# Postmarket Safety Communication for Protection of Public Health: A Comparison of Regulatory Policy in Australia, Canada, the European Union, and the United States

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

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

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

Since the rofecoxib controversy, postmarket regulation has changed considerably in the United States and the European Union,[3,4] underpinned by significant legislative amendments.[5–8] With international convergence and harmonization in pharmaceutical policy and standards,[9,10] these changes have had a global influence on other agencies, including Australian and Canadian regulators. An approach known as "life cycle regulation" now dominates, characterized by data collection and risk minimization planning in the premarket period and an expanded range of capabilities post marketing to identify, assess, and respond to evolving risks, including mandatory postmarketing studies and stronger conditions for safer use (**Box 1**).

Part of the rationale for life cycle regulation is that excessive risk aversion on the part of regulators could prevent patients from receiving the benefits of drug treatment. Accordingly, proponents of life cycle regulation contend that uncertainties about safety should not delay access to medicines, particularly as some adverse effects can only be identified post marketing.[3,11,12] Instead, patient harm can be avoided or minimized by proactive risk management.[1,12] Postmarket studies, monitoring, and communication of emerging

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**Box 1 Features of life cycle risk management regulation**

**At Marketing Approval**

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

- Further research (i.e., postmarket studies)
  - For the EMA and national EU regulators, this includes "postauthorization safety studies" and patient/disease registries (which may be voluntary or mandated)
  - For the FDA, this includes "postmarket requirements" (mandated) and "postmarket commitments" (agreed/voluntary).
- Routine or intensive monitoring of cases in ongoing trials or more detailed collection of spontaneous adverse event reports
- Labeling in the product information[a] (e.g., contraindications, dose restrictions, limiting indications and safety information)
- Educational and other interventions
  - Programs to influence and control the use of drugs by clinicians (e.g., DHPC[b] letters, consumer guides, educational materials and interventions, controlled distribution, and programs to prevent pregnancy in women taking teratogenic drugs, e.g., isotretinoin (called additional risk minimization measures by EU regulators and risk evaluation and mitigation strategies (REMS) by the FDA).

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

**Post Marketing**

Regulatory interventions include (as above):

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

[a]Product information encompasses the approved prescribing information (for healthcare professionals), consumer information, and in some cases, package inserts and labeling. Prescribing information is known in Australia as "Product information," in Canada as the Product Monograph, in the European Union as the "Summary of Product Characteristics," and in the United States as "Prescribing information."

[b]DHPC, Direct healthcare professional communications (European Union) – also known in the United States as "Dear Health Care Provider Letters" and in Canada as "Dear Health Care Professional Letters." EMA, European Medicines Agency; FDA, US Food and Drug Administration (United States); TGA, Therapeutic Goods Administration (Australia).

safety issues are key safeguards intended to ensure that unexpected harms are detected quickly and their impact is minimized.

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

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

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

## BASIS FOR THIS REVIEW

### Aims

Differences in regulatory policy may explain some variance in safety warnings, but major regulators' policies have not been compared in the scientific literature to date. Here we review relevant policies of the EMA, the FDA, Health Canada, and the Australian Therapeutic Goods Administration (TGA). Our objective was to assess current regulatory policies for postmarket

safety advisories and the related regulatory contexts focusing on governance, legislated authority, capability, and transparency of regulatory actions.

### Approach to the review

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

Excluded from the review were also other mechanisms that regulators use for postmarket safety communication, mainly changed wording in product information and "risk minimization" measures, such as educational resources.[29,30] Safety advisories differ from these forms of communication in their more expedited nature, attempting to actively communicate and publicize new information, sometimes before the risk is fully understood.

**Box 2 Analytical framework for postmarket safety communication policies**

**Governance:**
- Responsibility for assessing safety issues
- Responsibility for communicating and disseminating postmarket safety information
- Mechanisms and extent of public participation in decision making about postmarket safety and communications

**Legislative authority:**
- Authority to issue warnings and postmarket safety advisories
- Authority to require companies to issue direct healthcare professional communications

**Role of industry:**
- Industry involvement in postmarket safety communication and related regulatory activity

**Risk communication capability:**
- Goals of regulatory communication, in particular regarding behavior change
- Methods of communicating postmarket issues
- Monitoring and measurement of effectiveness
- Guidelines for writing and communicating risk
- Risk communication priority/strategy

**Transparency:**
- Minutes of expert committee meetings
- Documents explaining how regulatory decisions were made
- Accessibility of postmarket safety data

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

- Governance for postmarket safety communication and the extent of public participation in decision making about advisories
- Legislative authority for regulators to issue postmarket safety advisories or require industry to issue DHPCs
- The role of industry
- Risk communication capability, including how regulators communicate postmarket safety issues and their emphasis on behavioral change[35,36]
- Policy support for transparency regarding postmarket safety issues

Information for our review was gathered from relevant governing legislation related to safety advisories and systematic searches of government and regulators' websites for policy documents, guidelines for industry, information for the public, reports, and evaluations of relevant policies. (**Supplementary Materials – MethodsS1**).

