

The Importance of and Challenges with Adopting Life-Cycle Regulation and Reimbursement in Canada

Importance et défis de l'adoption du cycle de vie dans la réglementation et le remboursement au Canada



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Abstract

Regulatory and reimbursement decisions for drugs and vaccines are increasingly based on limited safety and efficacy evidence. In this environment, life-cycle approaches to evaluation are needed. A life-cycle approach grants market approval and/or positive reimbursement decisions based on an undertaking to conduct post-market clinical trials that address evidentiary uncertainties, relying on the collection and analysis of post-market data. In practice, however, both conditional regulatory and reimbursement decisions have proven problematic. Here we discuss some of the regulatory implications and unsettled ethical and pragmatic issues, taking lessons from the recent experiences of Israel in rapidly approving the Pfizer-BioNTech COVID-19 vaccine.

Résumé

Les décisions réglementaires et de remboursement des médicaments et des vaccins reposent de plus en plus sur des données limitées quant à leur innocuité et leur efficacité. Dans ce contexte, des approches visant l'évaluation du cycle de vie sont nécessaires. Une approche axée sur le cycle de vie accorde l'approbation de mise en marché ou les décisions de remboursement moyennant l'engagement de mener des essais cliniques post-commercialisation qui traitent les incertitudes concernant les données en s'appuyant sur la collecte et l'analyse de données post-commercialisation. Dans la pratique, cependant, les décisions réglementaires conditionnelles et les décisions de remboursement se sont avérées problématiques. Nous discutons ici de certaines des répercussions réglementaires et des problèmes éthiques et pragmatiques non résolus, en tirant les leçons de l'expérience dans l'approbation rapide du vaccin Pfizer-BioNTech COVID-19 en Israël.

Introduction

Health Canada has initiated public engagement on a national strategy to balance equitable access to high-cost drugs for rare diseases (HCDRDs) with sustainable Canadian health-care systems. The engagement process seeks feedback to ensure reimbursement decisions are informed by the best available evidence including alternative regulatory approval and reimbursement models, an expert panel to make ongoing recommendations, a national data system to capture real-world data and independent networks to facilitate data sharing (Health Canada 2020). Regulatory and reimbursement decisions for HCDRDs and for new drugs more broadly, especially in oncology, are increasingly accepting of and reliant on limited and emerging safety and efficacy evidence. This shift is partly due to new treatment paradigms that target patient subpopulations based on genetic or other biomarkers and pressures to accelerate patient access to new drugs (Breckenridge et al. 2016; Davis et al. 2016; Gibson et al. 2015). We argue that in this environment, life-cycle approaches to evaluation are needed because they trade static regulatory and reimbursement decisions for dynamic decision making. A life-cycle approach relies on the collection and analysis of post-market data, using platforms and methods that are designed to update and refine decisions based on

pre-specified decision rules. In practice, however, both conditional regulatory and reimbursement decisions have proven problematic. Post-market evidence does not necessarily accrue to sufficiently address uncertainties and reversing positive decisions rarely occurs, even when indicated (Pease et al. 2017; van de Wetering et al. 2017). Here we discuss some of the associated regulatory implications and unsettled ethical and pragmatic issues, taking lessons from the recent experiences of Israel in rapidly approving the Pfizer-BioNTech COVID-19 vaccine.

What Are the Origins of Life-Cycle Regulatory and Reimbursement Approaches?

The origins of the life-cycle approach are often attributed to the Institute of Medicine's (2007) report, which recommends that assessing the benefits and risks of drugs should be ongoing throughout their entire market life. The report was initiated following several highly salient drug withdrawals in the years prior and led to new powers to evaluate drugs in the post-market setting (Psaty et al. 2012). Similarly, in the context of reimbursement decisions, a life-cycle approach trades a one-time assessment for adaptive health technology assessment processes across the drug's life cycle to better align funding decisions with ongoing evidence generation (Gutiérrez-Ibarluzea et al. 2017; Husereau et al. 2016). The commonality between both approaches is the recognition of and attempt to mitigate evidentiary uncertainties that exist at the time of initial assessment. Over the past few decades, many jurisdictions have implemented policy and regulatory reforms in support of adopting a life-cycle approach to balance the often-opposing goals of providing timely patient access to new drugs, encouraging industry innovation and requiring comprehensive safety and efficacy data (Eichler et al. 2012). Striking the appropriate balance has become increasingly challenging with the rise of "niche" drug development, which targets small patient populations (Davis et al. 2016; Gibson et al. 2015).

