Commentary: Expedited Regulatory Review of Low-Value Drugs

Commentaire : Examens réglementaires expéditifs pour les médicaments de faible valeur

JONATHAN J. DARROW, SJD, LLM, JD, MBA
Assistant Professor
Program on Regulation, Therapeutics and Law (PORTAL)
Brigham and Women's Hospital and Harvard Medical School
Boston, MA

REED F. BEALL, PHD
Assistant Professor
Community Health Sciences and O'Brien Institute for Public Health
Cumming School of Medicine, University of Calgary
Calgary, AB

Abstract

Lexchin has criticized Health Canada's recently published draft guidance on accelerated drug review, expressing concern over agency conflicts of interest and observing that priority review and notice of compliance with conditions correlate poorly with therapeutic benefit. Although agency operations may be imperfect, perhaps the most important finding of Lexchin's research is that only 11% of newly approved drugs provide meaningful benefit over standard treatments. To improve the expedited review process in light of these findings, we suggest eliminating user fees and fully funding the review process with public monies, reserving the use of expedited approval pathways for when preliminary measures of benefit are so large that traditional approval thresholds can be met earlier in the clinical trial process, improving labelling to quantitatively communicate drug benefits and risks, and avoiding the use of titles such as "priority" review, which could imply a magnitude of clinical superiority that has not been established.

Résumé

Lexchin a critiqué la version provisoire des lignes directrices de Santé Canada sur l'examen accéléré des médicaments, publiée récemment, en se disant préoccupé par les conflits d'intérêt de l'institution et en observant qu'il y a une faible corrélation entre, d'une part,

l'examen prioritaire et les avis de conformité avec conditions et, d'autre part, les avantages thérapeutiques. Bien que les activités de l'institution soient imparfaites, la principale découverte de Lexchin est sans doute que seuls 11 % des médicaments nouvellement approuvés apportent un avantage significatif par rapport aux traitements habituels. Pour améliorer le processus d'examen à la lumière des résultats de Lexchin, nous proposons d'éliminer les frais de service et de financer entièrement le processus d'examen avec les fonds publics, tout en réservant les voies d'approbation accélérées pour les cas où le constat préliminaire des avantages est si important que les seuils d'approbation traditionnels peuvent être atteints plus tôt au cours de la phase d'essai clinique, en améliorant l'étiquetage pour communiquer quantitativement les avantages et risques liés aux médicaments et en évitant l'utilisation d'énoncés tels qu'« examen prioritaire » lesquels portent à croire à un degré de supériorité clinique qui n'a pas été établi.

Introduction

Over the past two decades, national drug regulatory agencies around the world have introduced special approval programs to accelerate the development and review of novel therapeutics. Because these programs promote the earlier availability of medicines and allow revenue to begin accruing sooner, they have been welcomed by seriously ill patients and the pharmaceutical industry alike. However, the value of expedited programs depends on the extent to which the associated drugs provide actual patient benefits while avoiding harm.

In an insightful new analysis, Lexchin critically examined two special pathways used by Health Canada to expedite the development and review of new medicines: priority review, which provides an accelerated review target of 180 days rather than the usual 300 days, and notice of compliance with conditions (NOC/c), which provides a review target of 200 days and allows approval based on "promising evidence" such as surrogate end points or Phase II trials, on the condition that post-approval studies confirm benefit (Health Canada 2019). Based on his previously published research spanning 2012 to 2019, Lexchin argued that Canada's drug regulatory agency has been unable to reliably identify high-value drugs, that drugs approved under the two special programs have a greater likelihood of acquiring a safety warning or being withdrawn for safety reasons and that the recently proposed guidance will not address these problems.

