Received: 19 November 2018 | Revised: 14 January 2019 | Accepted: 11 February 2019

DOI: 10.1002/pds.4762

WILEY

BRIEF REPORT

Secret safety warnings on medicines: A case study of information access requests

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Funding information
National Health and Medical Research Council, Grant/Award Number: APP1122332; Canadian Institutes of Health Research, Grant/Award Number: 378588

Abstract

Purpose: There has been less attention to the transparency of postmarket evidence of harmful effects of medicines than of premarket clinical trial data. This is a case study of requests for Australian "direct health professional communications" (DHPCs). These letters are used by regulators and manufacturers to inform clinicians of emergent evidence of harm. DHPCs are not made public by Australia's Therapeutic Goods Administration (TGA).

Methods: We requested all DHPCs sent out in Australia from 2007 to 2016 inclusive for 207 drugs that were subject to safety advisories over this decade in Canada, the United Kingdom, and/or the United States. We contacted 39 manufacturers (February to May 2018), with repeat requests to nonrespondents, and a follow-up freedom-of-information (FOI) request to the TGA.

Results: Fifteen companies provided information, either sending DHPCs (n = 4, on five drugs) or affirming none were sent out (n = 11). The remaining 24 of 39 (62%) companies did not provide DHPCs: nine (23%) refused the request, often citing commercial confidentiality; the rest provided no answer despite repeat requests. In total, we had no information for 170 of 207 (82%) of the drugs. Our FOI request to the TGA was unsuccessful.

Conclusions: Our experience highlights unacceptable secrecy concerning safety warnings previously sent to thousands of Australian clinicians. In the absence of explicit regulatory policy supporting disclosure, companies differed in their response. These letters warn of serious and often life-threatening harm and guide safer care; full ongoing public access is needed, ideally in searchable online databases.

KEYWORDS

access to information, drug-related side effects and adverse reactions, pharmacoepidemiology, pharmacovigilance, policy-making, risk communication

Marc Torka and Barbara Mintzes contributed equally to this article and are joint first authors.

Barbara Mintzes presented a preliminary version of this study at a seminar on *Regulation of Medicines, Commercial Bias and Public Safety* at the Charles Perkins Centre, University of Sydney, on May 3, 2018.

1 | INTRODUCTION

Secrecy about serious harmful effects of medicines has no place in modern medicine and should not be accepted by regulatory agencies. Adverse effects are a frequent cause of emergency department visits[1] and hospital admissions,[2] and improved access to information about harms of medicines may help reduce these events. However, regulatory approaches to transparency of evidence on the safety of medicines remain inconsistent. Within this context, a recent experience with a request for safety letters in Australia is described below.

1.1 | The need for transparency

Selective publication of premarket clinical trials is a recognised threat to public health and to the integrity of scientific evidence.[3] Although access remains imperfect, many gains have been made to transparency, including clinical trial registries and data platforms.[4] There has been less attention to the need for transparency about emergent postmarket evidence of harmful effects of medicines. With, on average, 1000 to 3000 participants in premarket studies, which are often of short durations,[5] it is unsurprising that evidence of rare or longer-term harm often emerges only after market approval. More rapid drug approvals and provisional approval pathways compound the problem of restricted premarket exposure.[6]

Seventeen medicines eventually withdrawn for safety reasons were prescribed 112 million times in the United States (US) prior to withdrawal.[7] Safer treatment options existed in most cases, suggesting inadequate physician awareness of mounting evidence of harm despite most having been subject to prior US black box warnings[8] or safety advisories.[9]

National drug regulatory agencies regularly issue safety advisories to warn professionals and the public of new evidence of harm. These warnings often provide practical advice, such as dose reductions or cautions about at-risk patients. Individually addressed "dear health professional letters" or "direct health professional communications" (DHPCs) are a commonly used communication tool. Manufacturers usually distribute DHPCs following regulatory review, which may be explicitly noted. For example, Health Canada often releases letters jointly with manufacturers. There has been increased harmonisation of DHPCs in the European Union (EU) and most EU regulators post DHPCs on their websites (De Bruin, ML, personal communication, September 2018). With the introduction of Risk Evaluation and Mitigation Strategies (REMS) in the US in 2007,[10] the US Food and Drug Administration (FDA) has switched to publishing DHPCs on its website as a REMS component for drugs with REMS (https://www.accessdata.fda.gov/scripts/cder/rems/). The FDA uses DHPCs less often as a communication tool than web-based safety alerts.

2 | METHODS

Our team is carrying out research on postmarket regulatory safety warnings in Australia, Canada, the United Kingdom (UK), and the US from 2007 to 2016,[11] with the aim of examining consistency of safety warnings among countries. Within this study, we identified lower numbers of advisories in Australia than in the other included countries.