What Are the Current Regulatory and Reimbursement Mechanisms in Canada that Support a Life-Cycle Approach?

Current knowledge of research and development pipelines of HCDRDs and oncology drugs predict increased reliance on conditional regulatory approvals, such as Canada's Notice of Compliance with Conditions (NOC/c) policy. This approvals process grants market access to promising drugs with the proviso that additional confirmatory trials are conducted to enhance evidence of a drug's safety and/or efficacy. The approval may be withdrawn if the trials fail to support a favourable benefit–risk profile or address outstanding uncertainties (Health Canada 2016). However, the NOC/c policy has been criticized for insufficient enforcement of confirmatory trials (Lexchin 2007).

Canada's NOC/c policy is not enshrined in statute or regulation; instead, conditional approvals rely on an agreement by manufacturers to fill evidentiary gaps after market approval in the form of a confidential letter of undertaking. From a statutory standpoint,

a drug granted approval under the NOC/c policy generally has the same market access as one granted an unconditional regulatory approval. As a result, Health Canada has had limited legal authority to enforce the completion of post-market clinical trials, instead leaving manufacturers to self-regulate. This has resulted in drugs approved under the NOC/c policy remaining on market for many years without fulfilling the agreed-upon clinical trials (Law 2014). The same has been found for post-market trials in the US (Herder 2019). Without robust enforcement mechanisms, there is little incentive for manufacturers to complete confirmatory trials once they are approved, and evidentiary uncertainties remain unaddressed. The European Medicines Agency is an outlier in how it manages conditional regulatory approvals; conditional approvals are limited to one year, and approvals must be renewed annually if there are still outstanding obligations. Automating review of conditional approvals is a relatively minor adjustment that could improve oversight and avoid “dangling” approvals that remain on market despite clinical trials that failed to confirm clinical benefit (Beaver and Pazdur 2021). Since the passing of Vanessa’s Law (*Protecting Canadians from Unsafe Drugs Act* 2014), Health Canada has acquired new powers that encourage on-market evaluation of drugs, including the power to order manufacturers to provide information, conduct tests and assessments and monitor experience of approved drugs. However, these powers are discretionary and intended to be used as a last resort only when a manufacturer is not willing to comply voluntarily (Health Canada 2021). It remains to be seen whether these new regulatory powers will result in more responsive on-market decision making.

While regulatory approval of drugs is solely within the jurisdiction of the federal government, deciding whether a drug will be covered by a public drug plan is the responsibility of each individual province. Under conditional reimbursement schemes, payers agree to reimburse a drug based on the collection of further evidence either to confirm its cost-effectiveness or to identify the subpopulations most likely to benefit from its use. On reassessment of the evidence, the drug can be delisted or reimbursement criteria can be refined to optimize the value realized within a limited budget (Piatkiewicz et al. 2018). In Canada, conditional reimbursement schemes have not been adopted widely due to restrictive legislative frameworks and fear of loss of provincial autonomy (Morgan et al. 2013b). Exceptions are product listing agreements (PLAs) through the pan-Canadian Pharmaceutical Alliance. PLAs are increasingly used to negotiate confidential prices for new drugs but their adoption across jurisdictions has been inconsistent and, perhaps more importantly, PLAs do not include mechanisms for on-market evaluation and reassessment (Morgan et al. 2013a).

What Are the Current Barriers to Adopting a Life-Cycle Approach?

