Health Canada Usage of Real World Evidence (RWE) in Regulatory Decision Making compared with FDA/EMA usage based on publicly available information

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ABSTRACT -- Purpose: Between January 2020 and December 2021, Health Canada provided a Summary Basis of Decision (SBD) for each of 110 products approved, including 29 oncology products and 21 non-oncology orphan drugs. This review sought to gain insight into how Real Word Evidence **(**RWE) impacts regulatory decision making. **Methods:** SBDs for oncology drugs and non-oncology orphan drugs were reviewed for evidence of use of the RWE or historical data to support regulatory decisions. This information was compared with both FDA and EMA reviews. **Results:** For the 29 Health Canada-approved oncology products, 11 were approved with Notice of Compliance with Conditions (NOCc) status. Two NOCc approvals received extensive RWE reviews, while two other approvals briefly mentioned the use of RWE/historical data. Of the 12 NOC approvals, one received RWE reviews. FDA also approved all 29 drugs, 14 of which received extensive comments on RWE and/or historical data and 8 of which mentioned RWE or historical data. EMA approved 25 of the 29 products and provided extensive comments on 10. Four products received a mention of RWE review. The percentages of submissions with RWE/historical reviews conducted by Health Canada, FDA and EMA were 24.1, 75.9 and 56.0 respectively. Of the 21 non-oncology orphan drugs, Health Canada provided priority review status to 11, with extensive RWE comments in 5 and the mention of RWE in 2 of the regular approvals. Two approvals that used third-party data were not included in the comparison. FDA approved 19 and provided extensive RWE assessment on 5 and mentioned use of historical data in 8. EMA approved 17 and provided extensive RWE and historical comments in 7 and mentioned historical data in 4. The percentages of submissions with RWE/historical reviews by Health Canada, FDA and EMA were 36.8, 68.4 and 64.7 respectively. **Conclusions:** Use of Real World Data is common among FDA/EMA reviews and Health Canada used RWE in recent NOCc and orphan drug approvals.

INTRODUCTION

Real world evidence (RWE) in medicine means evidence obtained from real world data (RWD), which are observational data obtained outside the context of randomized controlled trials (RCTs) and generated during routine clinical practice. RWE is generated by analyzing data obtained from patient registries, medical records or in some cases hybrid trials, pragmatic trials, and late phase trials (1). It has been acknowledged that RWD generated in non-clinical trial settings can provide evidence to support, supplement or replace traditional clinical trial data for regulatory decision making (2). The use of Real Word evidence (RWE) in the post-authorization phase for safety signal detection and risk-benefit monitoring during a drug's life cycle has been going on for decades. Knowledge about the use of RWD gained through post-marketing surveillance systems such as the U.S. Food and Drug Administration's (FDA) Sentinel Initiative facilitated scope expansion to include effectiveness evaluation (3). With the advent of electronic medical databases and the development of sophisticated methodologies to analyze large datasets, discussion surrounding the use of Real Word patient data in addition to clinical trials to support drug approval has been picking up momentum. The passage of the 2016

21st Century Cures Act (4) accelerated this development with FDA publishing the RWE Framework in 2018 and the European Medicines Agency (EMA) publishing the OPTIMAL initiative in 2019 and updated in 2022 (5).

As part of the R2D2 (Regulatory Review of Drugs and Devices) (6) project and additional follow-on initiatives (7), Health Canada outlined their intention to optimize the use of Real Word Data/Evidence (RWD/E) in the regulatory decision-making process. Health Canada and CADTH (Canadian Agency for Drugs and Technologies in Health) held a joint workshop in 2018 (8), launching an initiative to integrate RWE throughout the life cycle of drugs. At this workshop, they announced the intention to co-develop an action plan to optimize the process for the systematic use and integration of RWE into both regulatory and reimbursement decision-making in Canada. It was acknowledged at the workshop that the full integration of RWE will have a significant impact on how drugs are approved and paid for in Canada, but multiple challenges will need to be addressed for RWE's potential to be fulfilled.

On April 16, 2019, Health Canada published the document "Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making", acknowledging that the use of RWE in regulatory decision is increasing globally in the assessment of drug safety, efficacy and effectiveness (9). An accompanying document on the "Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle" highlighted some of the standards determined by Health Canada to be important in supporting regulatory decision making. The document also identified that certain diseases/disorders (such as rare diseases) posted constraints on conduct of RCT and studies based on RWE could be appropriate supporting evidence (10). A strategy document published in March 2020 spelled out how Health Canada in collaboration with CADTH will be operationalizing the incorporation of RWD/E into decision making (7).