## GOVERNANCE FOR POST MARKET SAFETY AND RISK MINIMIZATION

Within regulatory agencies, responsibility for postmarket safety communication can span different units according to their function (**Figure 1**). Safety advisories may form part of an overall communication strategy or may accompany other risk minimization measures as indicated in **Box 1**.

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

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

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

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

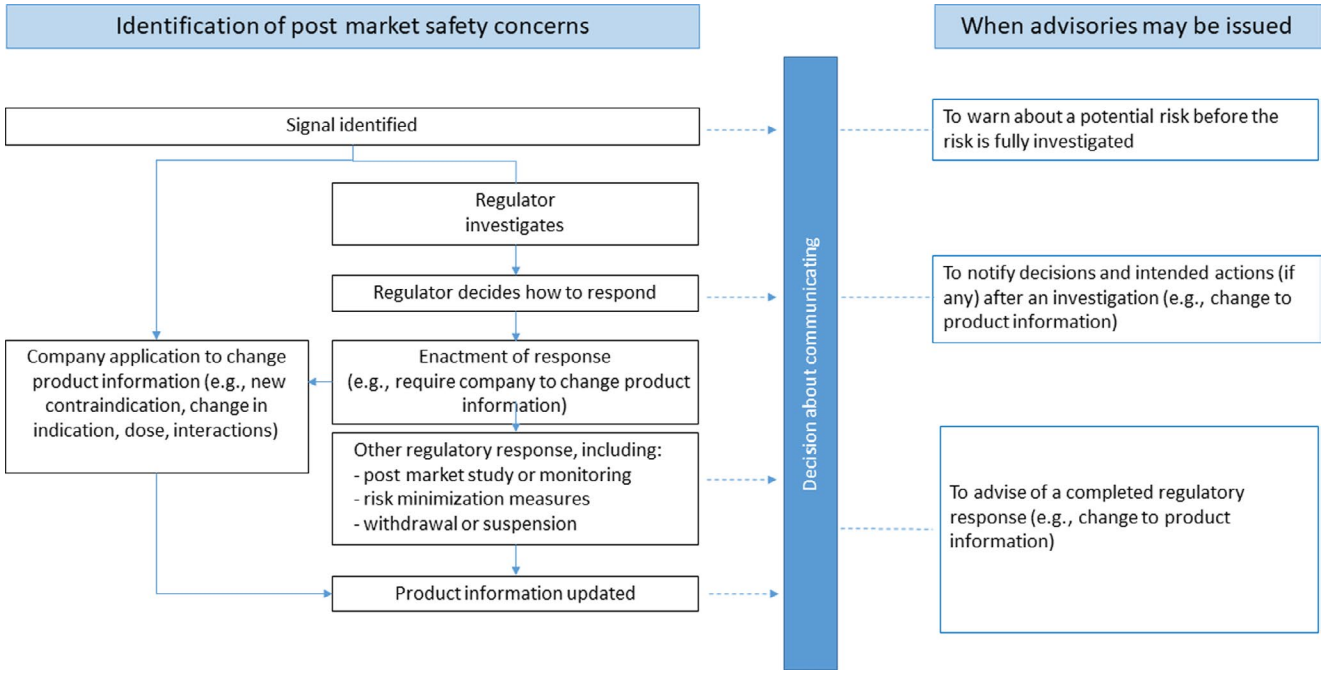


**Figure 1** Timing of advisories and identification of postmarket safety issues. [Colour figure can be viewed at wileyonlinelibrary.com]

### Differences among regulators

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

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

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

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

**EMA.** Since enactment of the 2012 EU pharmacovigilance legislation, responsibility for postmarket safety has been centralized in the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), replacing the Pharmacovigilance Working Party that advised the Committee for Medicinal Products for Human Use (CHMP).[45] Before the 2012 legislation, final decision making for pharmacovigilance was largely managed by EU countries' national regulatory agencies, with less consistency between countries.[46] The PRAC comprises representatives of EU regulatory agencies, individual scientific experts, and consumer and healthcare professional representatives. PRAC members take "rapporteur" roles for specific products, supported by their respective national regulatory agency and EMA staff. The PRAC makes recommendations to governing bodies within the EMA: to the CHMP for products centrally authorized across the European Union (after assessment by the EMA on behalf of all member states) by the European Commission, and to the Coordination Group for Mutual Recognition and Decentralized Procedures—Human for nationally authorized medicines, for which national EU regulators are the competent authorities.