Based on the current structure of Canada’s healthcare systems, there are various ethical, practical and regulatory barriers to adopting a life-cycle approach. Dynamic decision making based on post-market surveillance requires data generation in studies or clinical trials that blur the line between research and clinical care. Data generation may be required that exceeds standard of care. For example, additional diagnostic tests or monitoring visits may

be necessary to collect data sufficient for decision making. If characterized as research, institutional ethics review is required; if characterized as clinical care, consent processes need to acknowledge the uncertain risk and benefit profiles over the life cycle of a conditionally approved or reimbursed drug. There is a lack of consensus about the appropriate standard of consent in the post-market setting: Is it the higher standard required in research settings or the more flexible standard permitted in clinical care and health-system utilization of patient data for quality improvement (Largent et al. 2011)? Additionally, privileged access to an intervention that is contingent on participation in a post-market research protocol may be viewed as coercive, particularly where no other treatment options are available. Many of these concerns can be mitigated by comprehensive disclosure and consent requirements prior to initiating treatment. Patient privacy is also a factor as patient data are collected, shared and analyzed for research and regulatory decision-making purposes, in addition to patient care (Holland and Hope 2012). Public acceptance of health data sharing remains unsettled. While research suggests that participants and patients are generally supportive of sharing their personal health information for research purposes, many individuals distrust institutions that collect and share health information, representing a gap that should be addressed prior to widespread adoption (Darquy et al. 2016; Milne et al. 2019; Platt et al. 2018).

Practical issues also emerge. Once a drug is approved and marketed, it may become difficult to enroll patients in clinical trials or other data collection efforts because patients are able to access the drug outside clinical trials (Eichler et al. 2008). As a result, conditional approvals may undermine the required evidence-collection efforts to remove the conditions. Issues also arise from inadequacies in the design and analysis of post-market studies, which often necessitate departure from randomized controlled trials powered appropriately to enable causal inference (Davis et al. 2016). Administration, implementation and evaluation of conditional regulatory and reimbursement schemes are not well developed. It is unclear who should be responsible for the funding, design and implementation of data collection and analysis efforts. Placing the data collection burden on the manufacturer in the post-market environment raises concerns about clinical trial manipulation, lack of transparency and conflicts of interest (Light and Lexchin 2021). These concerns may be ameliorated through real-world evidence generated from routine clinical care. However, shifting the burden of evidence generation to health systems or government agencies may introduce new concerns. For example, post-market evidence would likely need to be shared with manufacturers to enable them to secure regulatory approval or reimbursement in different jurisdictions. Post-market data systems for HCDRDs, in particular, will need to be interoperable across multiple institutions and/or jurisdictions, requiring substantial investments and appropriate consent processes. In parallel, progress is needed in developing and standardizing health database terminology, coding, validation and statistical methods before real-world data derived from electronic health databases can be relied upon for regulatory and reimbursement decision making (Moore and Furberg 2015).

Finally, enforcement and evaluation of post-market data collection has been largely underwhelming. Most conditional regulatory and reimbursement agreements are commercial in nature, and therefore confidential, making it difficult to hold parties accountable for the promises made or to evaluate the decisions made based on post-market data collection. While the threat to withdraw funding or approval exists in theory, withdrawing a drug from the market or delisting it from a drug plan is difficult administratively and unpopular politically (Vitry et al. 2015). As a result, drugs may remain on the market or be reimbursed despite evidence that they provide little or no clinical benefit (Government of Canada 2019). There is a lack of consensus on the best way to manage patients who do respond positively to a drug that is withdrawn or defunded. Clear decision rules and exit strategies will be required prior to initiating post-market evidence generation (Pace et al. 2021). Both federal and provincial governments have a responsibility to enforce reassessments based on iterative evidence collection for approval and reimbursement decisions, respectively. A balance needs to be found between encouraging transparency and accountability and protecting commercial interests and promoting innovation. To this end, clear decision-making processes, dispute resolution mechanisms and evaluation frameworks should be built into conditional regulatory approvals and reimbursement agreements.

What Can We Learn from the Pfizer–Israel COVID-19 Vaccine Agreement?