On December 3, 2019, Health Canada, and the Canadian Society of Pharmaceutical Sciences (CSPS) jointly led a workshop on "Use of Real Word Data/Evidence to Inform Regulatory Decision Making". Experts from FDA, EMA, Health Canada, industry, and academia discussed the pros and cons of using RWE. The consensus that those experts came to was not about whether RWE would be incorporated into regulatory decision making but about when and how RWE can be appropriately leveraged while maintaining a high evidentiary bar (11).

Notwithstanding the noise about and the focus on the use of RWD/E in regulatory decision making, there has been very little evaluation on how information derived from Real Word patient data has been incorporated into review of clinical data, with even less assessment of how such information might have impacted regulatory decision making. However, two key review articles assessing the role and contribution of RWE in recent approvals of drug products by FDA and EMA were published simultaneously in the same journal in January 2022. The publication by Purpura et al. (12) evaluated New Drug Applications (NDAs) and Biological License Applications (BLAs) approved by FDA from 2019-2021. The study by Flynn et al. (13) reviewed Marketing Authorization Applications (MAAs) approved by EMA between 2018 and 2019. While Purpura review of FDA documents were from FDA public resources, Flynn used information collected from internal data sources and internal assessment reports. In Canada, such review information is available in Health Canada's Summary Basis of Decision documents (14), which represent brief summaries of the full assessment. SBDs are the only Canadian assessment documents available publicly; hence this review article focuses on evaluating information from SBDs to gain insight into how Health Canada may be using RWD/E in decision making.

METHODS

Data Sources

Health Canada Summary Basis of Decision (SBD) database (14)

The SBD webpage of Health Canada allows searches of review summaries written for all eligible drugs approved after September 2011. The development of this project was initiated between 2003 and 2004 in response to Health

Canada's commitment to increase transparency around the review of drugs and medical devices. The reviews are organized by year of approval and are searchable by names of drugs approved in Canada. The first product approved by Health Canada in 2020 was Noromby/Noromby HP on January 7, 2020, and the last product approved in 2021 was Trodelvy on December 23, 2021. An Excel spreadsheet was generated with all drugs approved by Health Canada between January 7, 2020, and December 23, 2021, covering products that were approved in the most recent two years.

SBDs of all products were searched to identify drug classifications and categorized based on the likelihood of approved products to have RWE/D in their submissions. A separate database was created for oncology drugs and non-oncology orphan drugs consisting mainly of PDFs generated from all sections of the SBD for each drug in the two categories for review. The approval status of each drug, classified into Notice of Compliance (NOC), Notice of Compliance with Conditions (NOCc) and Priority Review (PR), was also captured.

US FDA database (15)

For comparison of RWE used in regulatory decisions between Health Canada and FDA, selected SBDs were matched to corresponding FDA reviews downloaded from various websites (Drugs@FDA review documents which included multi-disciplinary reviews, Medical Reviews, Clinical Reviews) and Biological License Application Approvals which included Summary Basis for Regulatory Action (product review) and a database of reviews was created.

EU EMA database (16)

Similarly for comparison of RWE used by Health Canada to EMA, selected SBDs were matched to Committee for Medicinal Products for Human Use (CHMP) European public assessment reports (EPARs) and a database for corresponding oncology drug and non-oncology orphan drug products was created.

Review methodology

SBDs of products approved between January 2020 and December 2021 were reviewed to search for antineoplastic products (under SBD Section 1 "What was approved?" and approval status, NOC, NOCc or PR). All drugs with anti-neoplastic designations by Health Canada were grouped under oncology drugs. Sections 1, 2, 3, 7.1 and 7.2 were reviewed in detail for all oncology drugs. The focus was on the use of RWD/E and historical data for approval, so therefore Section 2 ("Why was [the product] approved?") and Section 7.1 ("Clinical Basis for Decision") were searched with the keywords "real", "historical", "history", "observation", "natural", "experience", "registry", "world" and "safety". The positive search results were adjudicated. For example, when keyword "history" was used in the phrase" disease history" rather than in the assessment of historical patient data, it was disallowed. At the end of searches, all SBDs, regardless of search results, were surveyed section by section to ensure that the search results were accurate and verified that those documents with no keyword search findings indeed held no suggestion that regulators had used anything other than phase 3 randomized trials for regulatory decision making. From the information derived, five categories of RWE-use were created to grade the RWD/E or historical data utilized by Health Canada:

1. Review and use of retrospective/prospective Real Word studies and use of historical control for patient population/endpoint comparisons
2. Review and use of retrospective/prospective Real Word studies for efficacy/safety comparison
3. Review and use of historical data for efficacy/safety comparison
4. Mention of the review of RWE – inconclusive whether it was used for decision making
5. Mention of the review of historical data – inconclusive whether it was used for decision making

Retrospective/prospective Real Word studies consisted mainly of studies collecting patient level data from registries, databases, or medical records. Historical control studies referred mainly to published trial data, meta-analysis, or review studies. Due to the complex nature of the assessment reports, assignments to specific categories may not be mutually

exclusive. For products that were not included in these categories, there was no evidence from the SBD that RWD/E or historical data was included as part of the review or played a role in influencing the decision.

Orphan drugs in the US were defined as treatments for diseases with prevalence ≤ 20 per 100,000 as defined in the Orphanet website (17). Canada, unlike US, Europe and Australia does not have an orphan drug policy or a definition for an orphan drug. The Canadian list of orphan drugs for this review was derived by comparing, the entire SBD list to the FDA orphan drug list (18) and EMA orphan drug designations (19). Oncology drugs in Canada were managed differently in terms of regulatory approvals and reimbursements from non-oncology drugs due to the severity of the disease and many of the oncology drugs met the criteria of an orphan drug (20). Those drugs that met both criteria to be oncology and orphan drugs were considered under oncology drugs only and a non-oncology orphan drug category for orphan drugs that did not treat cancer was created to avoid double counting.

SBDs from the list of non-oncology orphan drugs were reviewed in the same manner as for the oncology drugs and comparisons to FDA and EMA approvals were generated similarly to what was discussed above for oncology drugs.

FDA-approved products: Clinical Review reports (part of the Multi-Discipline Report) from corresponding oncology products and non-oncology orphan products were reviewed in a similar fashion as the Health Canada–approved products.

EMA-approved products: CHMP assessment reports (mainly EPARs) corresponding to Health Canada-approved products were reviewed in a similar manner to the Health Canada-approved products.

FDA's and EMA's published full assessment reports and reviews were more in-depth (often including comments on study design, data integrity, patient population selection and analysis methodology) than the summary reviews published by Health Canada. Decisions on assignments were made based on the impact on regulatory decision making in terms of efficacy and safety.

Quality Control

Data was reviewed and confirmed by two individuals reviewing all the documents independently. The methodology mentioned above for review was followed closely by both reviewers. As deem required, reviewers resolved any discordance via a discussion of relevant passages with a separate investigator.

RESULTS

From the Health Canada SBD database, 111 products were approved between January 2020 and December 2021. One product (GalliaPharm, which is for a gallium-68 generator) was removed as it was not intended for treatment. Of the 110 drugs approved, 29 were oncology drugs for cancer treatment, 21 were non-oncology orphan drugs according to FDA and EMA designations, nine were COVID-19 vaccines or treatments and 19 were biosimilars. The rest of the drug products covered various therapeutic areas such as gynecology, neurology, autoimmune diseases, and diabetes were classified as "others". Excluding biosimilars which are not new medicinal entities, oncology and non oncology orphan drugs accounted for more than 50% of the approvals for novel medicinal products. Figure 1 illustrates the distribution of Health Canada approvals by classifications as described.

The current review focused on oncology drugs and non-oncology orphan drugs. COVID-19 vaccines or treatments would likely include RWD/E in their full approvals after Interim Order authorizations, and so would likely be included in a future review. Health Canada has indicated through various RWE publications and meetings that the initial focus of the use of RWE will be in diseases that have small patient populations where randomized trials would be difficult to conduct. Both oncology drugs and non-oncology orphan drugs generally affect smaller populations, so these drug categories were selected for the current review.