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

For the EMA, public participation in regulatory decisions includes consumer, healthcare professional and additional expert representation on the PRAC, and public hearings. Public hearings are authorized by EU legislation but are held only when regulators consider them appropriate.[5] Public hearings have been held to discuss consumer perspectives on risk management of valproate teratogenicity and serious adverse effects of fluoroquinolones.[47,48]

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

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

**Health Canada.** Health Canada's governance of postmarket safety is shared across different directorates within the Health Products and Food Branch. The Marketed Health Products Directorate is responsible for postmarket issues including surveillance and risk communication (which is managed by the Office of Policy, Risk Advisory, and Advertising).[51,52] Responsibility for changes to prescribing information rests elsewhere, with the directorates responsible for premarket assessments and approval (the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate). Decisions regarding whether, for example, a postmarket prescribing information change necessitates an advisory therefore relies on consultation between different directorates.

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

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

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

TGA staff are primarily responsible for assessing postmarket safety issues and determining the appropriate response. The TGA had a dedicated expert advisory committee for postmarket safety until 2017, when it was abolished and its functions integrated into a single committee dealing with both prescription and nonprescription medicines. The current Advisory Committee on Medicines is consulted not only on premarket matters, primarily drug approvals, but also postmarket safety matters including emerging safety signals and risk management plans. The membership includes one consumer representative.[55] TGA regulations require public consultation for changes in scheduling (rules governing restrictions on access such as classification of medicines to prescription-only or over the counter), for which a separate committee provides advice, but not for other safety-related actions.[56,57]

## LEGAL AUTHORITY FOR POSTMARKET SAFETY ADVISORIES AND THE ROLE OF INDUSTRY

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

### Differences among regulators

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

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

FDA *Drug Safety Communication,* the FDA's primary postmarket safety communication, includes information for both healthcare professionals and consumers. It is disseminated via the FDA's website, email, and social media and described as "FDA's independent analysis of emerging information and FDA's scientific judgment as to the appropriate communication of this emerging

drug safety information to the public." Industry's role is limited to providing factual accuracy checks where required, with companies given 24 hours' notice prior to FDA issuing advisories.[58,59] *Drug Safety Communications* focus on emerging safety issues and can be issued early in regulatory investigation or after a product information change.[59]

DHPCs are regulated by the FDA in a limited way. Companies may choose to issue DHPCs voluntarily but cannot be compelled to do so by the FDA except as part of a REMS. REMS-related DHPCs may be imposed before or after drug approval, as a component of a communication plan.[21,30] FDA review of DHPC content is mandated when the DHPC is part of a REMS but can only be requested for letters issued voluntarily by companies;[60,61] only REMS DHPCs are available on the FDA website.

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

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

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

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

**Table 1 Types of postmarket safety advisories used by regulators**

| | Primary advisory type | Additional advisory types | DHPCs used? | Dissemination |
|---|---|---|---|---|
| EMA/European Union | DHPC[a] | Web alerts<br>National authorities' bulletins or alerts | Yes<br>Company writes; EMA approves | DHPCs: Companies distribute to healthcare professionals. Some national regulators and EMA[b] post on their websites.<br>National regulators may target professional societies, healthcare and consumer organizations. |
| FDA | *Drug Safety Communication* (online alert) | Podcasts | Only within postapproval REMS; company writes; FDA approves | REMS DHPCs are distributed by companies to healthcare professionals; available on FDA website.<br>*Drug Safety Communication*: FDA website, media, and digital channels to reach specific health professionals and consumers; distributed to some US federal authorities.[58] |
| Health Canada | Multiple forms including DHPC and online alerts/ notices | *Health Product Infowatch* (online drug bulletin)<br>Information Update (website alert)<br>Notice to hospitals<br>Public communication (must accompany any DHPC and is put on Health Canada website) | Yes, Health Canada or company may issue | DHPCs: Companies distribute to healthcare professionals and hospitals.<br>Health Canada posts advisories on its website and may target distribution to professional associations, health and consumer groups.[69] |
| TGA | Alert | *Medicine Safety Update* (online drug bulletin)<br>Direct communications to professional medical organizations and colleges (may not be publicly available) | No | DHPCs: not regulated, company distribution is not described in guidance or regulation (informal process).[74]<br>TGA may selectively disseminate information to professional societies and consumer groups.[145] |

