. An increased use of case–control studies, cohort studies, randomized clinical trials and meta-analysis for the recent decade has also been reported in previous studies(167).

Finally, high percentage of ‘Other’ as a source for DHPC published in the US can be explained by the publication of six DHPC for biologic products warning healthcare practitioners of the risk of allergic reactions with these products given the possible presence of natural rubber latex in the containers of influenza vaccines (02), hemophilus influenzae B vaccines (01), hepatitis vaccines (02) and pertussis vaccines (01), which may cause allergic reactions in latex sensitive individuals. These communications are a result of a FDA review of the “latex-free” claims made by MAHs, which concluded that the documentation provided by manufactures was inadequate to support such claim. As a result, the FDA mandated that the product information for such products be revised to include a warning that “the syringe tip caps may contain natural rubber latex, which may cause allergic reactions in latex-sensitive individuals.”

The majority of the non-overlapping safety drive DHPC between EU and US could be linked to one of several strategies used by the FDA for communication of safety risks,

namely Safety Labelling Changes, some of which included Black Box Warnings, and Drug Safety Communications. Such findings appear to support the alignment on ideology and scope of action between the two regulators, particularly on actively monitoring, identifying and reviewing new important safety information in the post-marketing setting, in spite of the different set of regulatory tools available and resulting actions recommended. For the final non-overlapping safety communications mapped to Injury, poisoning and procedural complications SOC, it should however be noted that 60.0% of these were medication error AE associated with two specific products (levetiracetam and tacrolimus for oral administration).

Finally, the average time between approval and publication of safety-driven DHPC was 11.7 years (globally), with an average of 8.1 years for biological medicinal products and an average of 12.7 years for small molecules, ranging between less than one year to 28 years. Published literature on safety communication of medicinal products also suggest that level of innovation is not clearly correlated with frequency and timing of serious safety issues that are identified post-approval(168). Taken together such evidence underlines the need for continuous close monitoring of the benefit-risk profile and risk management of medicinal products during their whole life cycle.

4. MA suspensions and withdrawals

The following section aims to perform an analysis on the determinants and nature of suspensions and withdrawals, both for small molecules and biologic medicinal products, in the EU and US territories, between the years of 2010 and 2015.

4.1 Materials and Methods

The EMA and FDA websites were searched for all medicinal products withdrawn in the 5-year period from 2010 to 2015. The data extracted included date of publication of withdrawal, INN and the reason for withdrawal. Information on whether earlier safety related actions, including suspension or previous assessments for the specific safety topic, had occurred for that given molecule was also retrieved from the relevant websites. Such safety concerns were classified according to the Medical Dictionary for Regulatory Activities (MedDRA version 20.0), using SOC level. Furthermore, the time between the initial approval date (for the specific territory) and the withdrawal was determined.

Approval date was retrieved from the EMA website, FDA Drugs@FDA database for FDA Approved Drug Products or DailyMed website[7].

The extracted data was summarized in Excel and populated according to the following variables:

- Brand name
- Drug type: biological or small molecule
- INN
- Anatomical Therapeutic Chemical (ATC) classification, both 1st level - anatomical main group (ATC I) and 4th level - chemical subgroup (ATC II)
- Status of MA
- Date of withdrawal/suspension
- Reason for withdrawal: commercial, legal, lack of efficacy, quality or safety
- Any other relevant information, including previous actions for same safety concern, such as recalled, suspended or recently assessed by the Health Authority for safety issues
- Safety topic description (SOC)
- Date of approval
- HA recommending withdrawal from use (EMA and/or US)

4.2 Results

4.2.1 Characterization overview

In the period of 2010 to 2015 a total of 91 medicinal products were found to have been withdrawn from use on either US and/or EU markets. These medicinal products corresponded to 67 different ATC codes and were mostly small molecules (71.4%).

[7] https://dailymed.nlm.nih.gov, accessed between Jan 2016 and Sep 2017.

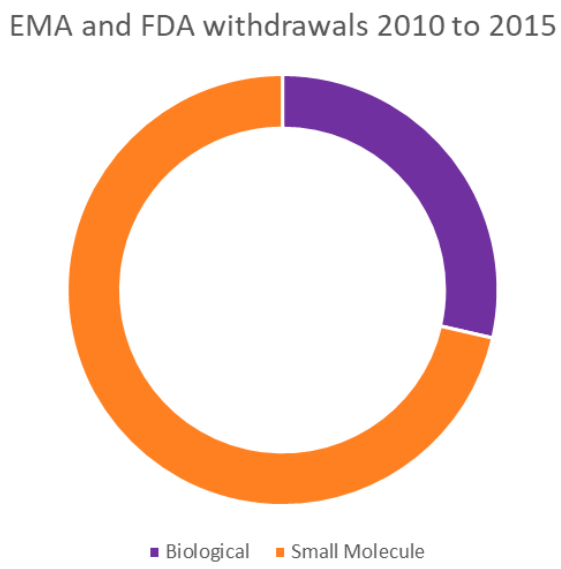


Figure 18 – Distribution of withdrawals (%) for the covering period independently of trigger both recommended by the EMA and the FDA by product type (biological vs small molecule).

Overall, the majority of the withdrawals occurred for commercial (71.4%) or legal reasons (19.8%), such as sunset clause. Remaining products withdrawn for safety concerns (5.5%), quality issues (1.1%) and lack of efficacy (1.1%).

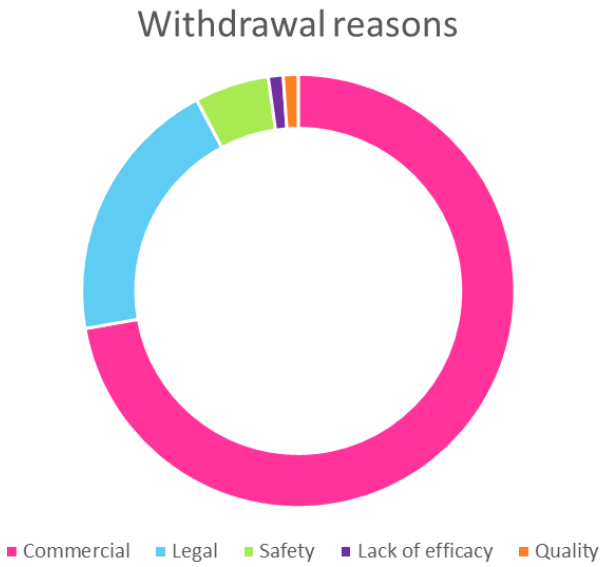


Figure 19 – Global distribution of withdrawals (%) for the covering period by reason.

During the covering period, one marketing authorization was suspended in EU. This concerned MACI (matrix-applied characterised autologous cultured chondrocytes) and

the absence of an authorised manufacturing site, which precludes the satisfaction of the requirements in Article 41 of Directive 2001/83/EC(169).

4.2.2 Regional distribution

Results showed that 92.3% of the withdrawals only took place in the EU, the majority of which for commercial (77.4%) or legal reasons (20.2%). One medicinal products was withdrawn because of safety reasons and another due to lack of efficacy. In the US territory, the majority of the withdrawals were safety-driven (57.1%) (Figure 20).

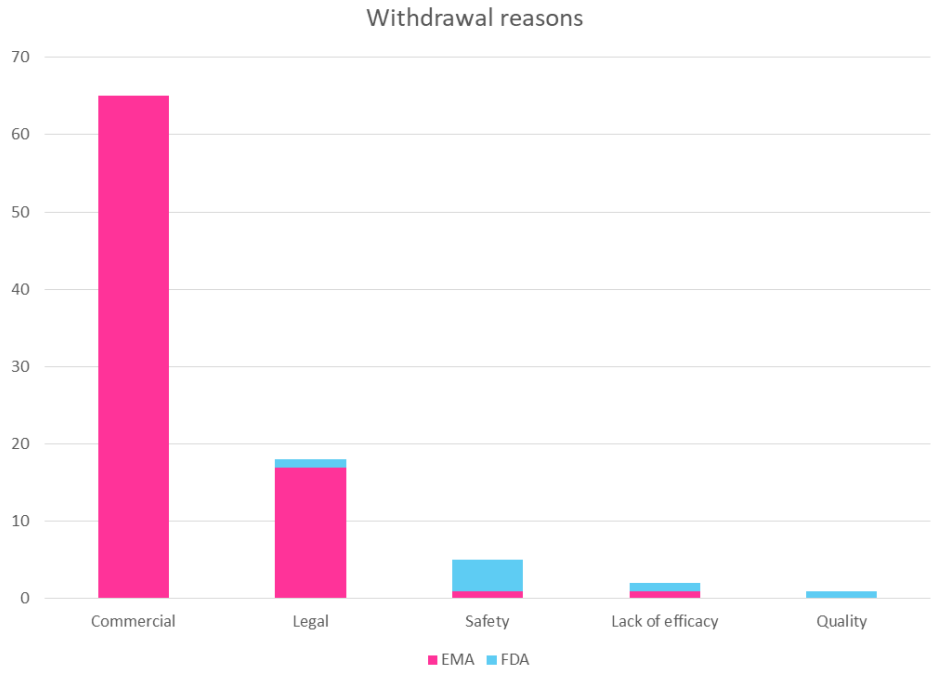


Figure 20 - Distribution of withdrawals (count) for the covering period both recommended by the EMA and the FDA by reason.

Only one product was withdrawn in both the US and the EU markets during the covering period. Drotrecogin alfa (Xigris) is a recombinant version of the endogenous activated Protein C, produced by genetic engineering from an established human cell line. Xigris was indicated for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. The product was approved in the US in 2001 and later in 2002 for the EU under exceptional circumstances. Following results of the PROWESS-SHOCK study, which showed the study did not meet the primary endpoint of a statistically significant reduction in 28-day all-cause mortality in patients with septic shock, the MAH announced a worldwide voluntary market withdrawal(170,171).

4.2.3 Safety-driven regulatory actions

Withdrawals and suspensions for safety reasons (11) were mostly linked to Cardiac disorders (76.9%) (Figure 21). These concerned a total of eight different ATC codes, with most of the sub-grouped products analysed belonging to the anatomical main groups of 'Alimentary tract and metabolism' (36.4%) and 'Cardiovascular system' (36.4%) (Figure 22).

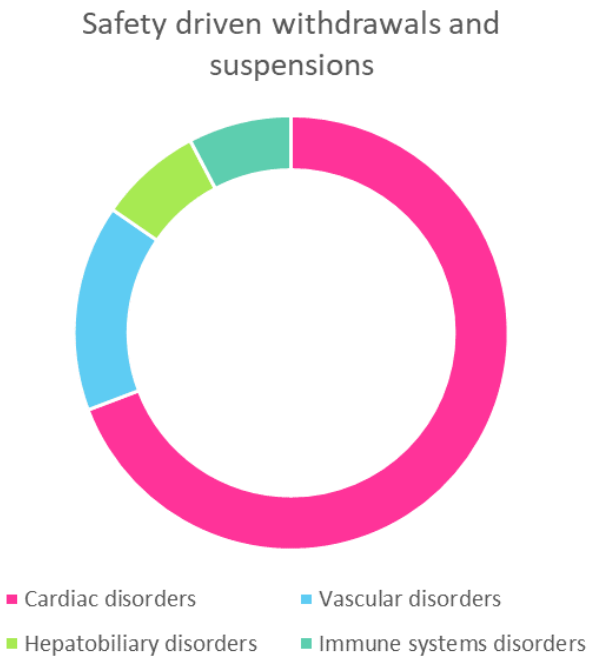


Figure 21 – Withdrawals and/or suspensions (%) mapped to MedDRA SOC as per the adverse drug reactions presented, for the covering period in both territories.