Table 1 depicts the approval designations for oncology drugs and non-oncology orphan drugs upon approval by Health Canada as well as the corresponding designations from FDA and EMA approvals. As both FDA and EMA sometimes give multiple designations to a single

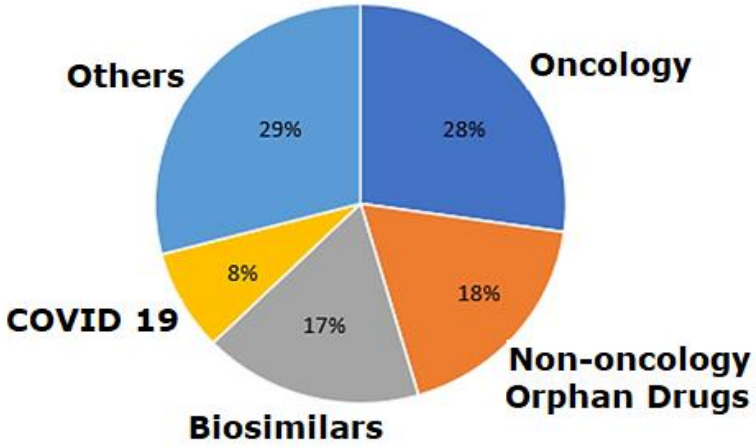

Figure 1. Percent of the total 110 drugs approved by Health Canada (2020-2021). Non-oncology orphan drugs were identified using published FDA and EMA data on lists of orphan drugs.

Table 1. Drug categories (oncology drugs and non-oncology orphan drugs) and corresponding approval designations by FDA/EMA

Drug categories	Health Canada		FDA[a]		EMA[a]	
Oncology	29	NOCc = 11 PR = 5	29	PR = 23 BT = 13 FT = 7	25[b]	CA = 9 PRIME= 1
Non-oncology orphan	21	NOCc = 0 PR = 11 3rd party = 2	19[c]	BT = 4 FT = 5 PR = 8	17[d]	CA = 1 AA = 1 PRIME = 2

[a]one drug can receive multiple designations
[b]four of the oncology drugs were not yet approved or EPAR was not ready from EMA at the end of 2021
[c]two of the products approved by Health Canada using third-party data did not have corresponding recent approvals by FDA
[d]two of the products approved by Health Canada using third-party data did not have corresponding recent approvals by EMA and two products are not yet approved
Health Canada designations: Notice of Compliance with Conditions (NOCc), PR = priority review
FDA designations: FT = fast track, PR = priority review, BT = breakthrough,
EMA designations: CA = conditional authorization/approval, AA = accelerated assessment, PRIME = priority medicines.

drug, the designations do not align perfectly with Canadian approvals, which award only one designation per drug. One observation is that most of Health Canada's NOCc approvals correspond to EMA's conditional approvals (CA).

For the 29 oncology products, 11 were approved with NOCc status by Health Canada, with extensive RWE reviews on 2 commenting on retrospective cohort studies (one supportive of regulatory decision). Two reviews briefly mentioned the use of historical data. One review from NOC approvals mentioned the use of RWE in regulatory decision making (Figure 2a, Table Suppl 1).

The two NOCc products where RWE information submitted by the sponsors was analyzed in the SBDs were Minjuvi (21) and Enhertu (22). Both reviews documented observational cohorts of matched populations for comparison of endpoints of overall response rate (ORR) and complete response (CR). The RWE was taken into consideration for regulatory decision making for Enhertu but not for Minjuvi. The two products for which RWE or historical data were mentioned in the SBD were Tepmetko (23), and Lumakras (24). For the two products, historical data or published evidence were mentioned as being supportive but the impact on regulatory decision is not clear.

For the 6 PR products, two received RWE comments. The Inqovi (25) review mentioned a comparison to a historical single-arm trial and for Tecartus (26) historical and published data were mentioned. For the12 NOC approvals of oncology products, only one product received RWE review. Mylotarg (27-28) was approved previously in the US for acute myeloid leukemia, subsequently was withdrawn from the market, and was then re-introduced again at a lower dose and in combination with chemotherapy. The submission to Health Canada, which was much later than in the US, included a meta-analysis of patients from prior studies and post-marketing exposure. Health Canada reviewed and commented on the relevance of using data from the meta-analysis but decided that was not sufficient for a pediatric indication.

FDA also approved all 29 drugs, 14 with either extensive comments on RWE and historical data or with RWE or historical data only. Eight of the approvals mentioned RWE or historical data. EMA approved 25 of the 29 products and provided extensive comments on both RWE and historical data or used only RWE or historical data on 10; four of the approvals mentioned RWE review (Tables Suppl 1 and 2). Thus, the percentages of submissions with reviews of RWE/historical data conducted by Health Canada, FDA and EMA were 24.1, 75.9 and 56.0 respectively. Figure 2a summarizes the percent of submissions with RWE (x-axis) and the extent of review by categories (y-axis) by Health Canada, FDA, and EMA.