EMA, European Medicines Agency; FDA, US Food and Drug Administration; REMS, risk evaluation and mitigation strategy; TGA, Therapeutic Goods Administration.
[a]EMA posting of DHPCs started February 2020. [b]Different terms are used by individual regulators for letters directly sent to health professionals as follows: EMA: Direct Health Professional Communication (DHPC); FDA: Dear Health Care Provider (DHCP) letters; Health Canada: Dear Health Care Professional Letter (DHCPL) for direct letters to health professionals, Health Professional Communication (HPC) includes letters to health professionals and notices to hospitals.

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

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

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

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

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

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

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

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

## RISK COMMUNICATION CAPABILITY AND MONITORING EFFECTIVENESS

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

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

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

Numerous examples demonstrate the variable responses to safety warnings. The rosiglitazone case saw regulators blamed for secrecy, delayed action, and delayed communication.[86] In contrast, regulatory warnings about increased suicidality with the use of antidepressants in young people were met by some physicians with disbelief and even hostility.[87,88] Natalizumab was reapproved after initial withdrawal because patients were willing to accept the risk of serious brain infections in return for the possible benefits in the treatment of multiple sclerosis.[89] Although these cases may also reflect disagreement with regulators' benefit–risk assessments, they indicate the importance of framing, context, and values in communication.

**Table 2 Differences in regulatory policy for postmarket safety advisories (also see Supplementary Materials – Table S2)**

| | EMA | FDA | Health Canada | TGA |
|---|---|---|---|---|
| 1. Governance and decision making | | | | |
| Separation of authority for postmarket decision making | Yes. PRAC responsible for postmarket assessment and recommendations. | No. Multiteam approach.[95] | No. Multiple departments involved. | No. Approvers assess applications to change product information. |
| Public involvement in postmarket safety governance | Consumer and healthcare representatives on PRAC. | Not routinely.[44] | Not routinely. | Not routinely. |
| 2. Legislative authority, industry responsibility and requirements | | | | |
| Regulators' responsibility for postmarket safety communication: described in regulation/legislation | Yes<br>Article 102, Directive 2001/83/EC on the Community code relating to medicinal products for human use.[5] | Yes<br>FDA Amendments Act (*FDAAA 2007*) | No | Partial (allows information release)<br>Subsection 61(5C) of the *Therapeutic Goods Act 1989* (amended 2010) |
| Regulatory requirements for industry postmarket safety communication | Regulation:<br>Company must inform the regulator about safety announcements. (Article 106a)[5]<br>Information to the public must be presented objectively and not be misleading. (Article 106a)[5]<br>Guidance:<br>Company should cooperate with regulator in preparing DHPCs.[50] | Regulation:<br>Company can be required to issue a DHPC as part of REMS. (*FDAAA*)[7]<br>Format of markings (e.g., "Drug safety warning") for DHPCs and envelopes are legislated but not when to issue. (CFR 200.5)[146]<br>Guidance:<br>REMS DHPCs must be approved by the FDA.<br>For non-REMS DHPCs, companies are encouraged to collaborate with the FDA.[61] | Regulation:<br>Not described in regulation.<br>Guidance:<br>Company "encouraged" to inform Health Canada about DHPCs.<br>Health Canada may request DHPCs and will issue a Health Canada alert if the company disagrees or delays.[71] | DHPCs are not regulated by TGA and no guidance is in place. |
| Industry involvement in regulator-issued alerts | Companies draft DHPCs for EMA review and approval. | No role of industry stated beyond fact-checking.[147] | Companies draft DHPCs for Health Canada review. | Company may review alerts for fact-checking.[145] |
| 3. Risk communication capacity | | | | |
| Regulatory goals for safety advisories | Inform and change behavior[50] | Inform[59] | Inform[35,69] | Inform[148] |
| Risk communication criteria, guidelines, and resources | Guidelines for regulators and industry[50]; specific guidelines for vaccine risk communications and young people.[101,102] | Guidance for industry and FDA for DHPCs.[61]<br>Guidance for classifying postmarket safety concerns.[147]<br>Risk communication guidance.[96] | Guidance for industry and template for DHPCs.[71,149]<br>Process, criteria, and description of all risk communication products (2008).[69] | Process, criteria, description, and template for regulatory alerts.[145] |
| Risk communications strategic activity and planning | Yes[150,151] | Yes[152] | Yes (2006, 2015)[36] | Not in public domain |
| Activities for monitoring effectiveness of advisories | Described in regulation, guidance, and strategy.[5,50,153]<br>Research undertaken.[63,99,100] | Required by regulation for REMS only.<br>Required by legislation to develop robust systems in partnership with academics and professionals.[7]<br>Research to examine effectiveness of *Drug Safety Communication* alert.[42,84,93,154] | Not described in regulation.<br>Evaluation framework published but unclear if implemented.[36] | Not described in legislation or guidance. |