Lessons from Lexchin's Work

Perhaps the most important lesson from Lexchin's work is that few new drugs provide substantial therapeutic benefit over what is available from existing treatments. In his most comprehensive analysis of 509 drugs approved between 1995 and 2016 for which independent therapeutic ratings were available, he found that only 55 (11%) provided meaningful therapeutic benefit (Lexchin 2018). Even among drugs receiving either type of expedited treatment, only 26% were found to have such a therapeutic benefit (Lexchin 2018) (separate analyses by Lexchin using more limited data found comparable figures of 36% for priority

alone [Lexchin 2015a] and 31% for NOC/c alone [Lexchin 2019]). Because a priority review serves to allocate limited agency resources, providing this faster review process to drugs that do not add substantial additional benefit dilutes the value of this pathway for manufacturers of drugs that do add meaningful therapeutic benefit. Advancing approval times also extends the effective patent period (Beall et al. 2019), increasing the financial reward for low-value products.

Another reason to exercise caution when contemplating the use of a new drug, especially those receiving expedited treatment, is that shorter clinical use and limited trial data mean that safety risks are less well characterized. Lexchin's work revealed that expedited drugs are more likely to receive a new safety warning or be withdrawn for safety reasons: 41% for a NOC/c (Lexchin 2015b) and 34% for priority review, versus 20% for a standard review (Lexchin 2012). Drugs receiving an NOC/c, by definition, are approved on the basis of more limited or uncertain data, with greater certainty expected to be achieved only after approval.

Although the therapeutic benefit of most new drugs, including most expedited drugs, is therefore disappointing according to independent expert reviews, it is less clear that Health Canada's record in expediting new drugs is itself problematic. Lexchin observed that regulatory grants of expedited status are frequently discordant with external appraisals of therapeutic value. He calculated kappa values, which are measures of interrater agreement with a theoretical maximum of 1, to be just 0.276 (priority and NOC/c together) and 0.334 (priority only), both in the "fair" range (Lexchin 2015a, 2018). However, when the data underlying the kappa values are presented differently, Health Canada's record appears less dismal. Of the 509 drugs approved between 1995 and 2016, 454 (89%) provided little or no additional value, of which Health Canada correctly declined to provide an expedited review to 337 (74% of 454) drugs (specificity). Of the 55 (11% of 509) drugs with additional value, Health Canada correctly identified and expedited 42 (76%) drugs (sensitivity; Lexchin 2018).

Improving both specificity and sensitivity simultaneously is desirable but challenging. Criteria for an expedited review could be tightened to reduce the number of low-value drugs given special treatment, but doing so could increase the number of higher-value drugs that are excluded, and vice versa. As Lexchin (2018) noted elsewhere, decisions to grant expedited treatment are made earlier in the development process, whereas the appraisals of therapeutic value on which he relied are made after more evidence is available, possibly explaining some of the discordance.

It is equally uncertain how Health Canada's approach to an expedited review causes more post-approval safety issues. The review programs, of course, cannot change the pharmacokinetics or pharmacodynamics of the drug substance but could affect the extent to which safety concerns are disclosed before versus after approval. Lexchin (2012) rejected the possibility that higher rates of post-market safety issues for expedited drugs could result from disease severity, but this conclusion is based on an earlier finding that rates of safety issues were similar between drugs receiving priority versus standard review within five

serious-disease categories – cancer, HIV/AIDS, inborn errors of metabolism, multiple sclerosis and the prevention of transplant rejection. These categories may be too broad to capture the types of differences likely to lead to the addition of a new safety warning. For example, drugs directed to later stages of disease or intended for use after previous lines of treatment have failed may be more likely to both receive expedited treatment and have unknown safety concerns, even within the same therapeutic category. Priority review may thus simply identify drugs that are more likely to receive safety warnings in any event, providing useful information to patients and clinicians, but little insight into whether regulators are striking the right balance.