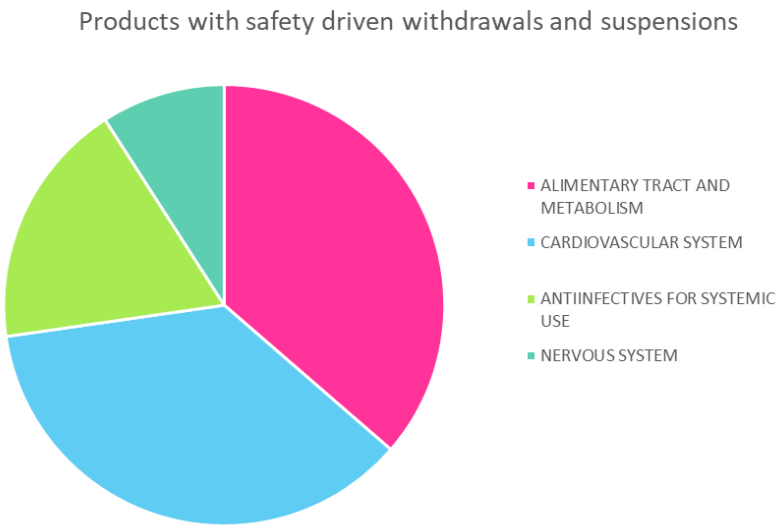


Figure 22 – Anatomical main group distribution (%) medicinal products with safety-related withdrawals and suspensions for the covering period in both territories.

4.2.4 FDA

With regards to the US territory, four withdrawals took place due to safety concerns. A brief description on each safety driven withdrawal case is presented below, including actions take within the EU territory, as applicable.

Sibutramine

On October 2010, the FDA recommended against the continued prescribing and use of sibutramine (a serotonin-noradrenaline re-uptake inhibitor used in the management of obesity) given the newly identify risks on cardiovascular safety, and requested the manufacturer to voluntarily withdraw this product from the market. Such recommendations were made three years after the drug's initial approval, and based on new data from the Sibutramine Cardiovascular Outcomes (SCOUT) trial, which demonstrated a 16% increase in risk of major adverse cardiovascular events, such as stroke or heart attack, in patients treated with sibutramine compared to patients taking a placebo(172). Preliminary data on the same clinical trial had been under discussion by the EMA since November 2009. The CHMP noted that the use of sibutramine was not in accordance with the prescribing information for most of the patients enrolled in the SCOUT study, as sibutramine is contra-indicated in patients with known cardiovascular disease and that the treatment duration in the study was also longer than normally recommended. However, because obese and overweight patients are likely to have a higher risk of cardiovascular events, the Committee was of the opinion that the data from the SCOUT are relevant for the use of the medicine in clinical practice. Based on such findings, on January 2010, the CHMP concluded that the benefit/risk ratio for sibutramine-containing medicinal products was not considered favourable and recommended the suspension of the MA for the sibutramine-containing medicinal products(173).

Propoxyphene

Also in 2010, healthcare professionals were notified that the manufacturer had agreed to withdraw propoxyphene, an opioid pain reliever used to treat mild to moderate pain, from the US market at the request of the FDA. The regulator's recommendation was based on the available data including findings from a new randomized clinical trial that showed significant changes to the electrical activity of the heart, such as prolonged PR interval, widened QRS complex and prolonged QT interval, even when propoxyphene was taken at therapeutic doses(174). EMA, on the other hand, had already completed a review of the safety and effectiveness of dextropropoxyphene-containing medicines on

2009, under an 'Article 31' referral. The EMA had concluded that the benefits of dextropropoxyphene did not outweigh its risks, and recommended that all marketing authorisations should be withdrawn throughout the European Union. Later on, at the request of the MAHs, the CHMP re-examined its opinion having confirmed its original recommendation that the marketing authorisations for the non-parenteral (tablets, capsules and suppositories) forms of dextropropoxyphene-containing medicines should be withdrawn. For the parenteral form (solution for injection), the CHMP recommended that the marketing authorisations be suspended until further data are available(174).

Octagam

Immune globulin intravenous (human) (Octagam) was initially granted MA in US in May 2004 (175) and in September 2010 both the manufacturer and the FDA notified healthcare professionals that, a voluntary market withdrawal of all lots of Octagam currently in the US market was being initiated due to previously reported thromboembolic events with this medicinal product(176). In EU, an Urgent Union procedure (Article 107i referral) was initiated based on the decision of the German and Swedish medicines regulatory agencies to suspend the marketing authorisations for Octagam following such reports. The CHMP evaluation concluded thromboembolic events could be related to the presence of impurities which could act as clotting/coagulation factors in the product introduced during the manufacturing process and therefore recommended (i) a recall of all batches of Octagam and associated names and (ii) a suspension of its marketing authorisation(175). Later on, an in-depth review of all available data on the safety and quality issues concluded that the unexpected presence of a pro-coagulant, factor XIa, was the main cause of the thromboembolic events and that a number of critical steps in the manufacturing process could explain the presence of substances that triggered the thromboembolic events. Given the number of corrective and preventive measures implemented by the MAH, including the requirement for performing post-marketing safety studies and the CHMP recommended lifting the suspension on April 2011. The same recommendations were then issued by the FDA on November 2011. Until this date, two more voluntary market withdrawals have taken place with different lots of Octagam in the US, in April 2016 and October 2017, with no associated reports of serious injury(177,178).

GammaGard Liquid

Certain lots of immune globulin intravenous (human) (GammaGard Liquid) were also withdrawn as a precautionary measure from the market in June 2010, following an

reports of an increased number of adverse event reports of allergic reactions associated with two lots of this product(174). GammaGard Liquid was approved in April 2005 and is indicated for the treatment of primary immunodeficiency disorders associated with defects in humoral immunity. No action was retrieved from the EU region.

4.2.5 EMA

Sitaxentan sodium was the only MA to be withdrawn from EU during the covering period for safety reasons. This medicinal product was approved for the treatment of patients with pulmonary arterial hypertension and had been known to be associated with liver toxicity. Since its initial marketing authorisation it had been contra-indicated in patients with mild to severe hepatic impairment and elevated aminotransferases prior to initiation of treatment. Voluntary worldwide market withdrawal was decided in December 2010, four years after its initial authorization in EU, given a new potentially life-threatening idiosyncratic risk of liver injury. At that time Thilen (sitaxentan sodium) was marketed in 16 EU Member States, in Australia and in Canada(179). On the other hand, such product was never approved in the US, but not due to liver toxicity concerns. After the initial submission of the new drug application in 2005, the FDA issued a total of three complete response letters to the sponsor. Initial letters contained concerns and observations to be satisfied before approval, including a request for an additional clinical trial; while the third requested another study to demonstrate the drug's effectiveness in exercise capacity. Ultimately, in 2007, US regulators did not grant approval for sitaxentan given their concern on a lack of efficacy as, although the data provided in the new drug application were suggestive of its effectiveness, the extent of improvement did not provide the substantial evidence of effectiveness needed for approval(83,180).

Despite the prevalence of commercially and legally driven withdrawals in EU already described, 39.0% of such products had been either suspended (8.5%), recalled (14.6%) or recently assessed by an European Health Authority (15.8%). Results show that safety-driven assessments were done for 20.3% of products later withdrawn for commercial or legal reasons, of which 33.3% (06) resulted in a recommendation to suspend the MA. A brief description of these cases is presented below.

Laropiprant/ nicotinic acid

On December 2012, the European Medicines Agency was made aware of the availability of preliminary results from a randomised clinical study (HPS2-THRIVE1) designed to assess the incremental benefit of nicotinic acid/laropiprant (as extended release formulation). Nicotinic acid/laropiprant, authorised in the EU as Tredaptive, Trevaclyn

and Pelzont since July 2008, was indicated for the treatment of dyslipidaemia. The preliminary results showed that no significant additional benefit in reducing the risk of major vascular events was found in taking laropiprant/ nicotinic acid together with a statin, compared with statin therapy alone. In addition, a higher frequency of non-fatal but serious side effects was seen in patients taking laropiprant/ nicotinic acid. A procedure under Article 20 was then initiated following which PRAC recommended the suspension of the marketing authorisations for nicotinic acid/laropiprant. To lift such suspension, the MAH would need to provide convincing data to identify a patient population in which the efficacy of nicotinic acid/laropiprant could demonstrated, and in which the benefit clearly outweighs the risks(181). The FDA on the other hand, had in fact issued a non-approval letter for nicotinic acid/laropiprant New Drug Application, requesting additional efficacy and safety data and suggesting the manufacturer to wait for the results of the HPS2-THRIVE cardiovascular outcomes study(182,183).

Rosiglitazone-containing products

On December 2010 the European Commission issued a decision for the suspension of the marketing authorization of rosiglitazone-containing medicines, following the availability of new studies questioning the cardiovascular safety of the medicine. Since its first authorisation in 2000, rosiglitazone had been recognised to be associated with fluid retention and increased risk of heart failure and its cardiovascular safety has always been kept under close review. Consequently, the use of rosiglitazone was restricted to a second-line treatment and contra-indicated in patients with heart failure or a history of heart failure. Further data from clinical trials, observational studies and meta-analyses of existing studies that became available since 2007 which suggested a possibly increased risk of ischaemic heart disease associated with the use of rosiglitazone and hence further restrictions on the use of these medicines in patients with ischaemic heart disease were introduced(184,185).

EMA later considered that the availability of these recent studies had added to the knowledge about rosiglitazone and overall, the accumulated data supported an increased cardiovascular risk of rosiglitazone. The Agency considered that no further risk minimisation activities could be identified which would be expected to reduce the risks of rosiglitazone-containing products to an acceptable level or predict which patients may be at risk, taking into account the restrictions and warnings already in place. Having concluded that the risks associated with the use of rosiglitazone in the treatment of type 2 diabetes mellitus outweigh its benefits, the marketing authorization was suspended. Such measures were to remain in place unless the marketing authorisation holder could

provide convincing data to identify a group of patients in whom the benefits of the medicines outweigh their risks. However the marketing authorizations for rosiglitazone/metformin and rosiglitazone expired on October 2013 and on July 2015, after the marketing authorization holder having failed to satisfy such requirements. Regarding rosiglitazone/glimepiride significant new data had not been submitted as part of the renewal application and the five-year marketing authorization also expired on June 2011(185).

On the other hand, the FDA issued on September 2010 and later on February 2011 a series of restrictions for prescribing and use of rosiglitazone-containing products. In addition to describing the cardiovascular risks, the drug labels were revised to state that rosiglitazone and rosiglitazone-containing medicines should only be used either in patients already being treated with these medicines, or in patients whose blood glucose levels could not be controlled with other anti-diabetic medicines and who, after consulting with their healthcare professional, do not wish to use pioglitazone-containing medicines. Additionally, as part of a REMS implemented in September 2010, healthcare providers and patients must enrol in a special program in order to prescribe and receive these drugs, the latter which would receive their medicine by mail order through specially certified pharmacies participating in the program(186).

Developments in 2013 include the new re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes trial, based on which the FDA requested modifications to the rosiglitazone REMS program to remove the requirements for restricted distribution(187).

4.2.6 Timing of regulatory action

For all of products studied, the median time between approval and withdrawal dates was 5.9 years (globally), with an average of 7 years for biological medicinal products and of 5.4 years for small molecules. With regards to safety driven withdrawals and suspensions, the median time between approval and the regulatory action dates was 8.3 years (globally), with an average of 4.5 years for biological medicinal products and an average of 9.1 years for small molecules. Additionally, 66.6% of the safety-related withdrawals were issued within 5 years after approval.