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

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

### Differences among regulators

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

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

The FDA has conducted research to help identify appropriate methods for assessing the impact of risk communication.[75,98]

**EMA.** EMA goals for safety communication include changing behavior, attitudes, and decisions of physicians and patients, and increasing public confidence in regulators (see **Table 2**). The EMA has conducted research to understand clinicians' and other stakeholders' preferences for communication,[63,99,100] and it systematically reviewed the impact of regulatory interventions.[77] Published guidance describes best practice in risk communication for industry (including DHPC templates) and national EU regulators, and advice for tailoring safety communications for vaccines and to younger people.[50,101,102]

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

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

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

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

**TGA.** While the TGA formally adopts many EMA guidance documents, including those for the development of risk management plans,[104] to date it has not published any guidance to industry on how it should undertake risk communication. Like the EMA, the TGA requires risk management plans to describe how the effectiveness of risk mitigation activities will be evaluated. For drugs approved in Europe earlier than in Australia, the Australian Risk Management Plan is substantively the EMA Risk Management Plan, adapted as required for the Australian context.[105] While EMA guidance suggests new risk mitigation requirements may be requested post marketing, as is authorized under EU law, there is no similar authority within TGA legislation. Updates to risk management plans are not made publicly available, nor are details of any evaluations conducted by companies, if these are in fact occurring.

## TRANSPARENCY

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

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

After the rofecoxib withdrawal, the FDA undertook to provide the public with access to information on safety signals even before their significance had been determined, allowing independent researchers to review and interpret the data.[91] However the availability of postmarket safety data remains limited and has not kept pace with improvements in the transparency of premarket data

**Table 3 Transparency of decision making and postmarket safety data**

| | EMA | FDA | Health Canada | TGA |
|---|---|---|---|---|
| Postmarket safety advisories | | | | |
| Sources describing decision making and background to advisory | • PRAC minutes<br>• PRAC assessment report for Referral procedures (include descriptions of data reviewed)<br>• Scientific conclusions: for product information changes; and for PSUR single assessments (PSUSA)<br>• PRAC recommendations for changes to product information following signal assessment translated in all EU languages | Data summary within each *Drug Safety Communication* | Summary safety reviews published if advisory arises from data investigated by Health Canada, but not by sponsors.<br>If a sponsor is compelled to provide safety information, it must be made publicly available.[64] Vanessa's Law allows Health Canada disclosure of evidence and reasoning supporting decision making on serious risks.[125] | Meeting statements for the Australian Committee on Medicines when postmarket safety issues are discussed. |
| Sponsor's contributions to process and decision making for advisories | The sponsor's role and views of the safety concern may be described in "Scientific Conclusions" for PSURs or PRAC assessment reports for referral procedures.<br>Industry DHPCs note that content has been agreed with the regulator. | No | Industry DHPCs published by regulator have a note that Health Canada agrees with the action taken. No details of discussions with industry. | No |
| Risk evaluation activities | | | | |
| Risk minimization activities, current and historical | The summary RMP is continually updated with changes.<br>Resolved issues not listed. | Databases of:<br>• REMS goals, materials, messages, & archives<br>• postmarket requirements (PMRs), postmarket commitments (PMCs) and their completion<br>No centralized list of all requirements for a single drug. | No | Summary Risk Management Plan at approval only. Updates are not publicly available. |
| Postmarket safety studies required by regulators described | • Descriptions in RMP<br>• Protocols and abstracts of results published in EU postmarket study registry (ENCEPP). Provision of data is voluntary | The study is briefly described in Summary Review at approval and on FDA website as "Post market commitments and completions." No details of study results are available | No | Descriptions in AUSPAR at approval only. Protocols available via EU ENCEPP (only where the same protocol applies in Australia) |
| Description of changes to product information and other approval history | • Yes[155]<br>• Procedural steps taken and scientific information after the authorization.<br>• Descriptions of the nature of label changes provided in EPAR for individual drugs—steps after authorization.<br>• List of all signals assessed and discussed by the PRAC and resulting changes to product information listed by meeting.[156]<br>• Outcomes of PSUR assessments: for centrally authorized medicines, EPAR; for nationally authorized medicinal products and "mixed" procedures, the Community register maintained by the European Commission[157] | No<br>Response letter from the FDA briefly describes change required.<br>Some FDA review memos published (e.g., canagliflozin, amputation). | Partial:<br>Post Authorization activity table (PAAT) for new drugs and subsequent entry biologics since 2012.<br>States that a change has occurred and the date but not the nature of the change. | No |