As with drug approval itself, the decision to grant expedited treatment should be free from conflicts of interest. Lexchin observed that sponsors financially benefit when their products are expedited and argued that Health Canada should therefore convene independent panels of clinical experts to determine which experimental products are the most promising. However, agency personnel are themselves independent experts, or should be (Ferrera et al. 2014; Freedman 1976), and convening expert panels imposes costs in terms of both time and money, partially undermining the goal of an expedited review before it has begun. Concerns exist about the extent to which regulatory agencies have been captured by the industry, such as by the payment of industry user fees (Darrow et al. 2017), but members of expert panels can (and frequently do) have similar or more severe conflicts of interest (Bélisle-Pipon et al. 2018; Hayes and Prasad 2018). Regardless of the identity of the expert, the drug sponsor will be providing the data on which the expert's decision or recommendation is based. Publicly funded testing of new drugs has been proposed (Baker 2008), but it has not yet received mainstream support.

Conclusion: Conflicts of Interest

Conflicts of interest are also problematic, according to Lexchin, when the agency officials who provide guidance to companies before submission also assess the resulting marketing submissions. The growth in expedited development programs means that agency personnel have increasingly served as *de facto* consultants to the industry (Darrow et al. 2014) – a role that arguably should be fulfilled by private firms – and it is important that regulators not commit themselves to approving a drug for which benefits do not outweigh risks. At the same time, this interest must be balanced against the reasonable expectations of sponsors that requirements will not change after applications have been submitted. If those providing guidance to sponsors are different from those ultimately making the approval decision, it will increase the risk of inconsistent interpretation of regulatory requirements on which a sponsor has justifiably relied and burden the agency by requiring that additional personnel become familiar with complex applications.

Nevertheless, there are four steps that could help Health Canada and its foreign counterparts to improve the integrity of drug review programs, including expedited review

processes. First, concerns over agency capture and conflicts of interest could be mitigated by eliminating user fees, fully funding regulatory agencies with public funds and more strictly limiting conflicts of interest of those invited to serve on advisory panels.

Second, trends toward lower evidence requirements (Darrow et al. 2020) could be reversed. Because approximately 89% of newly approved drugs provide little or no therapeutic advantage over standard treatment, there is no public health reason to rush most treatments to the market. Approval based on limited evidence, such as surrogate end points, non-randomized and unblinded trials or approval following Phase I or II trials, should be limited to exceptional cases for which preliminary measures of benefit are so large and convincing that traditional approval thresholds can be met earlier in the clinical trial process. Even among the 11% of drugs offering meaningful benefits, few will meet this standard (Darrow et al. 2018).

Third, the benefits and risks known to exist should be clearly communicated to patients and physicians using quantitative measures. Existing drug labelling is lengthy, complex and poorly understood (Shrank and Avorn 2007). A drug facts box, analogous to nutrition labelling, has been demonstrated to reduce exaggerated expectations of drug benefit/risk ratios (Schwartz et al. 2009). As is done in the UK, newly approved drugs could bear an inverted triangle on their labels for some time, such as five years or until confirmatory trials are completed. Such a symbol would serve as a warning that limited evidence is available to support benefit and that unknown risks might still emerge.

Fourth, expedited programs should not be given names that imply large benefits, because, by definition, such benefits have not been established at the time unapproved drugs receive the designation. In particular, the term "Breakthrough" may imply benefits that are not justified by the evidence (Darrow et al. 2018). Health Canada's use of "NOC/c" appropriately avoids this potential pitfall. "Priority review," although an accurate description of regulatory treatment, could be replaced with a more neutral title, such as a "180-day review", to avoid implying greater benefits than are actually provided.

Correspondence may be directed to: Dr. Jonathan J. Darrow, 1620 Tremont St., Suite 3030, Boston, MA 02120. He can be reached by phone at 347-792-2246 or by e-mail at jjdarrow@bwh.harvard.edu.

References

Baker, D. 2008. The Benefits and Savings from Publicly Funded Clinical Trials of Prescription Drugs. *International Journal of Health Services* 38(4): 731–50. doi:10.2190/HS.38.4.i.

Beall, R.F., L. Hardcastle, F. Clement and A. Hollis. 2019. How Will Recent Trade Agreements That Extend Market Protections for Brand-Name Prescription Pharmaceuticals Impact Expenditures and Generic Access in Canada? *Health Policy* 123(12): 1251–58. doi:10.1016/j.healthpol.2019.09.005.