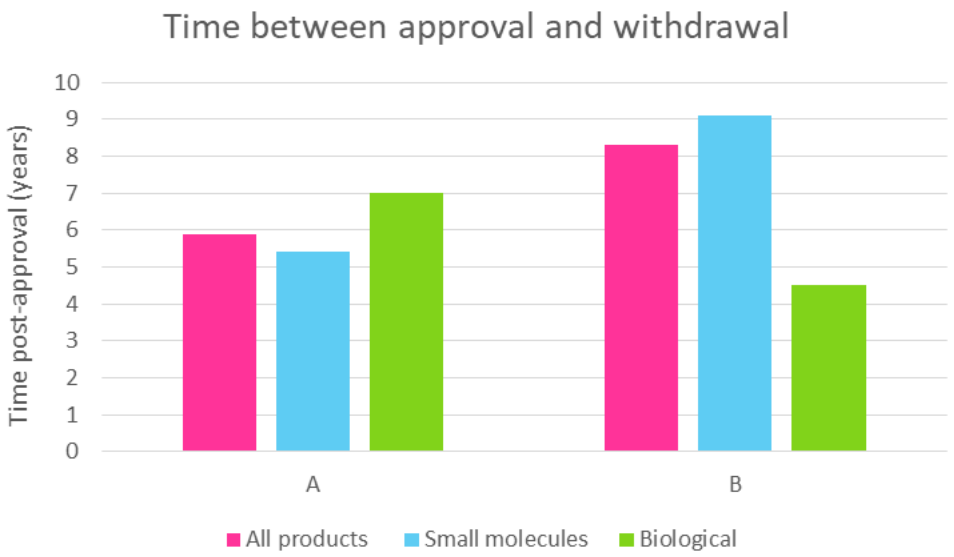


Figure 23 – Average time (years) between marketing authorization approval and withdrawal regardless of reason (A) for all products types (pink), for small molecules (blue) and for biologicals (green); and average time (years) between marketing authorization approval and safety driven withdrawal and/or suspension (B) for all products types (pink), for small molecules (blue) and for biologicals (green).

4.3 Discussion

Similarly to the results from DHPC analysis, data on withdrawals of marketing authorizations shows that such regulatory actions were pronominally taken for small molecules. Overall, the majority of the withdrawals occurred for commercial or legal reasons, with safety concerns being responsible for only 5.5% of the withdrawals. This figure is consistent with the 4.2% value obtained for safety market withdrawal of drugs approved in Canada between 1990 and 2009(188) and in line with European data from January 1999 to December 2009(87), although higher that the 2.9% reported for the United States between 1975 to 1999(98). The fact that no information was available from the FDA website on withdrawals for commercial reasons is a severe limitation for the overall comparison on global data.

Despite the more frequent withdrawals for non-safety concerns, results show safety-driven assessments in EU were done for 20.3% of products later withdrawn for commercial or legal reasons, of which 33.3% resulted in a recommendation to suspend the MA. This may suggest a higher frequency of emerging safety issues than the ones accounted for based on the public statement for withdrawal available at the EMA website.

From all the withdrawn products, only one was removed from the marked by both the FDA and the EMA, due to lack of efficacy. Multiple cases were presented discussing

different regulatory actions for the same safety concerns for a particular product. Such results seem to highlight not only the considerable differences with regards to pre-approval processes between the EU and the US, but also to reflect the distinct benefit-risk balance assessment based on the regulatory powers available for both bodies and emphasis in risk communication/ implementing risk minimization activities, which have resulted in multiple well known for conflicting regulatory decisions throughout the years.

Data from this analysis shows that majority of the withdrawals and suspensions for safety reasons was linked to Cardiac disorders (76.9%), which is consistent with previous findings for safety driven regulatory actions, particularly for small molecules(98,102,105)

Overall, for small molecules, the average time taken until withdrawal was lower than the average time taken for all safety-related regulatory actions (i.e. withdrawals and suspensions), regardless of the reason for removal from the market. This is due to the high proportion of withdrawals for small molecule type drugs in the EU territory for pure commercial reasons within one year of granting of the marketing authorization.

Average global figure of 8.3 years between approval and withdrawal for safety driven withdrawals and suspensions is higher than previous results(98,100,103) These findings can be explained partly by the long time lapse between approval and discontinuation of some products for the covering period (e.g. propoxyphene and sibutramine). Additionally, the different calculations used to determine time of action may also contribute, as previous publications determined time between approval date and date of first safety-driven regulatory action and or date of suspension, while this analysis calculated the time between medicinal product approval and withdrawal dates, even for products with previous safety findings or suspensions. Nonetheless, results also evidence that safety-related regulatory actions are mostly taken within the first 5 years after approval, which is in line with available literature.

On the other hand, figures obtained for biologicals, suggest that earlier action is taken for such type of products when compared to small molecules, however sample size is too small for further considerations.

5. Case study

5.1 Valproic acid and related substances

Valproic acid (2-propylpentanoic acid, N-dipropylacetic acid) is a branched short-chain fatty acid, derived from valeric acid, which was initially synthesized as an organic solvent. Its antiepileptic properties were recognized given its ability to protect experimental animals against seizures and its introduction for clinical use followed shortly after the publication of the first clinical study in 1964(189,190). The difference between valproate products (valproate sodium, divalproex sodium and valproic acid) is their solubility in water. As sodium valproate is very hygroscopic and in the gastrointestinal tract is impossible for it to disintegrate in equal form, without constant fluctuations, laboratories developed the sodium divalproate molecule(191).

In Europe, valproate and related substances (valproic acid, sodium valproate, valproate semisodium, and valpromide) have been used since 1967 to treat epilepsy and since 1995 to treat bipolar disorders. Nowadays, valproate is also indicated for the prophylaxis of migraine attacks in some of the EU Member states(192). In regards to the US territory, valproate products (valproate sodium, divalproex sodium and valproic acid) were initially granted market authorization in 1979 and are currently approved for the treatment of seizures, and manic or mixed episodes associated with bipolar disorder, and to prevent migraine headaches(193). However, the off-label use of valproate products for other psychiatric conditions, particularly as a mood stabilizer for patients with schizophrenia, appears to be prevelant(194–197). In fact, cumulatively until September 2017, a total of 321 individual cases (1.21%), out of 26.570 cases reported cumulatively, had been identified in EudraVigilance for valproic acid and off-label use(198).

Valproic acid (ATC code: N05AX) belongs to the pharmacotherapeutic group of psycholeptics; antipsychotics; other antipsychotics, and exerts its effects mainly on the central nervous system. Valproate's exact mechanism of action is not fully understood, but it is thought to act through potentiation of the inhibitory action of gamma amino butyric acid, either by further synthesis or further metabolism of the neurotransmitter. Valproate may also work by suppressing repetitive neuronal firing through inhibition of voltage-sensitive sodium channels, which has the effect of reducing excessive electrical activity in the brain(192,199–201).

Valproate is generally regarded as one of the first-line treatments for most forms of symptomatic and idiopathic generalized epilepsies. In patients with newly diagnosed

partial seizures (with or without secondary generalization) and/or primarily generalized tonic-clonic seizures, the efficacy of valproate is comparable to that of phenytoin, carbamazepine and phenobarbital(199,202).

As far as an overall safety profile with therapeutic use, the most common adverse effects are nausea, tremors, gastralgia, diarrhoea, extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, confusional state, aggression, agitation, disturbance in attention, hyponatraemia, anaemia, thrombocytopenia, hypersensitivity, transient and/or dose related alopecia, dysmenorrhea, haemorrhage, deafness and weight increased(200).

Additionally, like with other anti-epileptic medicines, use of valproate containing medicines in pregnant women increases the risk of birth defects in their children. Maternal use of valproic acid is however associated with a higher risk of certain birth defects than other anti-epileptic medicines. Data also suggests an association between in-utero exposure to valproate and the risk of developmental disorders (frequently associated with craniofacial abnormalities), particularly of verbal intelligence quotient(203).

5.2 EU safety-related regulatory actions

On April 2009, the Dutch national competent authority raised general concerns on the effectiveness and safety of valproic acid and valproate in regard to its use for acute treatment of manic episode and prevention of recurrence in patients with bipolar disorder. The Medicines Evaluation Board noted that there were differences among Member States in the marketing authorisations in this context and asked the CHMP to carry out a full assessment of the benefit-risk balance of valproic acid and valproate for this indication.

The CHMP reviewed the information supplied by the companies that make valproate-containing medicines to support the use of valproate-containing medicine in bipolar disorders, including published articles reporting the results of 16 clinical studies of valproate in acute mania (either in monotherapy or in combination) and in the prevention of recurrence of mood episodes in bipolar disorder. Following this review, PRAC recommended bipolar disorders indication was to be restricted to the treatment of manic episode when lithium is contraindicated or not tolerated. However, continuation of treatment after the manic episode can be considered in patients who have responded well to valproate. Furthermore updates to the product information were requested in

order to reflect the risks relating to the use during pregnancy, including the risk of birth defects and also the risk of developmental delay. At that point in time, the product information included warnings for valproic acid not to be used to treat epilepsy or bipolar disorders during pregnancy and in women of childbearing potential unless clearly necessary (e.g. in situations where other treatments are ineffective or not tolerated)(192,204).

In the years following this review, several further studies were published, which allowed for a better understanding and characterisation of the risk of long term potential neurodevelopmental effects following in utero exposure to valproate. These publications suggested that in some children the effects appear to persist and manifest as a range of neurodevelopmental abnormalities and autism spectrum disorder. This new data also stated that the risk of neurodevelopmental delay and autism spectrum disorder may be independent of maternal confounders(203,205–207). Therefore, in October 2013, the UK's National Competent Authority, the Medicines and Healthcare products Regulatory Agency (MHRA), triggered a referral under Article 31, requesting the PRAC to issue a recommendation on whether the balance of benefits and risks for these products was still positive in the approved indications, in female children, women of child bearing potential and pregnant women and whether the marketing authorisation for valproate and related substances should be maintained, varied, suspended or revoked. Additionally, the MHRA also argued that product information for valproic acid and related substances appeared to differ across EU Members and there was a need for further revisions in order to bring it in line with all the most current safety profile of the drug(208).

A decision was reached by the European Agency in October 2014. Data from pre-clinical studies, pharmaco-epidemiological studies, published literature and spontaneous was assessed, the views of the relevant experts (e.g. in neurology, psychiatry, child neuropsychiatry, obstetrics etc.) on the safety and efficacy of valproate and related substances in female children, women of childbearing potential and pregnant women, the views of patients, families and carers and of healthcare professionals regarding the implications, the understanding and awareness of the risks associated with valproate in-utero exposure were also considered.

PRAC review confirmed that intra-uterine exposure to valproate and related substances is associated with (i) an increased risk of developmental disorders in the offspring and (ii) a known risk of congenital anomalies. Based on these conclusions the following safety-related regulatory actions were recommended(192):

I. Updates to the product information
    a. Valproate and related substances should not be used in female children, women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated in the following indications: treatment of primary generalised epileptic seizures, secondary generalised epileptic seizures and partial epileptic seizures; treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate for acute mania.
    b. Valproate and related substances should be contraindicated in prophylaxis of migraine attacks in pregnancy and women of childbearing potential who are not using effective methods of contraception during treatment with valproate.
    c. Further changes to the product information such as warnings and precautions and updated information on the risks related to exposure during pregnancy should be implemented to better inform the healthcare professionals and women.