| | EMA | FDA | Health Canada | TGA |
|---|---|---|---|---|
| All revisions of product information available | Yes | Yes | No (Current version only) | No (Current version only. For drugs approved after 2010 the original is in the AUSPAR.) |
| Surveillance data | | | | |
| Signals being tracked | EMA provides a spreadsheet of all signals tracked, discussed, and whether they resulted in label changes. The internal EPITT database is not public. | List of issues being tracked in FAERS, but not the internal DARTTS database. | No | No |
| PSURs published | No (provided on request in person to EU citizens) | No | No | No |
| Adverse drug event reports | Eudravigilance: yes | FAERs: yes | Canada Vigilance adverse reaction online database | DAEN: yes |

For EMA, see: <https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-when>
AUSPAR, Australian Public Assessment Report; DAEN, Database of Adverse Event Notifications (database of adverse event reports submitted to the TGA); DARTTS, Document Archiving, Reporting, and Regulatory Tracking System (used to track significant safety issues related to marketed prescription and over-the-counter drugs); DHPC, direct healthcare professional communications; EMA, European Medicines Agency; ENCEPP, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; EPAR, European Public Assessment Report; EPITT, European Pharmacovigilance Issues Tracking Tool (a web-based system that tracks and monitors the safety of medicinal products); EU, European Union; FAERS, FDA Adverse Event Reporting System (FDA's database containing information on adverse event and medication error reports submitted to FDA); FDA, US Food and Drug Administration; TGA, Therapeutic Goods Administration (Australia); PRAC, Pharmacovigilance Risk Assessment Committee (EMA); PSUR, Periodic Safety Update Report; PSUSA, PSUR single assessments (the PSUR is reviewed once for all EMA member states); REMS, risk evaluation and mitigation strategy; RMP, Risk management plan.
[a] Vanessa's Law enabled the Minister to release certain confidential business information to certain people to protect or promote public health and safety. The results of any postmarket safety examination undertaken by the regulator must be made publicly available on the Government of Canada website. Health Canada intends to make meeting minutes available, and to include adverse event reports with decisions and product monograph on product register.[124]

in the form of clinical study reports.[113,114] Most regulators allow public access to spontaneous adverse report databases, but other postmarket data, including periodic safety update reports and results of postmarket studies undertaken as a condition of marketing approval, are often unavailable.[107,115]

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

### Differences among regulators

**Table 3** describes the documents available from each regulator in relation to postmarket safety. **Table 4** lists documentation available for two advisories for sodium glucose co-transporter -2 inhibitors. There was more documentation for EMA decisions than for all other regulators.[120]

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

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

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

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

Information is provided on many aspects of postmarket safety decision making, including PRAC meetings, summaries of PRAC assessments of postmarket signals, recommendations resulting in product information changes, and actions taken on postmarket safety reports (**Table 3**). Meeting materials, including draft documents for discussion and meeting transcripts are not available, and items may be omitted from summaries when considered necessary for commercial confidentiality. Detailed assessment reports are available for EMA referral procedures (specific postmarket investigations undertaken by the PRAC in response to an identified