Of the 21 non-oncology orphan drugs, Health Canada provided priority review status to 11 and extensive RWE comments on 5 of the 11 (Fig 2b, Table Suppl 3). In the review of Evrysdi (29), Health Canada mentioned in the SBD that efficacy of the drug was better than natural history of the disease. Three products, Trikafta (30), Firdapse (31) and Ruzurgi (32), incorporated Real Word safety data into their reviews as these products were approved in Canada some time after having been approved in the US and EU. Post-marketing safety data formed part of the data package in these approvals. For Zolgensma, post-marketing data supported two important risks identified in clinical settings (33). Also reviewed extensively and not in the PR list were Mayzent (34) and Increlex (35). For Mayzent, an increased risk seen in post-marketing observation added a contraindication.

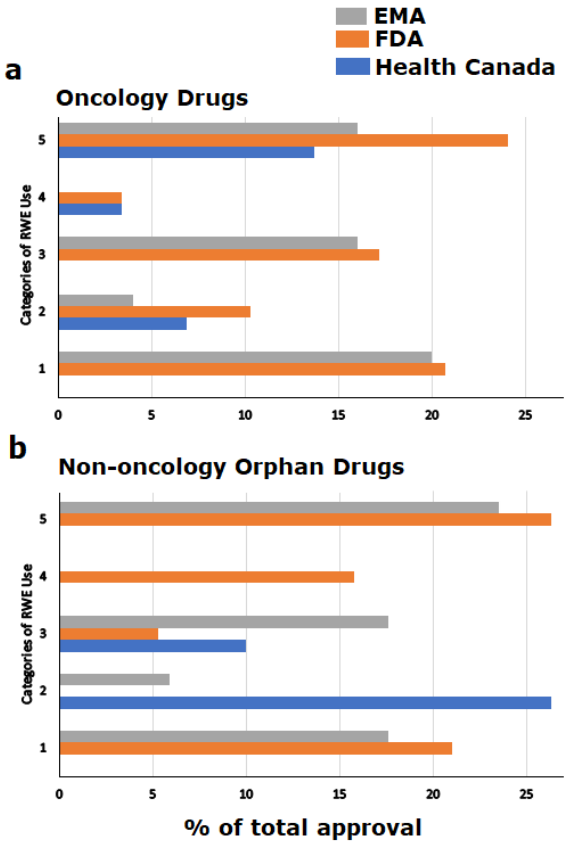

Figure 2. Comparing the use of Real World Data/Evidence (RWD/E) or historical data in oncology drug (Figure 2a, Tables Suppl 1 and 2) and non-oncology orphan drugs (Figure 2b, Tables Suppl 3 and 4) approvals between Health Canada SBDs and FDA/EMA review documents.
Categories of RWD/E use.

Keys:

1. Review and use of retrospective/prospective Real Word studies and use of historical control for patient population/endpoint comparisons.
2. Review and use of retrospective/prospective Real Word studies for efficacy/safety comparison
3. Review and use of historical data for efficacy/safety comparison
4. Mention of the review of RWE – inconclusive whether it was used for decision making
5. Mention of the review of historical data – inconclusive whether it was used for decision making

The SBD of Increlex cited European registries as well as observational studies that were completed and ongoing and concluded that the information supported the efficacy and safety of the product. Two products, Waymade-Trientine and MAR-Trientine, were approved under the policy

"Submissions Relying on Third-Party Data" (SRTD). These products were not included as part of the RWE reviews as the source of information included for these submissions is different than for new drugs approved under a more conventional policy. The total number of non-oncology orphan drugs used for comparison is 19.

FDA approved 19 of the 21 (2 third-party data approvals had no corresponding recent approvals) and provided extensive assessment on 5 and mentioned the use of historical data in 8. EMA approved 17 and provided extensive RWE and historical comments to 6 and mentioned historical data in 5 (Tables Suppl 3 and 4). The percentages of submissions with reviews of RWE/historical data conducted by Health Canada, FDA and EMA were 36.8, 68.4 and 64.7 respectively. Figure 2b summarizes the percent of submissions with RWE (x-axis) and the extent of review by categories (y-axis) by Health Canada, FDA and EMA.