II. Updates to the conditions to the MAH to include the need to implement further risk minimisation measures (RMM) such as:
    a. Educational materials aimed to better inform patients and healthcare professionals on the risks, particularly targeting neurologists, psychiatrists, general practitioners, obstetricians/gynaecologists, family planning centres, pharmacists, health visitors, midwife, and school nurses. These include a guide for prescribers, a patient booklet, an acknowledgment of risk information form and a DHPC.
    b. A drug utilisation study to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate. The study design should aim to evaluate and quantify the effectiveness of the risk minimisation measures, and should include a pre- and post-implementation analysis and assessment. The study should also be conducted in more than one EU Member State. As a result of this new requirement the marketing-authorisation holders to carry out joint post-authorisation safety study, valproic acid and related substances were added to the list of medicines under additional monitoring includes medicines authorised in the European Union in January 2015(209).

On November 2014, Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed above PRAC recommendations but several amendments were also made/included, namely a clarification about the population affected by the recommendations as these are also applicable to female adolescents (aged between 12 to 16-18 years) according to the ICH E11 age classification of the paediatric population; a clarification on the use of prolonged release formulation to avoid high peak plasma concentrations in the summary of product characteristics, and also a request for the first part of the package leaflet to be reviewed for clarity reasons(210).

Based on these requirements, two observational studies were designed:

- A Joint PASS Survey and Drug Utilisation Study among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of valproate in France, Germany, Spain, Sweden and United Kingdom (EUPAS11379), finalized on May 2017(211);
- And A Joint Drug Utilisation Study (DUS) of valproate and related substances, in Europe, using databases, in order to describe the prescribing practices before and after the dissemination of risk minimisation measures (e.g. educational materials and Dear Healthcare Professional Communication) and to assess the effectiveness of these measures in females through measure of prevalence of prior medication used before valproate (still ongoing)(212).

Besides the additional RMM implemented throughout EU territories, some countries have taken specific additional measures. For instance, in France a warning has been included on the outer packaging and additional DHPC circulated; a patient alert card and a pictogram on the outer packaging have been implemented more recently. French Health Authorities also published recommendations on how to replace valproate in female children, women of childbearing potential and pregnant women treated for epilepsy or bipolar disorder. The risk minimisation measures currently (November 2017) in place for valproic acid and related substances in the UK are presented in Table 6.

Table 6 – Risk minimisation measures currently (November 2017) in place for valproic acid and related substances within the UK

Educational Materials	Brief description
Checklist HCP – Risks in Female patients	Checklist for prescribers related to Valproate use in female patients.

Educational Materials	Brief description
HCP Booklet – Risks in Female patients	Healthcare professional risk minimisation booklet for Valproate in female patients (Annex IV - HCP Booklet – Risks in Female patients).
Letter for Pharmacists – HCP - Risks in Female patients	Communication letter to pharmacists explaining risk minimisation materials for managing patients taking Valproate based medicines
Letter for Prescribers - Risks in Female patients	Communication letter to specialists and specialist nurses/midwives managing patients treated with valproate-based medicines (Annex V – Letter for Prescribers - Risks in Female patients)
Letter for Primary Care HCP - Risks in Female patients	Communication letter to HCP's providing primary care, obstetric or family planning services to female patients taking Valproate containing medicines.
Letter for Specialists – Risks in Female patients	Communication letter explaining risk minimisation materials for specialists managing patients taking Valproate based medicines.
Patient Card – Risks in Female patients	Risk minimization Patient card for Valproate in female patients.
Patient Guide – Risks in Female patients	Patient Guide risk minimisation booklet for Valproate in female patients.
Valproate – Poster – Dispensary - Risks in Female patients	Additional materials for pharmacists (Annex VI – Poster-Dispensary - Risks in Female patients).
Safety Card - HCP - Risks in Female patients	Additional materials for HCP's providing primary care, obstetric or family planning services.
Shelf Barker - HCP - Risks in Female patients	Additional materials for HCP's providing primary care, obstetric or family planning services.

Similarly, since the EMA review in 2014, some EU member states have since carried out additional assessments of the impact of the measures at national level. In March 2017, French medicines regulator raised concerns about how effective the measures have been in increasing awareness and reducing valproate use appropriately in its various indications, and therefore asked EMA for a broad review on this topic(213).

EMA is currently examining the available evidence and consulting with relevant stakeholder groups. As a part of this new review of valproate use in pregnancy and women of childbearing age, the first ever public hearing was held by the Agency on 26 September 2017 in order to learn more directly from the different views and experiences of people who have taken valproate and those caring for such people.

On PRAC meeting of 5-8 February 2018, recommendations on new restrictions on use and a pregnancy prevention programme to be put in place have been made. Having examined the available evidence and consulted widely with healthcare professionals and with patients, including women and their children who have been affected by valproate use during pregnancy, through written submissions, expert meetings, meetings with stakeholders including healthcare professionals, patients' organisations, patients and their families, and via a public hearing, the PRAC noted that women were still not always receiving the right information in a timely manner and that further measures were needed to help avoid use during pregnancy. However, it was also clear that for some women, such as those with particular forms of epilepsy, valproate is the only appropriate treatment and might be life-saving(214).

Therefore, strengthening restrictions on the use of these products and introduction of new measures to require appropriate counselling and information for affected women have been proposed. Additionally, the MAHs of valproic acid and related substances have now been requested to carry out additional studies to further characterise the nature and extent of the risks posed by valproate and to monitor ongoing valproate use and the long-term effects from affected pregnancies(214).

In March 2018 CMDh endorsed the implementation of new measures to strengthen previous restrictions on valproate use and the requirements to inform female patients of the risks of malformations and developmental problems from valproate exposure in pregnancy. The CMDh position will now be sent to the European Commission, which will take a final legally binding decision valid across the EU(215).

5.3 US safety-related regulatory actions

On January 2008, the FDA issued new information to health care professionals, the general public and MAHs in regard to the increased risk of suicidal thoughts and behaviours in patients taking antiepileptics, as a result of suicidality reports from placebo-controlled studies for 11 antiepileptic drugs(216). Updates to the product label were requested for these products for Warnings and Information to Patients sections.

Additionally, the FDA also requested MAHs to submit a Risk Evaluation and Mitigation Strategy for each of these products. Medication Guide for patients was also to be implemented for several antiepileptics but not valproic acid. The latter constitutes of a handout developed by manufactures containing FDA-approved information about the risks of suicidal thoughts and behaviours associated with this class of drugs, which is to be distributed to patients, their families and caregivers when any of the referred antiepileptic products is dispensed(217,218).

In December of the following year, the FDA published an Information for Health Care Professionals (also referred to as a Healthcare Professional Information sheet) on the risk of neural tube birth defects following prenatal exposure to valproate. HCP were also notified of other major birth defects associated to in-utero exposure of valproate products, such as craniofacial defects and cardiovascular malformations. Subsequent changes to the label were implemented to full address these safety concerns. Furthermore, HCP were requested to inform women of childbearing potential about these risks, and consider alternative therapies, especially if using valproate to treat migraines or other conditions not usually considered life-threatening. In fact, women of childbearing potential should only use valproate if it is essential to manage their medical condition. Those who are not actively planning a pregnancy should use effective contraception, as birth defect risks are particularly high during the first trimester, before many women know they are pregnant. In addition, FDA also required a patient Medication Guide for valproate at this instance(219).

By 2011 other studies had been published concerning the safety profile of valproic acid and its use during pregnancy(220–223). Following the results of these epidemiologic studies the FDA issued a Drug Safety Communication informing the general public and HCPs that children born to mothers who take the anti-seizure medication valproate sodium, or related products, during pregnancy have an increased risk of lower cognitive test scores than children exposed to other anti-seizure medications during pregnancy. The long-term effects on cognitive development from exposure to valproate sodium or related products during pregnancy or whether these effects occur when fetal exposure is limited to less than the full duration of pregnancy, such as the first trimester, were however unknown at that point in time(224).

US Health Authority requested therefore an update to the valproic acid and related products' product information so that it could now capture the risk of lower cognitive test scores in the Warnings and Precautions section, the Use in Specific Populations: Pregnancy section. Medication Guides were also to be developed for this safety issue

and a drug safety podcast was released for HCPs(224,225). Current version of Medication Guide is present in Annex VII – Depakote US Medication guide.

Furthermore in 2013, the FDA made yet another safety announcement advising health care professionals and women in regard to the safety profile of valproate sodium and related substances, given the information from a recent study, suggesting a decrease in IQ scores in children whose mothers took them while pregnant. Label updates were once again recommended: valproate sodium and related products were now to be contraindicated and should not be taken by pregnant women for the prevention of migraine headaches and stronger warnings about use during pregnancy will also be included. Moreover, valproate's pregnancy category for migraine use was changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug)(226).

On the other hand, for valproate use in pregnant women with epilepsy or bipolar disorder, FDA recommended that valproate products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable. Valproate products will remain in pregnancy category D for treating epilepsy and manic episodes associated with bipolar disorder. With regard to women of childbearing age who are not pregnant, warnings were to be implemented for valproate not be taken for any condition unless the drug is considered essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking valproate products should also use effective birth control(226).

5.4 Quick comparison

Valproic acid and related substances have been approved and marketed for 38 to 50 years in US and EU markets respectively. From the review of literature article and published studies, both regulatory agencies have identified the same safety concerns in regard to the teratogenicity and the use of valproic acid and related products in children, women of childbearing potential and during pregnancy, particularly given the increased risk of congenital malformations, major structural abnormalities and serious neurodevelopmental effects. Over the years, these competent authorities have also taken several actions to inform both the healthcare practitioners and the general public of such safety issues, but also to address and mitigate these risks. In fact, updates on these risks were widely notified by the US medicines health authority in its website and through safety communications to the general public and even podcasts for the HCP. On

the other hand, the EMA website also includes a record of all final documents for each of the stages of the referrals and comprehensive transparency on the scientific rational for the safety regulatory actions taken. As a matter of fact, such regulatory actions include multiple updates to the product information and additional measures, common to both territories. The FDA requested manufactures to include a black box warning for fetal risk and a medication guide describing the risks of valproate for patients; while the EMA required MAHs to develop educational materials aimed to for HCPs (namely a guide for prescribers, a patient booklet, an acknowledgment of risk information form and a DHPC) as well as a drug utilisation study to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate.

Recent developments in regard to the to the use of valproate and related substances during pregnancy and in women of childbearing potential with no effective contraception in the treatment of manic episodes of bipolar disorder and on the need of additional RMM following the review of the effectiveness of the implemented RMM across all indications are being only discussed in the EU territory at this point in time.

A website is also available in the US territory providing patients and HCPs with some tools and information to learn more about valproic acid and its prescribing information, as well as further guidance on epilepsy and bipolar mania and its management. The medication guide can also be retrieved from here.

The distinct set of regulatory actions taken and attention given to valproate use in pregnancy and women of childbearing age can be justified not only by the structurally different pharmacovigilance mechanisms implemented, instruments available to regulators in each territory and post-marketing requirements, but also given the decision-making approaches of both organizations. Inconsistencies in both structure and content of the labelling information between EU and US territories and to some extent within in EU territories, given the approved indication for the treatment of migraines should be noted. Furthermore, one should take into consideration the fact that, in all of the safety reviews conducted for EU territory, the notification trigger has originated from a distinct a national competent authority, which could hint on the diversity of prioritization and analysis of new safety information for each of the member states, which only occurs in a plural union of states as the EU. No data was available in regard to overall patient exposure or prescription practices in both territories to allow further characterization or comparison.