**Table 4 Case study: transparency of decision making in SGLT2 inhibitor advisories for DKA and acute kidney injury**

| | | EMA | FDA | Health Canada | TGA |
|---|---|---|---|---|---|
| Advisories | Acute kidney injury | No | Alert (*Drug Safety Communication*) | Bulletin/Investigation report | No |
| | DKA | DHPC (before investigation)<br>Alert (on identification) | Alert × 2 (*Drug Safety Communication): before and after investigation* | Information Update (Web alert)<br>DHPC | Alert |
| Product information changed | Acute kidney injury | Yes (canagliflozin) | Yes (all SGLT2s) | Yes (canagliflozin and dapagliflozin) | Unknown |
| | DKA | Yes | Yes (boxed warning) | Yes (boxed warning) | Yes |
| Information about decision making | Acute kidney injury | • PRAC agendas and minutes<br>• PRAC scientific conclusion: PSUSA<br>Individual drug information:<br>• Risk Management Plan summary (updated)<br>• EPAR Procedural steps taken after authorization<br>• Web page listing full assessment history<br>• Revised product information and date of change (in EU languages) | *Drug Safety Communication* data summary section<br>Individual drug information:<br>• Letters to sponsors approving safety-related product information change (but not what was requested)<br>• All historical product information | Summary Safety Review<br>Individual drug information: Postauthorization Activity Table (Summary basis of decision): lists changes made after approval, including when applications made by sponsors (content of request not provided) | N/A |
| | DKA | • PRAC Minutes and agendas<br>• Referral procedure documents:<br>○ rationale for starting the review<br>○ timetable for procedure<br>○ PRAC list of questions to the sponsor<br>○ PRAC Assessment Report: Scientific conclusion<br>○ Press release<br>○ Information for prescribers and the public<br>Individual drug information:<br>• Risk Management Plan summary (updated)<br>• EPAR Procedural steps taken after authorization<br>• Web page listing full assessment history<br>• Revised product information and date of change (in EU languages) | As above | As above | N/A |

DHPC, direct health professional communication; DKA, diabetic ketoacidosis; EMA, European Medicines Agency; EPAR, European Public Assessment Report; EU, European Union; FDA, US Food and Drug Administration; N/A, not applicable; PRAC, Pharmacovigilance Risk Assessment Committee (EMA); PSUR, Periodic Safety Update Report; PSUSA, PSUR single assessment (the PSUR is reviewed once for all EMA member states); RMP, risk management plan; SGLT2, sodium glucose cotransporter-2; TGA, Therapeutic Goods Administration (Australia).

signal or issue on behalf of all EU member states). For these procedures, the PRAC assessment report describes the trigger for the safety concern, data, and decision-making rationales, along with descriptions of companies' contributions to the procedure. There is no equivalent documentation in other jurisdictions.

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

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

**Health Canada.** Published *Summary Safety Reviews* explain some regulatory postmarket safety decisions but appear to be published only for reviews undertaken by Health Canada, not by industry. Health Canada–approved risk management plans are not publicly available.[103] As part of its Regulatory Transparency and Openness Framework and Action Plan 2017–2018, Health Canada has said it will publish decisions made by Scientific Advisory Panels and Scientific Advisory Committees, as well as aggregated regulatory decision documents with product monographs and adverse

event reports.[124] Vanessa's Law requires the regulator to provide information about postmarket safety investigations it mandates or information it requests from companies.[125] Currently, limited information and meeting minutes are available for some postmarket safety decisions.

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

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

**TGA.** In 2009, amendments to the Therapeutic Goods Act (the Therapeutic Goods Amendment (Medical Devices and Other Measures) Act 2009) allowed the TGA to release more information to the public, including TGA and Expert Committee evaluations of new medicines, committee minutes, and details of pharmacovigilance activities required of companies.[72] The provisions allow a broad range of information to be released to the public referring to "any decision or action taken under this Act or the regulations." Despite this, there is little postmarket information in the public domain documenting safety-related decision making, changes to prescribing information, or risk management plans. Published meeting statements very briefly summarize Advisory Committee on Medicines discussions on those postmarket issues,[127] with the TGA stating that for postmarket safety discussions "the information referred to, and relied on, by the Advisory Committee on Medicines does not usually contain commercial-in-confidence material."[127]

## CONSIDERATIONS

### Postmarket safety governance and risk minimization frameworks

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

The PRAC's inclusion of both regulators and public representatives in postmarket safety decision making also contrasts with other regulators, who draw on nonregulatory healthcare professional expertise and consumer representation on an ad hoc basis (e.g., public consultations on opioid prescribing (Canada), fluoroquinolones and tendon rupture (FDA), valproate and birth defects (EMA), and codeine safety (TGA)).