Bélisle-Pipon, J.C., L. Rinquette, A.L. Cloutier, V. Doudenkova and B. Williams-Jones. 2018. Conflicts of Interest and the (In)dependence of Experts Advising Government on Immunization Policies. *Vaccine* 36(49): 7439–44. doi:10.1016/j.vaccine.2018.10.058.

Darrow, J.J., J. Avorn and A.S. Kesselheim. 2014. New FDA Breakthrough-Drug Category: Implications for Patients. *NEJM* 370(13): 1252–58. doi:10.1056/NEJMc1405337.

Darrow, J.J., J. Avorn and A.S. Kesselheim. 2017. Speed, Safety, and Industry Funding: From PDUFA I to PDUFA VI. *NEJM* 377(23): 2278–86. doi:10.1056/NEJMhle1710706.

Darrow, J.J., J. Avorn and A.S. Kesselheim. 2018. The FDA Breakthrough Drug Designation: Four Years of Experience. *NEJM* 378(15): 1444–53. doi:10.1056/NEJMhpr1713338.

Darrow, J.J., J. Avorn and A.S Kesselheim. 2020. FDA Regulation and Approval of Pharmaceuticals, 1983–2018. *JAMA* 323(2): 164–76. doi:10.1001/jama.2019.20288.

Ferrera, G.R., M.M. Alexander, C. Kirschner, W.P. Wiggins and J.J. Darrow. 2018. *The Legal and Ethical Environment of Business: An Integrated Approach*. Wolters Kluwer.

Freedman, J.O. 1976. Expertise and the Administrative Process. *Administrative Law Review* 28(3): 363–78.

Hayes, M.J. and V. Prasad. 2018. Financial Conflicts of Interest at FDA Drug Advisory Committee Meetings. *Hastings Center Report* 48(2): 10–13. doi:10.1002/hast.833.

Health Canada. 2019. Draft Guidance: Accelerated Review of Human Drug Submissions. Retrieved April 6, 2020. <https://www.canada.ca/en/health-canada/programs/consultation-draft-guidance-accelerated-review-human-drug-submissions.html>.

Lexchin, J. 2012. New Drugs and Safety: What Happened to New Active Substances Approved in Canada between 1995 and 2010? *Archives of Internal Medicine* 172(21): 1680–81. doi:10.1001/archinternmed.2012.4444.

Lexchin, J. 2015a. Health Canada's Use of Its Priority Review Process for New Drugs: A Cohort Study. *BMJ Open* 5(5): e0068162015. doi:10.1136/bmjopen-2014-006816.

Lexchin, J. 2015b. Post-Market Safety Warnings for Drugs Approved in Canada under the Notice of Compliance with Conditions Policy. *British Journal of Clinical Pharmacology* 79(5): 847–59. doi:10.1111/bcp.12552.

Lexchin, J. 2018. Health Canada's Use of Expedited Review Pathways and Therapeutic Innovation, 1995–2016: Cross-Sectional Analysis. *BMJ Open* 8(8): e023605. doi:10.1136/bmjopen-2018-023605.

Lexchin, J. 2019. Health Canada's Use of Its Notice of Compliance with Conditions Drug Approval Policy: A Retrospective Cohort Analysis. *International Journal of Health Services* 49(2): 294–305. doi:10.1177/0020731418821007.

Schwartz, L.M., S. Woloshin and H.G. Welch. 2009. Using a Drug Fact Box to Communicate Drug Benefits and Harms: Two Randomized Trials. *Annals of Internal Medicine* 150(8): 516–27. doi:10.7326/0003-4819-150-8-200904210-00106.

Shrank, W.H. and J. Avorn. 2007. Educating Patients about Their Medications: The Potential and Limitations of Written Drug Information. *Health Affairs* 26(3): 731–40. doi:10.1377/hlthaff.26.3.731.