The practical application of regulatory science:
Impact on regulatory policy and practice

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Abstract
As a reflection of the constantly evolving desire to understand how our environment impacts us and how what we do impacts our environment, an ever-growing number of specialised scientific disciplines are emerging. Quantum biology, nutrigenomics and computational social sciences are among those that capture the public's imagination. But underlying the efficient development and regulation of, and access to, the stunning diversity of novel therapies available now and being developed for the future, sits the discipline of regulatory science.

While this article will delve into the components and influences of regulatory science, we can begin by describing it as is the scientific and technical foundations on which regulations are based, especially for those involving health or safety. The origin of the term "regulatory science" is unknown. It likely took root in the late 1970s to address ways that the newly formed US Environmental Protection Agency could meet mandated deadlines to make decisions that would require using scientific approaches that were not meeting conventional scientific requirements. In 1985, Alan Moghissi established the Institute for Regulatory Science in the Commonwealth of Virginia as a non-profit organisation with the objective to perform scientific studies "at the interface between science and the regulatory system". Moghissi et al *have provided an extensive description of the history of regulatory science.*[1]

This article offers an overview designed to: identify important activities of regulatory science that can impact key stakeholders; provide examples of the practical application of these activities; and offer observations around implementing these activities.

Note: This article is based on a presentation given by Dr Larry Liberti at the TOPRA Annual Human Medicines Symposium 2017, London, UK.

Introduction

Today, regulatory science is a widely accepted concept that should permeate medicines development, regulatory review and lifecycle management. Every organisation, from sponsors to regulators, patient advocacy groups and think-tanks should use regulatory science as a driver of their activities. For example, the Innovative Medicines Initiative (IMI), a public-private European initiative, in 2008 identified its role in using regulatory science to further the advancement of critical areas: advancing medicines safety through improved predictive toxicology; stratifying patients and diseases to better target therapies; developing innovative clinical trial designs; informing new tools for benefit–risk assessment; characterising medicines cost-effectiveness in real world use; and investigating new licensing/authorisation approaches to expedite access to safe and effective medicines.[2]

For companies developing innovative new medicines, regulatory science provides the basis for globally aligned regulatory expectations, promulgated in guidelines by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The role of medicines regulators as nationally focused, retrospective assessors of data is rapidly shifting to that of prospective generators of public data and tools to help drive what has now become a global product development and regulatory enterprise, a key part of any truly effective 21st century healthcare system. Murray Lumpkin *et al* have provided compelling evidence that regulatory science will help to both drive and define the regulator's role in efficient healthcare.[3]

What is regulatory science?

While diverse definitions and approaches to implementing regulatory science exist, consequently, from the perspective of many science-based regulators, regulatory science must focus on developing new tools, standards, models, and approaches to assessing the efficacy, safety, manufacturing quality, and performance of medical products, in the service of public health.[4]

For the US FDA, regulatory science is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.[5] The FDA's "Advancing Regulatory Science Initiative" builds on the achievements of existing agency programmes, like the Critical Path Initiative's ground-breaking efforts to transform the way medical products are developed, evaluated, and manufactured. Elements of the FDA Safety and Innovation and subsequent acts, reflected in the Prescription Drug User Fee Acts (PDUFA) devote efforts specifically to "advancing regulatory science to promote public health innovation". This requires the FDA to develop a strategy and implementation plan to advance regulatory science. Some aspects of PDUFA VI impacted by regulatory science are discussed in the following sections.