The depth of public engagement in drug safety decisions varies,[129] and the most effective methods have not been determined. Techniques include consumer testing of patient communications, public consultation, public hearings, and consumer representation on advisory committees. There is growing concern about the independence of consumer voices due to evidence that industry funding may influence patient group representations to regulators.[118,130,131] Mechanisms for public participation must therefore provide safeguards against conflicts of interest as well as ensure adequately informed consumer input. An alternative model could be similar to the United Kingdom's National Institute for Health and Care Excellence (NICE) Citizens Council, an independent body of consumers consulted on a range of specific matters using a deliberative approach, to better understand community perspectives.[132]

### Legal authority and the role of industry

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

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

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

Finally, healthcare professionals are less likely to trust communications disseminated by industry.[63,92,135]

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

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

### Risk communication capability and monitoring effectiveness

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

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

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

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

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

### Transparency

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

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

The imperative for transparency comes from an ethical goal of public accountability and ensuring that decisions are made in the public interest. Given the commercial impacts of regulatory decisions, this remains critical. The transparency of postmarket data lags that of hard-won gains in the premarket arena. Beyond

this, improved public understanding of the risks, benefits, and uncertainties that inevitably surround drug safety data could support more rational drug use. When new medicines are approved, the average citizen expects this means that they are safe, and the dominant public concerns are of access and price. However, it is well known that serious safety issues often emerge in the early years of real-world use due to the limited data available at the time of approval.[19]

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

Regulators' decisions to make information public may be disputed and contested by industry through legal mechanisms; hence regulatory transparency should be supported with adequate powers under legislation. At the same time, regulators' actions in themselves create precedents, and the decisions made by regulators in individual cases become the basis of future actions, guidance, and rules.[106,144] The influence of industry on these individual decisions and thus on rulemaking may be substantial, highlighting the need for transparency.[112,144] Even without legislation, regulators can improve transparency. A Blueprint for FDA Transparency listed actions the regulator could take to improve transparency without legislative change, including greater disclosure of its own decisions and release of data from required postmarket studies.[107] Independent bodies with a legislated role (e.g., ombudsmen's offices) can play an important role in interpreting and enforcing public rights to information. Ultimately, transparency measures should be adequate to allow public confidence that conflicts of interest are being dealt with appropriately.

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

## CONCLUSION

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

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

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

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

## SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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## CONFLICT OF INTEREST

A.S. serves as the principal investigator on a grant from the US Food and Drug Administration on Risk Evaluation and Mitigation Strategy (REMS) Programs to Promote Appropriate Medication Use and Knowledge (75F40120C00044). M.L.D.B. is appointed as professor in Regulatory Science, for which the Chair is funded by the University of Copenhagen. In addition, she is director of the Copenhagen Center for Regulatory Science (CORS), based at the same university. CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, and LEO pharma) as well as patient organizations (Rare Diseases Denmark). The center is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and its research is not company-specific product or directly company related. Apart from the position at the University of Copenhagen, M.L.D.B. is employed part-time by Utrecht University as a senior researcher conducting research under the umbrella of the Utrecht-WHO Collaborating Center for Pharmaceutical Policy and Regulation. This center receives no direct funding or donations from private parties, including pharmaceutical industry. Research funding from public-private partnerships, e.g., IMI, The Escher Project (http://escher.lygature.org/) is accepted under the condition that no company-specific product or company related study is conducted. The Center has received unrestricted research funding from public sources, e.g., World Health Organization (WHO), Netherlands Organization for Health Research and Development (ZonMW), the Dutch National Health Care Institute (ZIN), EC Horizon 2020, the Dutch Medicines Evaluation Board (MEB), and the Dutch Ministry of Health. In 2017–2020, J.L. received payment for being on a panel at the American Diabetes Association, for talks at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, lawyer and a second brief on the role of promotion in generating prescriptions for Goodmans LLP and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives royalties from University of Toronto Press and James Lorimer & Co. Ltd. for books he has written. B.J.M. is a member of Health Action International (HAI-Europe Association), a nonprofit organization that supports public interests in pharmaceutical policy. She was a member of Health Canada's Expert Advisory Group on the Marketing of Opioids in 2018 and 2019, and acted as an expert witness for Health Canada in 2020 in a legal case related to marketing of an unregistered product. She has no other interests to declare and receives no funding from pharmaceutical companies. All other authors declared no competing interests for this work.

## DISCLAIMER

P.B. is an employee of the European Medicines Agency. The views expressed in this article are her personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.




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