Investigating the Statistical and Policy Frameworks Used to Gauge Potential Pharmacotherapy Recalls: A Scoping Review

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Introduction

- Canada's adverse drug reaction (ADR) frameworks are grounded in the *Protecting Canadians from Unsafe Drugs Act* (Vanessa's Law) and offers changes to the *Food and Drug Act*.
- Pharmacovigilance is a key safeguard in protecting patients, as potential adverse drug reactions (ADRs) are estimated to cause 3-7% of hospital admissions.
- Methodologies range from variations of case-controls studies to data mining/predictive analytics.
- Several key metrics, including the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), amongst others, are commonly used to establish a threshold for further investigation.
- Adequate policy frameworks provide the foundation for proper data collection and sound statistical analysis (e.g. mandatory reporting and centralized ADR databases).

Purpose

- To identify the statistical metrics and methods used in determining pharmacotherapy recalls, with a focus on Canada's existing framework.
- To investigate the advantages and disadvantages of specific approaches employed in signals management.

Objectives

- Develop an understanding and compare the difference between approaches used in signals management from the US FDA, Health Canada, and EU EMA.
- Translate possible strategies into a Canadian context to inform best practices.

Methodology/Methods

Data Collection:

- A literature search was conducted with PubMed, SCOPUS, and MEDLINE.
- Grey literature from the FDA, Health Canada, and the European Medicines Agency, mainly white papers, were also included in this review.

Data Analysis:

- Data charting as per JBI's Manual for Evidence Synthesis.
- PICO data compared with each health agency's methods and measures.
- Canada's ADR methods was examined in conjunction with international standards.

Results

Generic Pharmacotherapy Recall Process

ADR Data Collection and Management → Spontaneous ADR Generation & Data Analysis → Risk Mitigation for HCPs and Patients

Critical Points	Descriptions
Data Collection for ADRs	- In Canada, ADR reporting is mandatory only for hospitals, while independent clinics and private care facilities report on a voluntary basis. - Hospitals constitute a small portion of ADR reports (6%), most come from Marketing Authorization Holders (MHA). - Data collected is stored in HC's central database under the Canada Vigilance Program (now named MedEffect). - Foreign ADR reports are also examined; foreign reports outnumber domestic reports by a factor of 12x. - Other sources of ADR reports include case studies from the literature, WHO Vigimed, Periodic Safety Update Reports (PSURs), amongst others.
Signals Generation / Data Analysis	- HC relies on the Proportional Reporting Ratio (PRR) to trigger manual investigation. - Specific statistical methods used by Health Canada are not public, although they cite the use of Chi-squared, likelihood ratio, amongst other tests. - There appears to be no standardized tests (or combination of tests) or methods based on classes of drugs, although this is a commonality shared with EU EMA and the US FDA. - The current pipeline for signals generation and data analysis may take months to complete while the predictive value of PRR/ROR is most effective in the first year. - Causal relationship are established and weighed against potential downside and benefits prior to risk mitigation; this is standard practice across all pharmacovigilance agencies.
Risk Mitigation / Market Communications	- Once a risk to patients have been established, a wide spectrum of options are available (e.g. total recall, label changes, advisories, etc.) - Additional studies may be conducted, or MAHs may be required to conduct additional post-market monitoring activities (e.g. PSURs).

Conclusions and Implications

- The existing regulatory framework in Canada does not enable adequate data collection. Since only hospitals are required to report ADRs, a large part of the medical establishment (e.g. private clinics, LTC home) are excluded. This may contribute to unintentional widespread under-reporting and affect HC's ability to evaluate ADRs and conduct signals management.
- There is a disproportionate influence from industry in determining what ADRs are reported to HC. This is turn, poses a systemic conflict of interest as statistical analyses are rendered less effective because reports may be skewed.
- Unlike the EU EMA, there lacks transparency with how HC analyzes spontaneous ADR reports.
- There needs to be an expedited means to consolidate all available sources of data into a predictive platform that will automatically generate and evaluate ADR signals since the predictive value of reporting ratio drops off after 1 year (according to EU EMA).
- There appears to be inadequate post-market risk management. When a drug recall is determined, there are no effective means to communicate to healthcare providers and patients; this issue is most widespread with minor ADRs.
- There remains a need to validate different statistical metrics used in signals management. This issue is not unique to Canada, but for the field of pharmacovigilance. The EU EMA is currently a leader in validating their research methods.

Key References

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