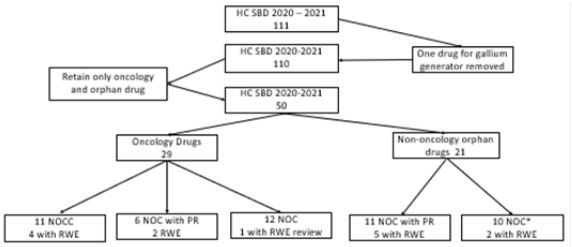

Figure 3. A summary of the review process of SBDs published by Health Canada between 2020 and 2021. The inclusion of RWE/historical data in the regulatory reviews is categorized according to approval status for oncology drugs and non-oncology orphan drugs. * Two of the products approved by Third Party Review (SRTD) were not included in Tables Suppl 3 and 4.

DISCUSSION

Regulatory agencies globally are considering incorporating RWE with a high evidentiary bar into regulatory decision making. Health Canada declared its intention to do so as part of the R2D2 regulatory modernization and suggested that RWE is highly relevant for treatments aimed at small patient populations. The rapid discovery of target mutations especially in cases of life-threatening cancers and some rare genetic diseases accelerated the discovery of novel targeted therapies directed at specific patient populations. However, the small size of these populations poses challenges for randomized controlled trials to complete in a timely manner. To advance these life-saving therapies to patients, Health Canada and other regulatory agencies are approving treatments based on single-arm, non-comparator trials. This review seeks to identify where RWE or historical data might have been used for regulatory decision making based on SBDs published by Health Canada on recently approved non-generic products in Canada.

SBDs are summary reports that provide scientific and evidence-based comments to support both pre-clinical and clinical decisions, including the benefit-risk evaluations of approved drugs. Information regarding the use of RWE in regulatory decision making would have been captured. In-depth reviews of the SBDs for all approved oncology drugs showed that Health Canada is using RWE more often in drugs with NOCc approvals, which is not a surprise as most of the drugs were approved based on results from a single-arm non-randomized trial. While Health Canada did provide comments to 4 of the NOCc approvals based on the RWE or historical data submitted for efficacy evaluation, the information was insufficient for a full approval. These RWE comments did serve to generate additional insight into the diseases studied and data may have been supportive. A similar proportion of non-oncology orphan drug SBDs included comments on RWE or historical data. Unlike for oncology drugs, the majority of the RWE reviews for non-oncology orphan drugs focused on post-marketing safety information, confirming adverse events observed in clinical trials or adding new adverse events in product labels. Many of these non-oncology orphan drugs were approved in Canada later than in the US and EU, and therefore reviewing and including post-marketing data for new emerging adverse events were essential to ensure safe use of the products.

Health Canada commented in some of the SBDs that resulted in NOCc approvals that the impact of the drug on clinical endpoints selected for evaluation was clinically meaningful and significant even within a single-arm trial, and conditional approvals were granted for the treatment. Such comments implied that the use of RWE to support approval is not required, at least

not for conditional approvals. Health Canada might have designated the Canadian Agency for Drugs and Technologies in Health (CADTH) as the main RWE reviewer, in which case the strength of RWE data would impact only on reimbursement rather than regulatory approvals. This is a departure from how other global agencies are reviewing key RWE data which is usually part of a regulatory submission and review. A recent publication on "Real World Evidence for Regulatory Decision Making: Guidance from around the world" highlighted a cross collaboration between Health Canada and its health technology assessment partner (CADTH) to optimize use of RWE in regulatory and reimbursement decision making. Among all countries surveyed and reported in the publication, only South Korea and Canada linked regulatory and reimbursement in terms of RWE usage. The paper also mentioned an ongoing Canadian study "The Canadian Real World study for value of cancer drugs (CanReValue) attempted to make reimbursement decisions on evaluation and validation of generated RWE. This multi-stakeholder study did not include Health Canada, thus further reducing the impact of RWE decision made by Health Canada (36). It will be of interest in later phases of this project to compare Health Canada and CADTH reviews especially on the use of RWE for decision making and how that will compare to other global agencies.

