Review

DIA

Therapeutic Innovation
& Regulatory Science
2020, Vol. 54(1) 195-199

https://doi.org/10.1007/s43441-019-00045-x

How Do Drug Regulatory Bodies Deal With Potential Innovative Therapies?

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Abstract

Given the extensive development of new molecules over the last 10 years, regulatory authorities (RAs) have been intensively working on evaluating how to identify and manage "innovative" drugs. The purpose of this article is to analyze whether RAs have procedures capable of ensuring access to innovative drug therapies and to understand what criteria RAs around the world (Europe, USA, Canada, Australia, and Japan) use to identify innovative drugs, comparing the different strategies and tools used to prioritize the assessment of the most promising drugs. All the RAs under review consistently use two elements to speed up drug access: (1) the handling (shortening) of approval times and the (2) management of the (limited) evidence available. No international RA utilizes any state-of-the-art method to evaluate the innovativeness of medicinal products. Harmonizing a definition and the criteria used to define pharmaceutical innovation would allow faster access to patients.

Keywords

drug innovation, FDA, EMA, HC, TGA, regulatory approval

Introduction

Some analysts believe that innovation is clearly declining, while others assume that the increase of approved drugs, for example, in selected therapeutic areas such as oncology and rare diseases, indicates that development/discovery is still satisfactory.[1,2] Given the extensive development of new molecules in the last 10 years, regulatory authorities (RAs) around the globe have been intensively working on evaluating how to identify and manage "innovative" drugs. The scientific community is struggling to answer 2 key questions: does a harmonized definition of innovative drug exist? And how can the degree of innovation be measured for a medicinal product?

These questions become of a paramount importance in light of the skyrocketing price of new drugs, which places at risk the economic sustainability of both publicly and privately funded health services. Moreover, it is of the utmost importance to be able to predict to what extent the real impact that innovative drugs have on the patient's benefit and quality of life.

However, one thing seems to be clear and accepted by all parties involved: a faster regulatory assessment is needed for this type of drugs in order to speed up patient access.

The purpose of this paper is to analyze whether RAs have specific procedures able to ensure access to innovative drug therapies and understand what criteria RAs around the world (Europe, USA, Canada, Australia, and Japan) use to identify innovative drugs, comparing different strategies and tools used to prioritize the assessment of the most promising drugs.

Results

Three articles (of 6) were considered relevant for the evaluation and were included in the analysis: Kesselheim et al,[3] Lexchin et al,[4] and Ward et al.[5]

In 2013, Kesselheim et al published a systematic review which identified the variety of methods used to measure innovation in the pharmaceutical field and analyzed whether the use of various definitions can lead to differing conclusions on the degree of innovation of a drug.[3] This systematic review identified 4 criteria used to define and measure innovation: (1) the number of newly approved molecules, (2) the evaluation of the therapeutic value, (3) the assessments of economic parameters (e.g., market shares or cost-effectiveness analyses), and (4) the number of patents. Kesselheim et al[3] found that when the parameter used to measure innovation is the number of new chemical/molecular entities approved, the level of innovation achieved is more optimistic, although overestimating the

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Submitted 31-Aug-2018; accepted 26-Nov-2018; published online 6-Jan-2020

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Table 1. Times Used by the Main Regulatory Agencies for Drug Evaluation, Authorization, and Special Designation.

		EMA	FDA	TGA	HC	PMDA
Approval time management	Fast procedures	Accelerated assessment (5 mo vs the standard 7 mo)[14]	Priority review (6 mo vs the standard 10 mo)[15]	Priority review (maximum time 150 d)[16]	Priority review (evaluation times are not accelerated but the dossier "skips the line" and is given priority)[17]	Priority review (9 mo vs the standard 12 mo)[18]
Investigation of the available evidence	Special Designations	PRIME[19]	Breakthrough therapy designation, Fast Track[b,15]	–	–	Sakigake (6-mo review)[20]
	Special Authorizations	Conditional approval[a,21] Approval under exceptional circumstances[a,14]	Accelerated approval[15]	Provisional approval [16]	Notice of compliance with conditions[22]	–