6. Limitations

This analysis presents some important limitations, particularly the fact that all the information was retrieved from the public domain, including health authority websites which may not capture the entire set of information necessary. This is the clear case of US DHPC for which there is no current database of retrieval. Additionally, DHPC in the EU space were considered only for Portugal and the UK and do not account for any other safety communication which could have been distributed for other countries. Similarly, US withdrawals for commercial reasons were not available in the FDA website.

Another limitation is that only safety issues linked to DHPC and drug withdrawals and/or suspensions were fully evaluated. Other forms of safety-related actions, such as changes in the drug labelling, including additions and changes to the US BBW, or requests for post-authorisation safety studies were not analysed.

Additionally, for further characterizing medicinal products with regards to their safety-related regulatory actions, it would also have been interesting to consider the assessment history, for instance through the study of the PSUR submission frequency, as well as the conditions of the MA, including whether such medicinal products belong to the list of medicines under additional monitoring.

Finally, the exact date a medicinal product is launched on the market is not available in the public domain and hence the presented results may overestimate elapsed time between widespread prescribing of a drug and the emergence of major safety concerns and subsequent safety-driven regulatory actions.

7. Conclusion

The incomplete safety profile of new medicinal products and the limited knowledge available on the benefit-risk profile of a drug at the time of granting a marketing authorisation is a well-established fact. The natural history of approved drugs comprehends the discovery of new and important safety information in the post-marketing setting and hence its timely identification and the response to drug-related risks is a crucial part of the mission of pharmacovigilance, health authorities and pharmaceutical companies.

Over the years, multiple studies have analysed safety-related regulatory actions, mostly for particular settings, such as for specific drug groups (e.g. biologicals, orphan

medicines and exceptional circumstances/ conditional (accelerated) approval procedures) or individual countries.

However, the lack of an overall recent picture of safety-driven regulatory actions for medicinal products, both small molecules and biologics, and the significant implications for pharmacovigilance activities following the new legal frameworks in 2007 (for the US) and in 2012 (for the EU) were the triggers of this study. The proposed analysis of the safety-driven regulatory actions between 2010 and 2015, in either of these two territories, aimed to better characterise and compare recommendations provided by the EMA and FDA, to assess the apparent lack of harmony in addressing specific safety issues, and to present a specific scenario depictive of the comparison exercise.

On that regard, a comprehensive description of the history, organizational structure, processes and objectives of two of the major regulatory authorities was performed. Substantial differences between FDA and EMA pertaining to pharmacovigilance activities and safety-driven regulatory actions were illustrated. Simultaneously, similarities in terms of aims, responsibilities and objectives, and important collaborative initiatives between these two regions were also described.

The results obtained indicate DHPC are more frequently distributed in the EU than the US. However, the majority of the safety risks associated to marketed products in the US territory had been divulged to HCP and the general public by other risk communication tools available to the FDA. There was a prevalence of both safety driven DHPC and withdrawals for small molecules and data retrieved supports previous findings that differences have been shown to exist in the nature of the safety-related regulatory actions for biologicals compared with small molecules. For the latter, cardiac disorders related AE appear as a leading trigger for safety-driven regulatory actions and data suggests more efforts still need to be allocated for tackling medication error-related adverse events. Spontaneous reports continues to account for the majority of the source data for triggering safety driven DHPC in all regions, but findings for clinical trials and epidemiological studies supports the observed increment use these sources in identifying and evaluating safety issues. With regards to timing of regulatory action, 66.6% of the safety-related withdrawals were issued within 5 years after approval, while 50.4% of the safety driven DHPC were issued within 6 years after approval.

The use of valproic acid in children, women of childbearing potential and potential and during pregnancy given the associated risks of congenital malformations, major structural abnormalities and serious neurodevelopmental effects was chosen as case

study. The distinct set of regulatory actions taken can be justified not only by the structurally different pharmacovigilance mechanisms implemented and instruments available to regulators in each territory but also given the inconsistencies in both structure and content of the labelling information between EU and US territories and to some extent within in EU territories.

Overall, all of the above comparison exercises allowed for the discussion on legislative framework and processes of the FDA and the EMA, which if analysed can help improve public awareness and may allow for a better insight and understanding on matters of divergent drug approvals and post-marketing safety recommendations, either it being signal management activities, label updates, additional risk minimization measures and withdrawals/suspensions.

Moreover, the dynamic nature of regulatory processes for pharmaceutical risk management is still present on today's exciting pharmacovigilance landscape and future regulatory standardization and increased collaboration may still be necessary to further help in reducing redundancy and support the review/assessment processes for the benefit of regulators, pharmaceutical industries and the patients.

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9. Annexes

Annex I - DHPC distributed in Portugal for rivastigmine and medication errors

NOVARTIS

Teresa Carqueja, MD
Directora Médica

Novartis Farma
Produtos Farmacêuticos SA
Apartado 200
2711-901 Sintra
PORTUGAL

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28 de Abril de 2010

***Comunicação Dirigida aos Profissionais de Saúde* sobre a utilização inadequada e erros de medicação associados a Exelon® adesivo transdérmico.**

Caro(a) colega,
A Novartis, após acordo com a EMA e com as Autoridades Competentes Nacionais, gostaria de recordar aos Profissionais de Saúde a importância da utilização e aplicação adequadas de Exelon®[1] (adesivo transdérmico de rivastigmina).

Resumo

- **Foram notificados erros de medicação e utilização inadequada de Exelon® adesivo transdérmico, alguns dos quais resultaram em sobredosagem de rivastigmina. Os sintomas de sobredosagem incluem náuseas, vómitos, diarreia, hipertensão e alucinações.**
- **As causas mais frequentemente notificadas são a não remoção do adesivo e a aplicação concomitante de mais do que um adesivo.**
- **É importante que os profissionais de saúde instruam os seus doentes e prestadores de cuidados sobre a utilização apropriada do adesivo transdérmico e, em particular, que:**
  - **Apenas deve ser aplicado um adesivo transdérmico por dia sobre pele saudável, numa das localizações recomendadas: parte superior ou inferior das costas ou parte superior do braço ou do tórax.**
  - **O adesivo transdérmico deve ser substituído por um novo após 24 horas. O adesivo do dia anterior deve ser retirado antes de se aplicar o novo adesivo num local diferente do corpo.**
  - **Para minimizar a irritação cutânea, deve ser evitada a reaplicação no mesmo local durante 14 dias.**
  - **O adesivo transdérmico não deve ser cortado.**

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[1] [1] Na União Europeia, Exelon® adesivo transdérmico está indicado no tratamento sintomático da demência de Alzheimer ligeira a moderadamente grave. Exelon® adesivo transdérmico está disponível em duas dosagens: 4,6 mg /24 horas e 9,5 mg /24 horas. O tratamento deve ser iniciado com 4,6 mg /24 h. Se esta dose for bem tolerada de acordo com o medico assistente, e após um período mínimo de quatro semanas de tratamento, deve ser aumentada para 9,5 mg /24 h, que é a dose eficaz recomendada.

NOVARTIS

Informação adicional sobre erros de medicação e uso inadequado

Após o início da comercialização foram recebidas notificações de erros de medicação e utilização inadequada com Exelon® adesivo transdérmico. Os erros mais frequentemente notificados foram erros de administração do medicamento, técnica incorrecta de utilização do medicamento e administração de dose incorrecta. As causas mais frequentemente notificadas são a não remoção do adesivo e a aplicação concomitante de mais de um adesivo. Outros erros frequentes são a aplicação em zonas não recomendadas ou na mesma área durante várias semanas, o corte do adesivo e erros de dosagem (prescrição / dispensa). Os profissionais de saúde, os prestadores de cuidados ou os próprios doentes têm estado na origem destes erros.

Os casos de sobredosagem notificados resultaram de erros de medicação e utilização inadequada de Exelon® adesivo transdérmico (por ex.: aplicação de múltiplos adesivos ao mesmo tempo). Os sintomas típicos associados à sobredosagem incluem náuseas, vómitos, diarreia, hipertensão e alucinações. Podem também ocorrer bradicardia e/ou síncope, que podem estar associadas a mal-estar geral ou quedas. Tal como acontece com os erros de medicação e má utilização em geral, estas situações podem ter consequências clínicas graves, incluindo morte, se não forem corrigidas atempadamente e acompanhadas de forma adequada. Em caso de sobredosagem, todos os adesivos de Exelon® devem ser imediatamente retirados.

Por favor, consulte a secção 4.9 Sobredosagem do Resumo das Características do Medicamento para mais informação sobre as acções a tomar em caso de sobredosagem relacionada com Exelon® adesivo transdérmico.

Informação adicional sobre recomendações para os profissionais de saúde

Os profissionais de saúde devem estar bem informados sobre a utilização e administração correctas de Exelon® adesivo transdérmico, conforme descrito no Resumo das Características do Medicamento (RCM). Os médicos devem instruir adequadamente doentes e prestadores de cuidados antes do início da terapêutica com Exelon® adesivo transdérmico. A terapêutica com rivastigmina apenas deve ser iniciada se estiver disponível um cuidador para administrar e monitorizar regularmente o tratamento.

Contacte para notificar

Os profissionais de saúde devem notificar quaisquer reacções adversas associadas à utilização de Exelon® ao INFARMED I.P através da ficha de notificação de reacções adversas ou dos seguintes contactos: telefone 21 798 71 40, fax 21 798 73 97 e endereço electrónico farmacovigilancia@infarmed.pt.

Os acontecimentos adversos também podem ser notificados à Novartis através dos seguintes contactos: telefone 21 000 86 00, fax 21 000 88 25 e endereço electrónico clinicalsafety.pt@novartis.com.

NOVARTIS

Comunicação de informação

Caso tenha quaisquer questões ou necessite de informação adicional no que diz respeito ao uso de Exelon® (rivastigmina), por favor contacte o Departamento Médico (Dra. Teresa Carqueja) através do telefone 21 000 86 00.

Com os melhores cumprimentos,

NOVARTIS FARMA, Produtos Farmacêuticos S.A.

Teresa Carqueja
Directora Médica

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Annex II - DHPC distributed in the United Kingdom for rivastigmine and medication errors

NOVARTIS

13-APRIL-2010

Novartis Ref: EXE10-047

Direct Healthcare Professional Communication on **the inappropriate use of and medication errors associated with Exelon® 4.6 mg/24 h transdermal patch and Exelon® 9.5 mg/24 h transdermal patch.**

Dear colleague,
Novartis, in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA), would like to remind Healthcare Professionals of the importance of the proper use and application of Exelon® transdermal patch (rivastigmine transdermal patch) and the need to instruct patients and caregivers on correct application techniques for the use of Exelon Patch.[1]

Summary of key information

- **Medication errors and inappropriate use of Exelon® transdermal patch have been reported, some of these resulting in rivastigmine overdose. Symptoms of overdose include nausea, vomiting, diarrhoea, hypertension, and hallucinations.**
- **The most frequent reported causes are lack of patch removal and application of more than one patch at the same time.**
- **It is important for healthcare professionals to instruct patients and caregivers on the proper use of the transdermal patch and particularly that :**
    - **Only one transdermal patch should be applied per day to healthy skin on one of the recommended locations: the upper or lower back, or upper arm or chest**
    - **The patch should be replaced by a new one after 24 hours, and the previous day's patch must be removed before applying a new patch to a different skin location;**
    - **To minimize skin irritation, application to the same skin location within 14 days should be avoided.**
    - **The transdermal patch should not be cut into pieces.**

Further information on medication errors and inappropriate use

Post-marketing reports of medication errors and inappropriate use have been received with Exelon® transdermal patch. The most common errors reported were drug administration error, wrong technique in drug usage process, and incorrect dose administered. The most frequent reported causes are lack of patch removal and

[1] In the United Kingdom, Exelon® transdermal patch is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. Exelon® transdermal patch is available in two dosage strengths 4.6 mg /24 hours and 9.5 mg /24 hours. Treatment is started with 4.6 mg /24h. After a minimum of four weeks and if well tolerated according to the treating physicians, the daily dose should be increased to 9.5 mg /24h which is the recommended effective dose.

application of more than one patch at the same time. Other common errors are application on non-recommended sites or on the same area for several weeks, cutting the patch into several pieces, and error of dosages (prescription / dispensation). Healthcare professionals, caregivers, or the patients themselves have been involved in these errors.