Unlike many regulators, the Australian Therapeutic Goods Administration (TGA) does not post DHPCs on its website.[12] We therefore contacted TGA personnel to request copies of these letters and were informed that the TGA has no central file. We were advised to request DHPCs from the manufacturers of drugs that were subject to warnings in the other countries in our study, followed by a freedom of information (FOI) request to the TGA if required. We pursued this strategy after exhausting other avenues such as drug information services.

We identified 207 drugs from 39 companies with no publicly available Australian safety advisories from January 1, 2007, to December 31, 2016, although regulators in Canada, the UK, and/or the US had issued advisories during this time period (Appendix S1). We excluded drugs with multiple generic versions and/or for which the originator drug was unclear or no longer available. Our team contacted the Australian branch of the 39 companies by email (38) or telephone (1) from February to May 2018. We sent out a repeat request to nonrespondents 2 weeks later, with further email and phone contacts to clarify initial responses. We have included all company responses received up to January 1, 2019.

KEY POINTS

- There has been less attention to the need for transparency about postmarket evidence of harmful effects of medicines than for premarket clinical trial data.
- "Direct health professional communications" (DHPCs) are a key tool used by regulators and manufacturers to inform clinicians about postmarket safety warnings. In Australia, DHPCs are not publicly accessible.
- We requested DHPCs for 207 drugs from 39 manufacturers; 15 companies provided information; 24 (62%) did not, several citing commercial confidentiality.
- Our experience highlights the need for explicit transparency policies on postmarket safety communication to ensure public access to information needed for safe prescribing and medicine use.

3 | RESULTS

3.1 | Pharmaceutical companies' responses to our requests

In the absence of a clear Australian disclosure policy for DHPCs, companies' responses varied (Table 1). In total, 24 of 39 (61.5%) companies did not provide DHPCs or clarify if they existed. Appendix S1 lists the companies and brands for which we requested information, organised according to company response.

TABLE 1 Company responses

	Response Type	Information Provided	Companies n = 39 (%)	Examples of Company Responses
No information (n = 24)	Refuse	Nondisclosure	9 (23.1)	• The documents you have requested are confidential. • Dear HCP letters not readily available through the TGA are not provided to the general public by [company]. • Unfortunately, we are unable to disclose such information for research purposes as they are Commercial in Confidence. • The safety advice outlined in these communications may be out of date, and was intended for a specific audience at the date of distribution. • With respect to your request, I have referred this to relevant [company] personnel and wish to advise that [company] will not be providing you with copies of any safety notices in relation to [products] sent directly to healthcare professionals in the period 2007 to 2016. • [Company] have investigated the feasibility of providing this information and unfortunately we are unable to fulfil your request. • We appreciate the research that you are conducting … however, currently, we are unable to prioritise answering your request due to our limited resources. • Unfortunately we are unable to assist you any further.
	Ignore	No answer	7 (17.9)	• No reply or automatic return email stating "We will get back to you soon"
	Delay	No further answer	5 (12.8)	• I have been advised that your project is being discussed by management and they will get back to you with a decision soon • I will discuss with the central safety team and get back to you. • The process involved in obtaining this information is quite lengthy and we are working on obtaining information that you require.
	Deflect	No further answer—refers to TGA	3 (7.7)	• Any [company] letters distributed to Health Care Professionals about emergent adverse drug reactions or newly identified safety concerns are done in consultation with the TGA, and information relating to these issues are accessible on the TGA website.
Information provided (n = 15)	Agree	Confirms no letters were sent	11 (28.2)	• I have been informed by our Medical Director that no new letter on [product] has been sent to the healthcare professionals (HCPs) recently. • HQ confirmed that there was no DHCP letter issued in 2007-2016.
	Agree	Letters provided	4 (10.3)	• We have reviewed the "Dear Health Care Professional" letters regarding safety concerns between 2007-2016 for [products]. There were two identified safety communications meeting these inclusion criteria. Copies of these letters are attached.

Among the 24 companies who did not provide DHPCs, the most common response was to *refuse* our request (n = 9; 23.1%). These nine companies referred to the information in DHPCs as "commercial in confidence" or "not provided to the general public." One stated that the information was "intended for a specific audience at the date of distribution" and "may be out of date" despite the research context behind our request. Three companies simply refused to provide information without a rationale.

Seven companies (17.9%) *ignored* our request, either via an automatic email reply ("We will get back to you soon") or *no answer* despite a repeat request. An additional five companies (12.8%) promised to process our request but provided *no further answer* to follow-up requests. Some companies referred to complex internal decision-making, such as the need for discussion with international headquarters. In one case, fulfilling our request was deemed too "lengthy" a process.

Three companies (7.7%) referred us back to the TGA. One company stated that "Any [company] letters distributed to Health Care Professionals about emergent adverse drug reactions or newly identified safety concerns are done in consultation with the TGA, and information relating to these issues are accessible on the TGA website." Another deflected responsibility to the TGA: "… Please also note that a copy of each DHCP letter has been sent to the TGA, who you may wish to contact."