[a]"Conditional approval" is a procedure that usually turns into a standard procedure once the company presents the necessary data to EMA during the post-authorization phase; on the other hand, "Approval Under Exceptional Circumstances" is an authorization status that persists given the unfeasibility for the company to present further data during the postauthorization phase, for example, rare diseases.
[b]"Breakthrough Therapy" is a designation established on preliminary clinical data; "Fast Track" is a designation that can be requested using only pre-clinical data.

importance of some drugs. On the other hand, when assessments of innovation were based on the therapeutic value, economic parameters or new patents, they produce unclear or negative results. Notably, in the studies analyzed, the assessment of medicinal products based on the parameter of therapeutic value resulted in a negative opinion on their innovativeness. Two other studies (Lexchin et al[4] and Ward et al[5]), designed as observational studies, aimed at assessing the therapeutic innovativeness of drugs approved in Canada and the UK during the past 20 years. What is interesting to notice is that these papers used different tools to assess the degree of innovation of the approved medicinal products.

In particular, Lexchin et al[4] evaluated therapeutic innovation of approved drugs in Canada during the time-lapse 1997-2012 using the Patented Medicine Prices Review Board (PMPRB) and Prescrire International. The PMPRB is a federal agency responsible for calculating the maximum introductory price for all new patented medications introduced in the Canadian market.[4] Prescrire, on the other hand, is an independent bulletin that assesses the therapeutic value of medicines using a specific multistep process method.

Ward et al,[5] instead, based their estimation of the innovativeness of drugs approved in the UK between 2001 and 2012 using the published criteria proposed by Aronson et al[6] and Ferner et al.[7] Such criteria define innovation using both health and nonhealth elements, which incorporate both clinical usefulness and the process through which an innovation arises (e.g., new target, novel mechanism of action).[5]

All the available evidence considered has been generated from post hoc evaluations of innovativeness carried out when a drug was already approved by a regulatory agency. Furthermore, none of the published literature mentions or suggests that a single harmonized definition of "drug innovation" is currently available, or that anyone is working on such a project.

Hence, it is compelling to analyze how the RAs identify innovativeness of a drug at such an early stage, in the period before the approval, when the knowledge about the drug is, inevitably, limited. To assess such inquiry, the publicly available information on the websites of the 5 major international regulatory agencies—the EMA, FDA, HC, TGA, and the PMDA—was analyzed. It is important to note that no RA seems to have developed an official definition for pharmaceutical innovation. However, every RA adopts faster authorization pathways for the most promising drugs with the objective to ensure prompter patient access to these medicinal products.

All the RAs under review consistently use two elements to speed up drug access: (1) the handling (shortening) of approval times and the (2) management of the (limited) evidence available (Table 1).

All the agencies provide faster procedures, mostly consisting of reducing dossier review time. It is interesting to note that the Canadian Agency has a special system called "Priority Review of Drug Submissions" that allows certain dossiers to be evaluated before others waiting for assessment. This "skip the line" method allows the RA to prioritize the most promising drugs, without reducing the necessary time for assessment. Conversely, the management of the evidence available at the time of the submission of the dossier, which often consist of an immature clinical data package, increases the complexity of the decision assessment process. The RAs deal with this issue by channeling promising drugs through specific regulatory pathways or special authorizations (Table 1). Special authorizations (conditional approval—EMA; accelerated approval—FDA; provisional approval—TGA; notice of compliance with conditions—HC) are assigned to drugs that show uncertainties regarding safety and efficacy during their evaluation. These types of authorization are

Table 2. Requirements Necessary to Access Special Designations/Authorizations.