Overdose with rivastigmine resulting from medication errors and inappropriate use of Exelon® transdermal patch (e.g. application of multiple patches at a time) has been reported. The typical symptoms reported in association with overdose include nausea, vomiting, diarrhoea, hypertension, and hallucinations. Bradycardia and/or syncope, that may be associated with malaise or falls, may also occur. As with medication errors and misuse in general, serious medical outcomes, possibly including death, may occur if the medication errors and misuse are not corrected in a timely manner and properly managed. In case of overdose, all Exelon® transdermal patches should be immediately removed. Please refer to section 4.9 Overdose in the attached Summary of Product Characteristics and Patient Information Leaflet for additional details concerning the proper management of overdose related to Exelon® transdermal patch.

Further information on recommendations to healthcare professionals

Healthcare professionals should be well informed on the proper use and administration of Exelon® transdermal patch as described in the Summary of Product Characteristics and must follow the instruction on "HOW TO USE EXELON" as described in Section 3 of the attached Patient Information Leaflet. Physicians should advise patients and caregivers accordingly prior to initiating therapy with Exelon® transdermal patch. Therapy with rivastigmine should only be started if a caregiver is available to regularly administer and monitor the treatment.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of Exelon to the MHRA. Reporting forms and information can be found at http://www.yellowcard.gov.uk. Adverse events should also be reported directly to Novartis Pharmaceuticals UK Ltd on 01276 698370.

Communication information

Should you have any questions or require additional information regarding the use of Exelon (rivastigmine), please contact Novartis Medical Information on 01276 698370.

Yours faithfully,

Dr. Tim Cave
Medical Director
Chief Scientific Officer UK
Novartis Pharmaceuticals UK

Enclosed.
Exelon Patch Summary of Product Characteristics
Exelon Patch Patient Information Leaflet

Annex III - DHPC distributed in the United States for rivastigmine and medication errors

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

September 13, 2010

IMPORTANT DRUG WARNING

Dear Healthcare Professional Communication **regarding medication errors associated with the use of Exelon® Patch (rivastigmine transdermal system).**

EXELON® PATCH (rivastigmine transdermal system) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease.

Dear Colleague,

Novartis Pharmaceuticals Corporation, in agreement with the Food and Drug Administration, would like to remind Healthcare Professionals of the importance of the proper use and application of Exelon® Patch (rivastigmine transdermal system) and the need to instruct patients and caregivers on correct application techniques for the use of Exelon Patch.

Key messages

- Medication errors with Exelon patches have resulted in serious adverse events; some cases have required hospitalization, and rarely, led to death.
- The majority of medication errors have involved not removing the old patch prior to applying a new one and the application of multiple patches at one time.
- **It is important for healthcare professionals to instruct patients and caregivers on the proper use of the transdermal patch and particularly that:**
    - **only one transdermal patch should be applied per day to healthy skin on only one of the recommended locations: the upper or lower back, or upper arm or chest;**
    - **the patch should be replaced by a new one after 24 hours, and the previous day's patch must be removed before applying a new patch to a different skin location;**
    - **to help minimize skin irritation, application to the same skin location within 14 days should be avoided; and**
    - **the transdermal patch should not be cut into pieces.**

Further information on medication errors

Novartis has received post-marketing reports of medication errors associated with the use of Exelon® Patch. The most common types of medication errors reported were drug administration error, wrong technique in drug usage process, and incorrect dose administered. The most frequently reported medication errors involve not removing the old patch prior to applying a new one and application of more than one patch at the same time. Other common errors are application on non-recommended sites or on the same area for several weeks, cutting the patch into several pieces, and dosing errors during prescribing or dispensing. Healthcare professionals, caregivers, or the patients themselves have been involved in these errors.

Overdose with rivastigmine has been reported. The typical symptoms reported in association with overdose include nausea, vomiting, diarrhea, hypertension, and hallucinations. Bradycardia or syncope that may be associated with malaise or falls, has also occurred. Serious medical outcomes, including death, may occur if medication errors involving Exelon® Patch are not corrected in a timely manner and properly managed. In case of overdose, all Exelon® patches should be immediately removed and no further patch should be applied for the next 24 hours. Please refer to section 10 Overdosage in the attached insert labeling for additional details concerning the proper management of overdose related to Exelon® Patch.

Further information and recommendations to healthcare professionals

Healthcare professionals should be well informed on the proper use and administration of Exelon® Patch as described in the attached insert labeling. Patients and caregivers must follow the instructions on "HOW TO USE EXELON" as described in the attached FDA-Approved Patient Labeling. Physicians should advise patients and caregivers accordingly prior to initiating therapy with Exelon® Patch.

Important Safety Information

Exelon Patch is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives, or other components of the formulation.

Medication errors with Exelon Patch have resulted in serious adverse events; some cases have required hospitalization, and rarely, led to death. The majority of medication errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time. Only one Exelon Patch should be worn at a time.

At higher-than-recommended doses, Exelon Patch use is associated with significant gastrointestinal adverse reactions, including nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss. For this reason, patients administered Exelon Patch should always be started at a dose of 4.6 mg/24 hours and titrated to the maintenance dose of 9.5 mg/24 hours. If treatment with Exelon Patch is interrupted for longer than three days, treatment should be reinitiated with the lowest daily dose to reduce the possibility of severe vomiting and its potentially serious sequelae. It is critical to inform patients and caregivers that if therapy has been interrupted for more than three days, the next dose should not be administered until they have discussed this with the physician.

In a clinical trial, the most commonly observed adverse reactions with Exelon Patch occurring at a frequency of at least 5% and greater than placebo with administration of 9.5 mg/24 hours

were nausea, vomiting, and diarrhea (7%, 6%, 6% for Exelon Patch 9.5 mg/24 hours versus 5%, 3%, 3% for placebo, respectively).

Weight should be monitored during therapy with Exelon Patch. Weight loss (≥7% of baseline weight) occurred in 3% of subjects receiving the 9.5 mg/24 hours dose of Exelon Patch in clinical trials. Patients with body weight below 50 KG may experience more adverse events and may be more likely to discontinue Exelon Patch due to adverse events.

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic drugs. Rivastigmine might interfere with the activity of anticholinergic medications.

Due to increased cholinergic activity, cholinesterase inhibitors may increase gastric acid secretion and/or have vagotonic effects on heart rate. Caution is recommended in patients with sick sinus syndrome, conduction defects, gastroduodenal ulcerative conditions (including those predisposed by concomitant medications), gastrointestinal bleeding, asthma or chronic obstructive pulmonary disease, urinary obstruction, and seizures.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of Exelon to the Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch .

Communication information

Should you have any questions or require additional information regarding the use of Exelon (rivastigmine), please contact Novartis Pharmaceuticals Corporation at 1-888-669-6682.

Todd Gruber, MD
Executive Director, Pharmacovigilance
Drug Safety & Epidemiology

Darlene Jody, MD
Head, Medical & Scientific Affairs
Specialty Medicines

Annex IV - HCP Booklet – Risks in Female patients

Important Information for Healthcare Professionals on the Risks of Valproate▼ in Female Patients

This booklet must be read before considering prescribing valproate. It is provided as part of the risk minimization measures developed to inform prescribers of the risks associated with the use of valproate by females of childbearing potential and during pregnancy.

This booklet was last updated in
January 2016

▼ This medicinal product is subject to additional monitoring.

This booklet provides up-to-date information about the risk of neurodevelopmental disorders in children of women who have taken valproate during pregnancy in addition to the known risk of congenital malformations in exposed babies.

This booklet should be used in conjunction with the Patient Guide. To learn more about valproate, please read the complete Summary of Product Characteristics before prescribing valproate.

Adverse event reporting

Adverse events should be reported. Reporting forms and information can be found at **www.mhra.gov.uk/yellowcard**

Adverse events should also be reported to the Sanofi drug safety department on **01483 554242**, or to the relevant manufacturer of the product if not Sanofi.

What you should know about the risks of valproic acid use in female patients

VALPROATE contains valproic acid, an active ingredient with known teratogenic effects which may result in congenital malformations. Available data also show that in utero exposure to valproate can be associated with an increased risk of developmental disorders. These risks are briefly described below.

1. Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of women with epilepsy exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29), which represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%[1]. Available data show the risk is dose dependent. The risk is greatest at higher doses (above 1g daily). A threshold dose below which no risk exists cannot be established based on available data.

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

2. Developmental disorders

Exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies[2–5] in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptic drugs[6]. Although the role of confounding cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long-term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population[7].

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)[8].

Treatment of female patients with valproate

A. Female child first prescription

After medical evaluation, if you are considering prescribing valproate to your patient:

✓ Confirm that treatment with valproate is appropriate for your patient (i.e. alternative treatments are ineffective or not tolerated).

✓ Discuss the following topics with your patient and relevant family members/ care-givers:

- Risks to pregnancy that are associated with the underlying condition;
- Risks related to treatment, including risks related to valproate when used in pregnancy;
- Need for an effective contraception method to avoid unplanned pregnancy;
- Need for regular review of treatment.

✓ Assess the most appropriate timing to provide advice on effective contraception methods and refer your patient to a specialist if needed.

✓ Ensure that your patient/family members/caregivers of the patient have understood the potential consequences when used in pregnancy and has/have an adequate level of understanding of the risks.

✓ Give a copy of the Patient Guide to your patient

✓ Complete the checklist with your patient and keep a copy in the patient's medical records.

✓ Advise your patient to contact you immediately if she thinks she might be pregnant or becomes pregnant.

✓ Plan to review the need for treatment when she is able to become pregnant.

B. Woman of childbearing age who is not planning pregnancy

After medical evaluation, you are considering prescribing valproate to your patient:

✓ Confirm that treatment with valproate is appropriate for your patient (i.e. alternative treatments are ineffective or not tolerated).

✓ Discuss the following topics with your patient:

- Risks to pregnancy that are associated with the underlying condition;
- Risks related to treatment, including risks related to valproate when used in pregnancy;
- Need for an effective contraception method to avoid unplanned pregnancy;
- Need for regular review of treatment.

✓ Assess the relevance of preconception counselling.

✓ Ensure that your patient has understood the potential risks to the child of using valproate during pregnancy and has an adequate level of understanding of the risks, and that she understands the importance of using contraception to avoid unplanned pregnancy.

✓ Give a copy of the Patient Guide to your patient.

✓ Complete the checklist with your patient and keep a copy in the patient's medical records.

✓ Advise your patient to contact you:

- if she thinks she might be pregnant or becomes pregnant;
- in case of any adverse events associated with her treatment.