The COVID-19 pandemic has highlighted the importance of conditional regulatory approvals and other accelerated pathways in conjunction with supporting post-market data collection infrastructure. Recently, a redacted version of the Real-World Epidemiological Evidence Collaboration Agreement (the Agreement) was released that covers the purchase of the Pfizer-BioNTech COVID-19 vaccine for use in Israel (Israel Ministry of Health 2021). The parties agreed to “share information and data regarding the distribution, administration and use of the [vaccine], including to track its benefits” (Israel Ministry of Health 2021). The parties agreed to share epidemiological data collected through the Israeli Ministry of Health’s vaccination program in aggregate form to be jointly analyzed by the parties. The Agreement clarified that all data would continue to be owned by the Ministry of Health, regardless of transfer, but Pfizer was granted rights under the agreement to use the data for research and development purposes, regulatory submissions and scientific or other legitimate publications. The parties agreed to jointly prepare and publish results from the project in academic journals. The Agreement lists the data endpoints the parties will collaborate on, including subgroup analyses, as well as the specifics of the weekly data transfers including confirmed COVID-19 cases, hospitalizations, severe and critical cases, ventilator use, deaths, symptomatic cases, total vaccinees with demographic data and case counts by demographic.

Israel was able to enter into this type of agreement as a result of its robust national healthcare database, which contains data collected through health maintenance organizations. In addition, all healthcare providers in Israel also use electronic health records (EHRs), and the entire Israeli population is covered by the state’s healthcare system (Lovis and

Gamzu 2015). Israel is, therefore, better positioned than many other countries, especially federated countries such as Canada, with respect to post-market surveillance infrastructure. However, ethical concerns about the Agreement have been raised. Specifically, Israeli privacy expert Tehilla Shwartz Altshuler from the Israel Democracy Institute has expressed concern with respect to individual privacy if subgroup analyses are utilized, as well as the risk of exposure in the event of a cyber-attack when data are shared with a company outside of the health system (*France 24* 2021).

While the Agreement may be perceived as a positive step toward the integration of real-world data with regulatory decision making, it also highlights the outstanding issues and concerns that must be addressed before conditional agreements can be adopted more widely. Unlike Israel, most other countries, including Canada, do not have the requisite data infrastructure to collect and share data efficiently. Health data collection is the responsibility of each province, and as a result, health data are siloed within jurisdictions and institutions and EHRs have been inconsistently adopted and implemented. There remains limited capacity to share information across and within jurisdictional borders because of restrictive data and privacy laws and policies, and even if data were able to flow more freely, a lack of harmonization in systems would likely hinder interoperability (Katz et al. 2018).

Concluding Thoughts

Despite continued interest in adopting a life-cycle approach, many of the concerns discussed above have prevented the expected benefits from being realized in practice. The lack of success to date can be attributed to maladapted systems and infrastructure rather than a reflection of the value of a life-cycle approach. There have been some efforts to increase cooperation between the regulatory and reimbursement processes in Canada, such as the aligned review process between Health Canada, the Canadian Agency for Drugs and Technologies in Health and the Institut national d'excellence en santé et en services sociaux (Government of Canada 2018). However, to benefit from a life-cycle approach, Canada's health, regulatory and reimbursement systems and supporting data infrastructures need to be modernized. Enforcement and accountability measures need to be implemented that can identify and remove drugs that fail to confirm clinical benefit and/or cost-effectiveness while respecting the needs of individual patients for whom there is evidence of valuable benefit. While the new powers under Vanessa's Law (*Protecting Canadians from Unsafe Drugs Act* 2014) are an important step to improving Health Canada's ability to monitor the on-market performance of drugs, stronger mechanisms are needed to support the widespread adoption of conditional regulatory and reimbursement mechanisms. Finally, multi-stakeholder deliberative platforms and processes are needed to resolve the ethical concerns associated with the widespread use of administrative health data collection in the post-market setting. Ethical concerns need to be resolved in the traditional separation of clinical care and clinical research, and the equity interests of specific patient groups need to be weighed against the sustainability of health systems. While Israel's agreement with Pfizer highlights the benefits of having the ability to

capture population-level data to support healthcare planning, it also emphasizes the need to better understand and settle outstanding privacy and ethical concerns with trading data for access to new drugs.

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