	EMA		FDA		TGA	HC	PMDA
	Conditional approval/ under exceptional circumstances	PRIME	Accelerated approval	Breakthrough therapy designation/ Fast track	Provisional approval	Notice of compliance with conditions	Sakigake
Unmet medical need, a severe illness, or a life-threatening disease	✓	✓	✓	✓	✓	✓	–
Surrogate endpoints/biomarkers	✓	✓	✓	✓	✓	✓	–
Significant improvement of treatment compared to existing therapies	–	✓	–	✓	✓	✓	✓
Interaction between companies and regulatory agencies during the development phase (early dialogue/ scientific advice)	Possible if requested	Automatic	Automatic	Automatic	Possible if requested	Possible if requested	Automatic

temporary and require the generation of new data in the post-authorization phase to be converted into a full authorization. The one exception to this rule comes from the EMA's "marketing authorization under exceptional circumstances" whereby the company is not expected to produce further efficacy and safety evidence after initial approval, because of the impossibility to produce such data, for example, too few patients affected by a rare disease.

Another key point is the criteria used by the various agencies to designate drugs with the highest priority to access the market. Table 2 shows the requirements necessary to access the specific routes/authorizations that the various agencies use. In order to be eligible for special designations and authorization procedures, EMA, FDA, TGA, and HC demand that the drug responds to the following conditions: an "unmet medical need," a severe illness, or a life-threatening disease. Another criterion adopted by all the RAs considered for this study is the significant improvement of a treatment compared to existing therapies (a concept similar to added therapeutic value for which additional comparative data must be submitted). This principle seems to be used more for special designations rather than specific authorization procedures. Furthermore, the opportunity to submit less reliable evidence (based, for example, on surrogate endpoints or the use of biomarkers) is another factor that all the agencies consider when assessing special designations and authorizations. Moreover, special designations/authorizations give access to a regulatory pathway that entails greater interaction between companies and regulatory agencies during the development of the drug. Such an approach is mostly used for peculiar pathologies. The special designations Prime, Accelerated Approval, Breakthrough Therapy / Fast Track, and Sakigake automatically entail greater interaction between the two stakeholders; while Conditional Approval / Under Exceptional Circumstances, Provisional Approval, and Notice of Compliance With Conditions give this opportunity if requested by the company. It is important to remember that having a special designation (Prime, Breakthrough Therapy / Fast Track, Sakigake) generally represents the means of access for faster authorization procedures.

Discussion

In general, this analysis shows that a globally accepted definition of "innovative drug" is currently missing. However, all RAs provide faster assessment paths for new or more promising drugs and the concept of innovation is managed mostly throughout the acceleration of the evaluation process, increasing the risk of lowering the standard levels usually required at the time of the marketing approvals. It is interesting to notice that the criteria used to authorize these assessment paths are essentially homogeneous and mainly concern the severity of the disease, the absence of therapeutic alternatives, the therapeutic value of the drug in the current context. This unavoidably leads to the argument as to why a universally accepted definition of innovative drug is lacking. Furthermore, no common procedure has been established to evaluate over time, in the postmarketing phase, the RAs' efficiency in confirming the potential innovation. As a matter of fact, a recent systematic review showed that the quantity and quality of postapproval clinical evidence varied substantially for novel drugs, initially approved on the basis of limited evidence, and that few controlled studies were published after approval confirming efficacy.[8] In order to overcome this shortcoming, all RAs should collaborate to find a common definition and approach to assess innovativeness of medicinal products, especially since pharmaceutical companies apply for approval of a product almost at the same time in most countries. It is noteworthy to point out that only FDA and HC have been considering the therapeutic value of the drug for many years as an access criterion for special designations/approvals. This concept was introduced in Japan in 2014, in EMA—with Prime—in 2016 and in Australia in 2017.

There has been extensive debate about the topic of innovative drugs and what defines a pharmaceutical innovation. Furthermore, all the analyses found in literature regarding this

topic are based on post hoc evaluations. It is of the outmost importance, in order to ensure greater clinical and quality of life benefits for the patients, to elucidate how these decisions are made by the RAs.