C. Woman of childbearing age who is planning pregnancy

✓ Remind your patients of teratogenic risks and risks of developmental disorders that can be seriously debilitating when taking valproate during pregnancy but also the risks of untreated seizures or bipolar disorder.

✓ Reassess the benefit/risk of valproate therapy, whatever the indication:

- Consider if stopping treatment or switching to an alternative is appropriate.
- If, further to a careful evaluation of the risks and benefits, valproate treatment is to be continued:
  - ✓ It is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible.
  - ✓ The use of a prolonged-release formulation may be preferable to other treatment forms.

  There is no dose threshold considered to be without any risk but the risk of birth defects and developmental disorders is higher at greater doses.
- Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
- Folic acid supplementation may decrease the general risk of neural tube defects but there is some evidence that it does not reduce the risk of birth defects associated with in utero valproate exposure.

✓ Refer your patient to specialists for preconception advice.

✓ Ensure that your patient has understood the potential risks to the pregnancy, and has an adequate level of understanding of the risks.

✓ Give a copy of the Patient Guide to your patient.

✓ Complete the checklist with your patient and keep a copy in the patient's medical records.

✓ Advise your patient to contact their family doctor and specialist as soon as she thinks she might be pregnant or becomes pregnant in order to initiate appropriate pregnancy monitoring, including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations.

D. Woman with unplanned pregnancy

✓ Schedule an urgent consultation with your patient to review treatment as soon as possible to reconsider the benefits and risks of valproate.

✓ Explain why she should continue with her treatment until you have seen her, unless you are able to give other advice based on your assessment of the situation.

- If, further to a careful evaluation of the risks and benefits, valproate treatment is to be continued:
  - ✓ It is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible.
  - ✓ The use of a prolonged-release formulation may be preferable to other treatment forms.
- Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.

✓ Ensure that your patient:

- has fully understood the risks related to valproate and consider further counselling.
- has received the Patient Guide.

✓ Complete the checklist with your patient and keep a copy in the patient's medical records. This record is the opportunity to assess whether the patient has fully understood the risks.

✓ Initiate specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Summary

A. Female child first prescription

1. Explain potential risks of the disease itself as well as the future risks for the unborn child and the risks associated with use of valproate in pregnancy
2. Assess your patient's need for treatment with valproate
3. Inform your patient about the need to use effective contraception as soon as it is relevant
4. Ensure that your patient has received the Patient Guide
5. Where applicable, advise your patient to contact you immediately if she thinks she might be pregnant or becomes pregnant.

B. Woman of childbearing age who is not planning pregnancy

1. Explain potential risks of treatment and of untreated disease for the unborn child
2. Assess your patient's need for treatment with valproate
3. Inform your patient about the need to use effective contraception
4. Ensure that your patient has received the Patient Guide
5. Advise your patient to contact you immediately if she thinks she might be pregnant or becomes pregnant.

C. Woman of childbearing age who is planning pregnancy

1. Explain potential risks of the disease itself on the unborn child, independent from valproate's own risks.
2. Reassess benefit/risk of patient's therapy
3. Adapt current treatment
4. Advise your patient to contact you if she thinks she might be pregnant or becomes pregnant
5. Ensure that your patient has received the Patient Guide.

D. Woman with unplanned pregnancy

1. Inform her to keep taking her treatment until you have seen her
2. Schedule an urgent consultation
3. Re-assess the benefit/risk of her therapy
4. Ensure that your patient has understood the risks related to valproate and consider counselling
5. Ensure that your patient has received the Patient Guide.

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For further copies of this information booklet please contact Sanofi medical information department on

0845 372 7101

or email

UK-Medicalinformation@sanofi.com

SAGB.VPA.15.12.1440 January 2016

Annex V – Letter for Prescribers - Risks in Female patients

July 2017

Important Safety Information – Action needed – Please Read

Valproate medicines: only for use when no other treatment is effective or tolerated in girls, women of childbearing age, and women who are pregnant or planning pregnancy; important actions required

This letter is for specialists and specialist nurses/midwives managing patients treated with valproate-based medicines (sodium valproate [Epilim▼, Episenta▼]; valproic acid, sodium valproate [Epilim▼]; valproate semisodium [Depakote▼]), and general practitioners who provide primary care to these patients.

Dear Healthcare Professional

This letter is sent in follow-up to the communication issued by the Medicines and Healthcare products Regulatory Agency in January 2015, and a further mailing on behalf of all valproate manufacturers in February 2016. It supplements the Patient Safety Alert on valproate issued by the MHRA and NHS Improvement on 6 April 2017 and those subsequently sent in Scotland, Wales and Northern Ireland. Previous communications advised that **valproate should only be used in girls, women of child bearing age and those who are pregnant or planning pregnancy when no other treatment is effective or tolerated.** This is because **children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30–40% of cases) and/or congenital malformations (in approximately 10% of cases).**

Despite these communications, valproate continues to be used frequently in this patient group. A recent survey of women of childbearing age taking valproate for epilepsy has identified that 20% had not been informed of these risks and 80% had not received any written information from their HCPs. Prescribing data show little change in the rate of prescription of valproate to girls and women of childbearing age since 2015, regardless of the indication. **A significant number of patients remain at risk of inadvertent exposure to valproate in pregnancy and further efforts and actions are needed from prescribers and dispensers of valproate to reduce the risks that this entails**.

Please turn over to see the actions that you are being asked to perform.

THE RISK: Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30–40% of cases) and/or congenital malformations (in approximately 10% of cases).

For this reason, you are asked to take the following actions:

- **DO NOT prescribe valproate to female children, female adolescents, women of childbearing potential, or pregnant women UNLESS other treatments are not effective or other treatments are not tolerated.**

- **ONLY doctors experienced in managing epilepsy or bipolar disorder should prescribe valproate to these patients, and must supervise ongoing treatment with a review annually, at a minimum.**

- **If you prescribe valproate YOU MUST INFORM all girls and women of childbearing age of the following, and ensure the information is understood:**
    1. **the risks to a baby from taking valproate during pregnancy;**
    2. **the need to use effective contraception while taking valproate;**
    3. **the need for regular (at least annual) review of treatment;**
    4. **the need to rapidly consult you if planning a pregnancy or becomes pregnant**

- **If you are a General Practitioner caring for girls or women of childbearing age taking valproate, YOU MUST ENSURE that your patient is seen by the specialist responsible for prescribing valproate at least annually, and as a matter of urgency if she is planning pregnancy or becomes pregnant.**

To support effective prescribing practice, the enclosed booklet "Important Information for Healthcare Professionals on the Risks of Valproate in Female Patients" provides information on the risks and actions you are required to take.

Also enclosed is an information booklet to provide to patients: "Valproate Patient Guide". This is intended to be distributed by specialists initiating and supervising treatment with valproate, and you should give a copy to every girl or woman of childbearing age taking valproate. In addition, General Practitioners and Pharmacists are encouraged to provide copies to these patients who are not already aware of the information, alongside a reminder card provided by pharmacists when valproate is dispended.

Additional copies of both booklets can be ordered, at no cost, by contacting Sanofi Medical Information on 0845 372 7101 or by emailing UK-medicalinformation@sanofi.com. They can also be downloaded from the EMC website (www.medicines.org.uk) where they will be found linked with entries for medicines containing valproate.

Finally, a checklist has been developed to use during patient consultations. This will help ensure that the key points regarding the risks of valproate are discussed with the patient, and then when valproate is prescribed it is not being used inappropriately. This should be used with every girl and women of childbearing age when valproate is FIRST PRESCRIBED and at EVERY subsequent review, at least annually.

The checklist is printed at the end of this letter, and additional copies can be downloaded from the EMC website (www.medicines.org.uk) where they will be found linked with entries for medicines containing valproate.

You may find it helpful to keep this letter, and refer especially to pages 2 and 4 when initiating or reviewing valproate in girls and women of childbearing age. It may be helpful to display these two pages as a ready reference for relevant prescribers.

Call for reporting:
All valproate-containing drugs are subject to additional monitoring. Any suspected adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to the pharmaceutical company proving the valproate preparation, contactable at the address indicated on the packaging, in the Summary of Product Characteristics or Patient Leaflet, or in the BNF.

Thank you for your co-operation in following these requirements. This will help ensure appropriate use of valproate in this patient group and minimise these significant risks.

Yours faithfully

Dr Andrew Hockey FFPM
Consultant in Pharmaceutical Medicine, and
Medical Head – General Medicines, Sanofi UK

This letter is sent at the request and with the approval of the Medicines and Healthcare products Regulatory Agency.

Treatment with valproate for female patients: Checklist for patients and prescribers

A. Checklist for Prescribers

Name of Patient /carer	
I confirm that the above named patient does not respond adequately or tolerate other treatments or medical treatments and requires valproate	☐

I have discussed with the above named Patient/carer:

The overall risks of an approximately 10% chance of birth defects and up to 30–40% chance of a wide range of early developmental problems that can lead to significant learning difficulties in children exposed to treatment with valproate during pregnancy.	☐
Individual risk can be minimised by use of the lowest possible effective dose	☐
The need for contraception (if child bearing age)	☐
The need for regular review of the need for treatment	☐
The need for urgent review if the patient is planning a pregnancy	☐
I have given the patient/carer a copy of the patient information booklet	☐

Name of Prescriber **Date**

B. Patient /Carer Checklist

I understand:	
Why treatment with valproate rather than another medicine is considered necessary for me	☐
The risks of an approximately 10% chance of birth defects and up to 30–40% chance of a wide range of early developmental problems that can lead to significant learning difficulties in children exposed to treatment with valproate during pregnancy.	☐
That I am advised to use contraception if not planning a pregnancy	☐
That my treatment should be reviewed regularly	☐
That I should request an urgent review if planning a pregnancy PRIOR to attempting to conceive	☐

Name of Patient/ Carer **Date**

Annex VI – Poster- Dispensary - Risks in Female patients

FOR DISPENSARY USE ONLY

WARNING ON USE OF VALPROATE▼

THE RISK – WHO AND WHAT

Valproate should only be used in girls, women of child bearing age and those who are pregnant or planning pregnancy, when other treatments are ineffective or not tolerated.

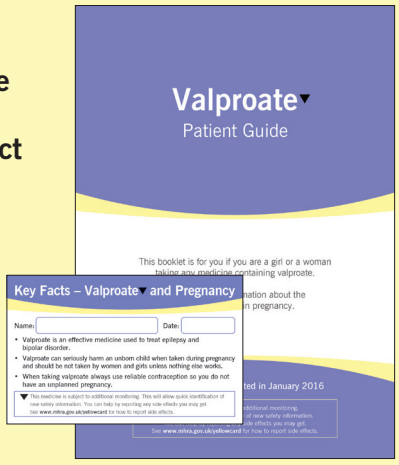
Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to **30-40%** of cases) and congenital malformations (in approximately **10%** of cases).

To support effective practice, *Valproate Patient Cards* and *Valproate Patient Guides* are available for you to provide to female patients taking valproate.

These materials highlight the risks of taking valproate whilst pregnant and remind patients use effective contraception and to see their prescriber urgently should they be planning, or become, pregnant.