Fifteen companies (38.5%) provided a clear answer to our request. We received eight DHPCs from four companies, on five products. The remaining 11 companies confirmed that no DHPCs were sent out.

In three cases, companies requested our research protocol before replying. Although we sent the protocol, only one of the three provided us with the requested information.

3.2 | Unsuccessful freedom of information request

Following our requests to companies, we submitted an FOI request to the TGA for remaining missing information, as advised by the TGA. After an initial refusal, we restricted the time frame of requested letters. The

TGA again refused: "Specifically the work involved in processing your request would substantially and unreasonably divert resources of the TGA from its other operations."[13]

4 | DISCUSSION

The idea that a warning letter that has gone out to thousands of individual health professionals would be considered confidential is counterintuitive. However, as is described above, this is the situation we encountered when we tried to obtain Australian DHPCs. In total, we received no response about whether a safety letter was issued in Australia for 170 of 207 (82.1%) of the drugs subject to publicly available advisories in Canada, the UK, or the US. We were also unable to obtain missing letters directly from the TGA through an FOI request.

Among the nine companies that refused to provide DHPCs (Appendix S1), eight are included in a 2016 audit of company transparency policies.[14] Seven have committed to registering all trials, all eight share summary trial results, and all have policies to share Clinical Study Reports and individual patient data. Current standards for clinical trial transparency, albeit incompletely implemented, stand in stark contrast to these companies' Australian subsidiaries' refusal to share safety warnings.

We suspect that this inconsistency reflects the limited attention thus far to the need for full disclosure of postmarket evidence on medicine safety. Many regulators, including the TGA, allow public access to adverse drug reaction databases. However, the Periodic Safety Update Reports (PSURs) required for new drugs are generally not made public. The EMA supports access to PSURs, but only on request.[15] Health Canada publishes summary safety reports, but only releases the full report on request. A report provided in 2017 in response to a request had 39 of 61 pages extensively redacted.[16]

In our opinion, a one-time mailing of a DHPC to a clinician, otherwise inaccessible, provides inadequate warning. Clinicians may overlook a mailing or forget its contents. Not all DHPCs lead to changes in product information. Piecemeal public access to communication of harms is inconsistent with the potentially lifesaving role of this communication. The safety advisories issued in the other countries often described serious and, in some cases, fatal adverse events.

5 | CONCLUSIONS AND RECOMMENDATIONS

Our experience highlights unacceptable company and regulatory secrecy concerning safety warnings previously sent to thousands of Australian clinicians. These letters often warn of serious harm and aim to guide prescribing and medicine use. Although the TGA treats DHPCs as manufacturers' property, several companies stressed joint development. The TGA does not have legislated authority over DHPCs,[17] and no public information describes the extent of the TGA's role in initiating them.

The varied response we received from manufacturers reflects a policy vacuum, in which companies are free to choose whether or not to release DHPCs. This is unacceptable from a public health perspective. Stronger, well-defined limits to commercial confidentiality are needed. A secret warning is no warning at all. To ensure ongoing access to critical safety information, a searchable online database of all postmarket safety warnings on medicines, including DHPCs, should be made publicly available.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

ACKNOWLEDGEMENTS

Funding for our team's research on regulatory safety advisories was provided by the National Health and Medical Research Council, Australia, grant number App1122332, and the Canadian Institutes of Health Research, grant number 378588.

CONFLICT OF INTEREST

B.M. was retained as an expert witness in 2015 and 2016 by the law firm representing the plaintiffs in an application for a Canadian class action on cardiovascular risks of testosterone supplements. L.P. is an employee of George Clinical, a clinical research organisation, run by the George Institute for Global Health. George Clinical receives funding for conduct of clinical trials from various pharmaceutical companies. In 2015-2018, J.L. was a paid consultant on three research projects, on indication-based prescribing (US AHRQ funding), conservative diagnosis (Gordon and Betty Moore Foundation) and a publicly funded Ontario GP formulary. He was a paid panel member on Pharmacare in Canada (Canadian Institute, non-profit) and was paid to write a brief for a law firm. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. None of the other authors have any competing interests to declare.

AUTHOR'S CONTRIBUTION

M.T. and B.M. jointly carried out the analysis, prepared initial and consecutive drafts of the paper, and are joint first authors. M.T. carried out data collection. All authors provided conceptual input on design, analysis, and reporting, edited drafts of this article, and approved the final version. B.M. is guarantor.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Torka M, Mintzes B, Bhasale A, Fabbri A, Perry L, Lexchin J. Secret safety warnings on medicines: A case study of information access requests. *Pharmacoepidemiol Drug Saf*. 2019;28:551–555. https://doi.org/10.1002/pds.4762