In FDA or EMA assessment reports, comments on RWE information submitted were more frequent and evaluations more extensive than in Health Canada's SBDs. Detailed reviews of such assessments were published recently for FDA (11, 37) and EMA (5,13) approvals. These RWE studies were conducted mainly by using patient registries, electronic patient records, claims databases or longitudinal data collections. Both FDA and EMA commented on the design of studies, the patient population selection, the methodology used for data imputation and analysis used to eliminate bias. While not all comments were positive, the rationale for negative decisions was documented in order to provide guidance for refinements in future applications. This type of feedback and input are very valuable for the advancement of RWE development for regulatory decision making. Some of the products approved by FDA that had no comments on RWE were ones that FDA approved several years earlier than Health Canada, and it is possible that the manufacturers did not include RWE in their FDA submissions simply because the use of RWE had not yet been formally incorporated by FDA as part of the regulatory decision making.

FDA has the longest historical record of accepting RWE into regulatory decision making, dating back to 1958 (37) and has the most sophisticated platform set up at multiple levels to generate and evaluate impact of RWE on product effectiveness and safety. However due to inconsistencies in review across different FDA divisions, recent reviews commented that trying to parse out whether RWE submitted was substantial, supportive, or other has not always been feasible (12, 37). EMA on the other hand savoyed a more holistic approach working on multiple fronts in establishing the evidentiary value of RWE. EMA sought to understand when a randomized clinical trial and when RWE as best placed to provide robust, decision-ready evidence rather than a more board brush incorporation of RWE (5). Health Canada can definitely benefit from experience and approaches adopted by FDA and EMA. An additional factor to consider is that FDA and EMA serve much larger patient populations, equipped with more resources than Health Canada and are able to build cross-disciplinary teams of clinicians, epidemiologists, statisticians, and data scientists to advance methodology in the incorporation of RWE for regulatory use.

Numerous publications on global RWE-policy framework had been made available by regulatory agencies either on-line or by published literature as summarized by Burns et.al. (36), publications on in-depth analysis of regulatory review reports to ascertain quantitatively the impact of RWE on regulatory decision making were very limited. Purpura et.al. (12), Fynn et.al. (13) and more recently Mahendraratnam et. al (37) were the only recent publications on how RWE might have impacted regulatory decision made at a product level by FDA and EMA. The current publication is the first review article to provide insight into the use of RWE in the review of products approved by Health Canada in 2020 and 2021. In-depth reviews of SBDs suggested

that Health Canada utilized less RWE in regulatory decision compared to FDA and EMA. The comparison was limited and challenged by different structures of the published reports, however these comparisons of with or without RWE were believed to be robust. It is expected with the regulation modernization and the introduction of more agile regulations for the management of COVID-19 during the pandemic, use of RWE by Health Canada may further increase and the data in this article can serve as a baseline for future assessment. Health Canada provided a high percentage of RWE assessment to oncology products with NOCc approvals in 2021, suggesting a positive trend towards the inclusion of more RWE reviews in future submissions. This will provide submission-sponsors with more insight into how RWE may be used for regulatory decision making in Canada in the future.

Three limitations were noted in this publication. First, assessment reports publicly available from Health Canada were summary reports which made the comparison to full assessment reports from FDA and FMA a challenge. The goal of the publication was however, to compare more quantitatively with or without the use of RWE, thus minimizing the impact of the details of the reports on our conclusion. The second limitation was the small number of keywords used for searches of RWE information. Regulatory assessment reports were complex including data submitted by sponsors and extensive and sometimes board spectrum comments from reviewers. The narrow set of keywords allowed laser focus on the detection of prominent use of RWE in regulatory decision-making process. In addition, when these keywords were not present, the entire document was reviewed to ensure that no RWE was included in the review. It was not expected that the search strategy would result in missing information. The third limitation was the study only focused on oncology drugs and non-oncology orphan drugs rather than the entire list of drugs approved. Health Canada mentioned repeatedly in published guidelines that RWE review would initiate with drugs treating diseases covering small patient populations. Information gathered from orphan-drug approvals could potentially be generalized to other products and provided a proxy for RWE use in future drug approvals in Canada.

CONCLUSION

The use of RWE in regulatory decision is increasing around the world. Global regulatory agencies have been active in developing frameworks, policies, and guidances to instruct how RWE could be used for regulatory decision making. Health Canada appears to be behind both FDA and EMA in utilization of RWE in the decision making. An increased use of RWE in regulatory decision making or an enhanced collaboration with health technology group to develop common platform for RWE review could be potential future opportunities.

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