ACTION FOR THE PHARMACIST/PHARMACY STAFF

- ✓ **When dispensing any valproate preparation to female children, female adolescents, women of childbearing potential or pregnant women CHECK that their prescriber has discussed the risks of in utero exposure with them and they are aware of these.**
- ✓ **If the prescriber HAS NOT DISCUSSED the risk with the patient, contact the prescriber and remind them of their responsibility to do so and ask them to arrange an urgent follow-up appointment with the patient.**
- ✓ **PROVIDE a *Valproate Patient Card* every time you dispense a valproate preparation to female children, female adolescents, and women of childbearing potential or pregnant woman.**
- ✓ **ASK if they have received a *Valproate Patient Guide* (booklet), and if not provide a copy.**
- ✓ **ADVISE to always use contraception and to see their prescriber urgently should they be planning, or become, pregnant.**



Copies of the *Valproate Patient Guide* and *Valproate Patient Cards* can be ordered, at no cost, by contacting Sanofi Medical Information on

0845 372 7101 or by emailing **UK-medicalinformation@sanofi.com**

The *Patient Guide* and *Cards* can also be downloaded from the EMC website

www.medicines.org.uk

where it will be found linked with entries for medicines containing valproate.

CALL FOR REPORTING

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your patients may get. See **www.mhra.gov.uk/yellowcard** for how to report side effects.

June 2017
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Annex VII – Depakote US Medication guide

MEDICATION GUIDE

DEPAKOTE ER (dep-a-kOte)

(divalproex sodium)

Extended Release Tablets

DEPAKOTE (dep-a-kOte)

(divalproex sodium)

Tablets

DEPAKOTE (dep-a-kOte)

(divalproex sodium delayed release capsules)

Sprinkle Capsules

DEPAKENE (dep-a-keen)

(valproic acid)

Capsules and Oral Solution

Read this Medication Guide before you start taking Depakote or Depakene and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about Depakote and Depakene?

Do not stop taking Depakote or Depakene without first talking to your healthcare provider.

Stopping Depakote or Depakene suddenly can cause serious problems.

Depakote and Depakene can cause serious side effects, including:

1. **Serious liver damage that can cause death, especially in children younger than 2 years old.** The risk of getting this serious liver damage is more likely to happen within the first 6 months of treatment.
   Call your healthcare provider right away if you get any of the following symptoms:
   - nausea or vomiting that does not go away
   - loss of appetite
   - pain on the right side of your stomach (abdomen)
   - dark urine
   - swelling of your face
   - yellowing of your skin or the whites of your eyes

   In some cases, liver damage may continue despite stopping the drug.
2. **Depakote or Depakene may harm your unborn baby.**
   - If you take Depakote or Depakene during pregnancy for any medical condition, your baby is at risk for serious birth defects that affect the brain and spinal cord and are called spina bifida or neural tube defects. These defects occur in 1 to 2 out of every 100 babies born to mothers who use this medicine during pregnancy. These defects can begin in the

first month, even before you know you are pregnant. Other birth defects that affect the structures of the heart, head, arms, legs, and the opening where the urine comes out (urethra) on the bottom of the penis can also happen.

- Birth defects may occur even in children born to women who are not taking any medicines and do not have other risk factors.
- Taking folic acid supplements before getting pregnant and during early pregnancy can lower the chance of having a baby with a neural tube defect.
- If you take Depakote or Depakene during pregnancy for any medical condition, your child is at risk for having a lower IQ.
- There may be other medicines to treat your condition that have a lower chance of causing birth defects and decreased IQ in your child.
- Women who are pregnant must not take Depakote or Depakene to prevent migraine headaches.
- **All women of child-bearing age should talk to their healthcare provider about using other possible treatments instead of Depakote or Depakene. If the decision is made to use Depakote or Depakene, you should use effective birth control (contraception).**
- Tell your healthcare provider right away if you become pregnant while taking Depakote or Depakene. You and your healthcare provider should decide if you will continue to take Depakote or Depakene while you are pregnant.
  Pregnancy Registry: If you become pregnant while taking Depakote or Depakene, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.

3. **Inflammation of your pancreas that can cause death.**

   Call your healthcare provider right away if you have any of these symptoms:
   - severe stomach pain that you may also feel in your back
   - nausea or vomiting that does not go away

4. **Like other antiepileptic drugs, Depakote or Depakene may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

   Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - attempts to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses

- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop Depakote or Depakene without first talking to a healthcare provider. Stopping Depakote or Depakene suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy can cause seizures that do not stop (status epilepticus).

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What are Depakote and Depakene?

Depakote and Depakene come in different dosage forms with different usages.

Depakote Tablets and Depakote Extended Release Tablets are prescription medicines used:

- to treat manic episodes associated with bipolar disorder.
- alone or with other medicines to treat:
  - complex partial seizures in adults and children 10 years of age and older
  - simple and complex absence seizures, with or without other seizure types
- to prevent migraine headaches

Depakene (solution and liquid capsules) and Depakote Sprinkles are prescription medicines used alone or with other medicines, to treat:

- complex partial seizures in adults and children 10 years of age and older
- simple and complex absence seizures, with or without other seizure types

Who should not take Depakote or Depakene?

Do not take Depakote or Depakene if you:

- have liver problems
- have or think you have a genetic liver problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)
- are allergic to divalproex sodium, valproic acid, sodium valproate, or any of the ingredients in Depakote or Depakene. See the end of this leaflet for a complete list of ingredients in Depakote and Depakene.
- have a genetic problem called urea cycle disorder
- are pregnant for the prevention of migraine headaches

What should I tell my healthcare provider before taking Depakote or Depakene?

Before you take Depakote or Depakene, tell your healthcare provider if you:

- have a genetic liver problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)
- drink alcohol
- are pregnant or breastfeeding. Depakote or Depakene can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take Depakote or Depakene.
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, herbal supplements and medicines that you take for a short period of time.

Taking Depakote or Depakene with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist each time you get a new medicine.

How should I take Depakote or Depakene?

- Take Depakote or Depakene exactly as your healthcare provider tells you. Your healthcare provider will tell you how much Depakote or Depakene to take and when to take it.
- Your healthcare provider may change your dose.
- Do not change your dose of Depakote or Depakene without talking to your healthcare provider.
- **Do not stop taking Depakote or Depakene without first talking to your healthcare provider**. Stopping Depakote or Depakene suddenly can cause serious problems.
- Swallow Depakote tablets, Depakote ER tablets or Depakene capsules whole. Do not crush or chew Depakote tablets, Depakote ER tablets, or Depakene capsules. Tell your healthcare provider if you cannot swallow Depakote or Depakene whole. You may need a different medicine.
- Depakote Sprinkle Capsules may be swallowed whole, or they may be opened and the contents may be sprinkled on a small amount of soft food, such as applesauce or pudding. See the Patient Instructions for Use at the end of this Medication Guide for detailed instructions on how to use Depakote Sprinkle Capsules.
- If you take too much Depakote or Depakene, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking Depakote or Depakene?

- Depakote and Depakene can cause drowsiness and dizziness. Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking Depakote or Depakene, until you talk with your doctor. Taking Depakote or Depakene with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive a car or operate dangerous machinery until you know how Depakote or Depakene affect you. Depakote and Depakene can slow your thinking and motor skills.

What are the possible side effects of Depakote or Depakene?

- See **"What is the most important information I should know about Depakote or Depakene?"**

Depakote or Depakene may cause other serious side effects including:

- **Bleeding problems:** red or purple spots on your skin, bruising, pain and swelling into your joints due to bleeding or bleeding from your mouth or nose.
- **High ammonia levels in your blood:** feeling tired, vomiting, changes in mental status.
- **Low body temperature (hypothermia):** drop in your body temperature to less than 95^0F, feeling tired, confusion, coma.
- **Allergic (hypersensitivity) reactions:** fever, skin rash, hives, sores in your mouth, blistering and peeling of your skin, swelling of your lymph nodes, swelling of your face, eyes, lips, tongue, or throat, trouble swallowing or breathing.
- **Drowsiness or sleepiness in the elderly.** This extreme drowsiness may cause you to eat or drink less than you normally would. Tell your doctor if you are not able to eat or drink as you normally do. Your doctor may start you at a lower dose of Depakote or Depakene.

Call your healthcare provider right away, if you have any of the symptoms listed above.

The common side effects of Depakote and Depakene include:

- nausea
- headache
- sleepiness
- vomiting
- weakness
- tremor
- dizziness
- stomach pain
- blurry vision
- double vision
- diarrhea
- increased appetite
- weight gain
- hair loss
- loss of appetite
- problems with walking or coordination

These are not all of the possible side effects of **Depakote or Depakene**. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Depakote or Depakene?

- Store Depakote Extended Release Tablets between 59°F to 86°F (15°C to 30°C).

- Store Depakote Delayed Release Tablets below 86°F (30°C).
- Store Depakote Sprinkle Capsules below 77°F (25°C).
- Store Depakene Capsules at 59°F to 77°F (15°C to 25°C).
- Store Depakene Oral Solution below 86°F (30°C).

Keep Depakote or Depakene and all medicines out of the reach of children.

General information about the safe and effective use of Depakote or Depakene

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Depakote or Depakene for a condition for which it was not prescribed. Do not give Depakote or Depakene to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Depakote or Depakene. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Depakote or Depakene that is written for health professionals.

For more information, go to www.rxabbvie.com or call 1-800-633-9110.

What are the ingredients in Depakote or Depakene?

Depakote:

Active ingredient: divalproex sodium

Inactive ingredients:

- **Depakote Extended Release Tablets:** FD&C Blue No. 1, hypromellose, lactose, microcrystalline cellulose, polyethylene glycol, potassium sorbate, propylene glycol, silicon dioxide, titanium dioxide, and triacetin. The 500 mg tablets also contain iron oxide and polydextrose.
- **Depakote Tablets:** cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, and vanillin.

  Individual tablets also contain:
  125 mg tablets: FD&C Blue No. 1 and FD&C Red No. 40,
  250 mg tablets: FD&C Yellow No. 6 and iron oxide,
  500 mg tablets: D&C Red No. 30, FD&C Blue No. 2, and iron oxide.
- **Depakote Sprinkle Capsules:** cellulosic polymers, D&C Red No. 28, FD&C Blue No. 1 gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.

Depakene:

Active ingredient: valproic acid

Inactive ingredients:

- **Depakene Capsules:** corn oil, FD&C Yellow No. 6, gelatin, glycerin, iron oxide, methylparaben, propylparaben, and titanium dioxide.
- **Depakene Oral Solution:** FD&C Red No. 40, glycerin, methylparaben, propylparaben, sorbitol, sucrose, water, and natural and artificial flavors.

Depakote ER:

250 mg is Mfd. by AbbVie LTD, Barceloneta, PR 00617
500 mg is Mfd. by AbbVie Inc., North Chicago, IL 60064 U.S.A. or
AbbVie LTD, Barceloneta, PR 00617
For AbbVie Inc., North Chicago, IL 60064 U.S.A.

Depakote Tablets:

Mfd. by AbbVie LTD, Barceloneta, PR 00617
For AbbVie Inc., North Chicago, IL 60064, U.S.A.

Depakote Sprinkle Capsules:

AbbVie Inc., North Chicago, IL 60064, U.S.A.

Depakene Capsules:

Mfd. by Banner Pharmacaps, Inc., High Point, NC 27265 U.S.A.
For AbbVie Inc., North Chicago, IL 60064, U.S.A.

Depakene Oral solution:

Mfd. by AbbVie Inc., North Chicago, IL 60064, U.S.A.
OR by DPT Laboratories, Ltd., San Antonio, TX 78215, U.S.A.
For AbbVie Inc., North Chicago, IL 60064, U.S.A.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: March 2017

03-B501

Annex VIII - Supplementary Data File

The accompanying Excel spreadsheet shows the raw data collated and used for the analysis of safety-related regulatory actions in the EU and US territories with regards to direct communication with Health Care Providers and withdrawals.

Filename: Raw_data_Ana_Tiago