The reality is that no international RA utilizes any state-of-the-art method to evaluate the innovativeness of medicinal products. As a matter of fact, the methods and criteria used by the various RAs to assess whether a medicinal product should be considered innovative or not can be considered analogous as they are all based on added therapeutic value, economic parameters and patents. This reflects a situation where no relevant change has occurred in the evaluation of drug innovativeness. So, the same question arises again: Why has no one worked and collaborated on a common definition of innovativeness? All the necessary tools are already on the table.

Within the context of European HTA bodies and payers, Italy has recently adopted specific criteria to recognize and reword innovation. Indeed, the Italian Medicines Agency grants an "innovative status" to products based on the evaluation of the unmet medical need, the added therapeutic value compared to existing therapeutic options and the overall quality of clinical evidence, assessed through the GRADE system. Obtaining the innovative status implies substantial benefits for manufacturers (i.e., dedicated funds and a facilitated market entry). In France, all medicinal products that obtain a marketing authorization are subject to the assessment of the added therapeutic value (*Amélioration du service médical rendu* or ASMR), which is based on 4 criteria: (1) availability of comparators; (2) quality of the evidence; (3) added benefits versus its comparator in terms of efficacy, safety, and quality of life; (4) the unmet clinical need.[9,10] Such criteria represent the basis to identify innovation and have a direct influence on the price of the drug (the potential price rises when the added therapeutic value is higher). In addition, in the French system a fast-track procedure to accelerate market entry of potentially innovative products can sometimes be used, in which case the ASMR can be assessed prior to the marketing authorization being granted. Similarly, Germany, Belgium, and the Netherlands have adopted predefined scales for the assessment of the therapeutic added value.[11] Because of the similarities in these systems, evolving toward a common evaluation of the added therapeutic value seems to be a reachable target at the HTA level.

In general, maintaining the spotlight on the accelerated pathways for innovative drugs and not focusing on creating a globally accepted definition for these medicinal products, is reflecting negatively on the patient's clinical outcomes.[12,13] So how can the RAs ensure that only truly innovative drugs will be given access to priority review pathways / authorizations? These negative judgments suggest that the criteria used by the various RAs are not stringent enough to give access to the accelerated pathways only to the legitimately innovative drugs.

Harmonizing the criteria used to define pharmaceutical innovation would allow faster access of these products to specific regulatory pathways and special designations. Such an approach would benefit all stakeholders involved in the development of innovative drugs: pharmaceutical companies would be aware of the requirements they need to meet in order to obtain "innovative" status, regulators could more promptly give access to the specific routes and authorizations, HTA bodies and payers would have additional elements for their own evaluations, and most importantly the patients would be ensured more rapid access to the necessary drugs.

Methods

The websites of the major international regulatory agencies were consulted looking for any public document or position paper dedicated to the issue of innovation. The RAs considered for this study were the European Medicines Agency (EMA), The American Food and Drug Administration (FDA), Health Canada (HC), the Australian Therapeutic Goods Administration (TGA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

A literature search of publicly available data was performed using the bibliographical library PubMed of the last ten years (2008-2017). The search terms used were *innovativeness*, *innovation*, *innovative*, and *drug*, as free text.

Study Highlights

Given the extensive development of new molecules over the last 10 years, regulatory authorities (RAs) around the globe have been intensively working on evaluating how to identify and manage "innovative" drugs. The purpose of this paper is to analyze whether RAs have procedures capable to ensure access to innovative drug therapies and understand what criteria RAs around the world (Europe, USA, Canada, Australia, and Japan) use to identify innovative drugs. Harmonizing the criteria used to define pharmaceutical innovation would allow faster access of these products to specific regulatory pathways and special designations. Such an approach would benefit all stakeholders involved in the development of innovative drugs: pharmaceutical companies would be aware of the requirements they need to meet in order to obtain "innovative" status, regulators could more promptly give access to the specific routes and authorizations, HTA bodies and payers would have additional elements for their own evaluations, and the patients would be ensured more rapid access to the necessary drugs.

Author Note

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the Italian Medicines Agency (AIFA).

Declaration of Conflicting Interests

No potential conflicts were declared.

Funding

No financial support of the research, authorship, and/or publication of this article was declared.

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References

1. Munos BH, Chin WW, Edwards AM, Yamamoto KR, Friend SH. A call for sharing: adapting pharmaceutical research to new realities. *Sci Transl Med*. 2009;1(9).
2. Haffner ME. Adopting orphan drugs—two dozen years of treating rare diseases. *N Engl J Med*. 2006;354(5):445-447.
3. Kesselheim AS, Wang B, Avorn J. Defining "innovativeness" in drug development: a systematic review. *Clin Pharmacol Ther*. 2013;94(3):336-348.
4. Lexchin J. How safe and innovative are first-in-class drugs approved by Health Canada: a cohort study. *Healthc Policy*. 2016;12(2):65-75.
5. Ward DJ, Slade A, Genus T, Martino OI, Stevens AJ. How innovative are new drugs launched in the UK? A retrospective study of new drugs listed in the British National Formulary (BNF) 2001–2012. *BMJ Open*. 2014;4(10):e006235.
6. Aronson JK, Ferner RE, Hughes DA. Defining rewardable innovation in drug therapy. *Nat Rev Drug Discov*. 2012;11(4):253-254.
7. Ferner RE, Hughes DA, Aronson JK. NICE and new: appraising innovation. *BMJ*. 2010;340(jan05 2):b5493-b5493.
8. Pease AM, Krumholz HM, Downing NS, Aminawung JA, Shah ND, Ross JS. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *BMJ*. 2017;357: j1680.
9. Rapport sur la réforme des modalités d'évaluation des médicaments. https://solidarites-sante.gouv.fr/IMG/pdf/rapport_polton_-_evaluation_medicaments.pdf. Accessed November 12, 2018.
10. 8ème Conseil stratégique des industries de santé (CSIS) - Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation. http://m.enseignementsup-recherche.gouv.fr/cid132716/8eme-conseil-strategique-des-industries-de-sante-csis.html. Accessed November 12, 2018.
11. Boucaud-Maitre D, Altman JJ. Do the EMA accelerated assessment procedure and the FDA priority review ensure a therapeutic added value? 2006–2015: a cohort study. *Eur J Clin Pharmacol*. 2016;72(10):1275-1281.
12. Naci H, Mossialos E. Accelerated access to new drugs and technologies. *BMJ*. 2017;359:j5387.
13. Arnerić SP, Kern VD, Stephenson DT. Regulatory-accepted drug development tools are needed to accelerate innovative CNS disease treatments. *Biochemical Pharmacology*. 2018; 151, 291-306. https://doi.org/https://doi.org/10.1016/j.bcp.2018.01.043
14. Regulation (EC) No 726/2004. European Commission. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf. Accessed November 30, 2018.
15. U.S. Food and Drug Administration. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. https://www.fda.gov/ForPatients/Approvals/Fast/default.htm. Updated February 23, 2018.
16. Therapeutic Goods Administration. Consultation: Expedited pathways for prescription medicines – Eligibility criteria and designation process. (2016).
17. Health Canada. Guidance for Industry - Priority Review of Drug Submissions - Canada.ca. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/priority-review/drug-submissions.html. Accessed January 19, 2018.
18. Pharmaceutical and Medical Devices Agency. Reviews | Pharmaceuticals and Medical Devices Agency. https://www.pmda.go.jp/english/review-services/reviews/0001.html. Accessed January 19, 2018.
19. EMA. European Medicines Agency - Research and development - PRIME: priority medicines. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp. Accessed January 19, 2018.
20. Pharmaceutical and Medical Devices Agency. Strategy of SAKIGAKE. (2014).
21. COMMISSION REGULATION (EC) No 507/2006. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf. Accessed November 30, 2018.
22. Health Canada. Guidance Document: Notice of Compliance with Conditions (NOC/c) - Canada.ca. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/notice-compliance-conditions.html. Accessed January 19, 2018.