Figure 1: Gap analysis of agency and company decision-making practices.
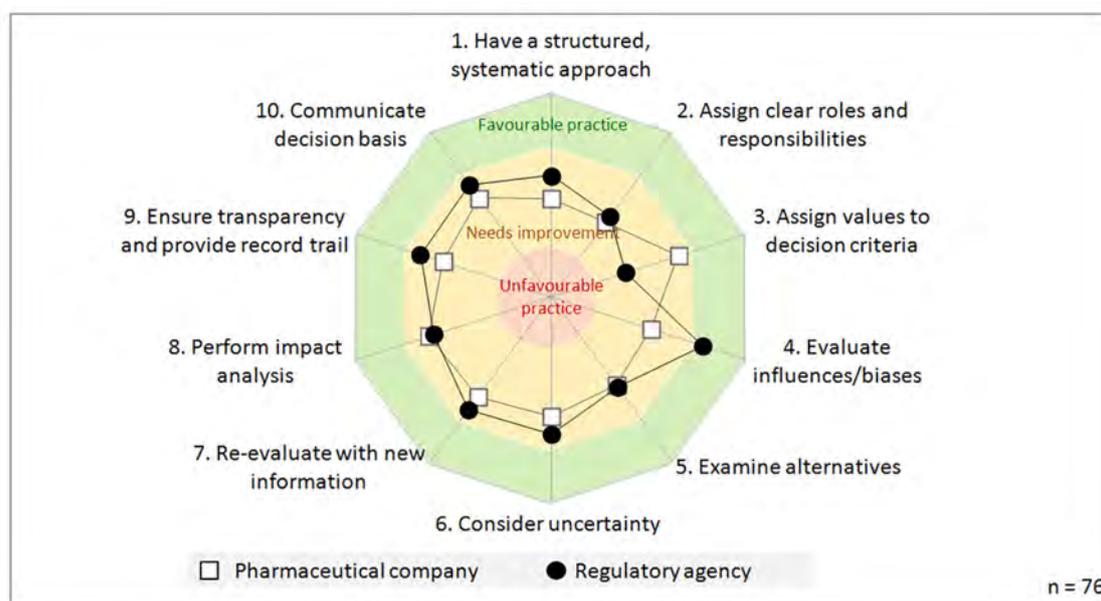
Organisational-level agency and company responses were mapped against the 10 quality decision-making practices, demonstrating key differences between company and agency practices and confirming the need for improvement and training in decision-making for both groups.

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) defines regulatory science as "the science to adjust the achievements of science and technology with a view to make use of them for people and society in the most desirable way, by making exact prediction, assessment, and judgment based on evidence". Regulatory Science Network Netherlands (CBG-MEB) similarly focuses on the practical applications of this science (*www.regulatoryscience.nl*).

Regulatory science, therefore, can inform various aspects of a medicine's lifespan. The next sections focus on three areas influenced by regulatory science: benefit–risk assessment, regulatory decision-making and advancing the efficient use of accelerated regulatory frameworks.

Evaluating and assessing medicine benefits and risks

Just as regulatory science underpins the lifecycle management approach to regulation, it consequently supports a systematic approach to the development and refinements of tools for benefit–risk assessments, including risk evaluation and mitigation strategies.[6] PDUFA VI focuses on using regulatory science to ensure the proper use of benefit–risk assessment in regulatory decision-making. Building on its initial work entitled "Structured Approach to Benefit–Risk Assessment in Drug Regulatory Decision-Making",[7] the agency is charged with implementation of a structured benefit–risk assessment process that includes the incorporation of the patient's voice in drug development and decision-making,

A 2012 international survey of mature regulatory agencies and international pharmaceutical companies concluded that the respondents believed that it is possible to develop an overarching benefit–risk framework that should involve relevant stakeholders in the development, validation and application of a universal framework.[8]

A wide variety of tools and approaches has been identified for the assessment of benefits and risks, each with its own strengths and limitations (see *http://protectbenefitrisk.eu/methods.html*). Nevertheless, a large degree of consistency can be found across these approaches. Using a systematic methodology driven by regulatory science, an overarching 8-step framework termed the Universal Methodology for Benefit–Risk Assessment (UMBRA) was developed.[9] Standardised methodologies such as those based on UMBRA[10] and the outputs of the Benefit Risk Action Team (CIRS-BRAT) modelling approach (*www.cirs-brat.org*), together with the revision to the ICH Guideline on enhancing the format and structure of benefit–risk information in ICH efficacy [M4E(R2)] and the International Summary Approach to Benefit Risk Evaluation (iSABRE) initiative (*www.cirsci.org/global-development-track/isabre/*) recognise that regulatory science can underpin a systematic approach to benefit–risk assessment that is bringing concordance across systems and stakeholders.

Facilitating sound and transparent decision-making

"An organisation that seeks to improve its decisions should also routinely measure the quality of its decision-making."[11]

The impact of decision-making during the development and the regulatory review of medicines greatly influences the delivery of new medicinal products. To better characterise how pharmaceutical companies, regulators and health technology assessors make their respective decisions, a methodical approach was undertaken

Figure 2: New active substance median approval time by review type for six regulatory authorities in 2012–2016.
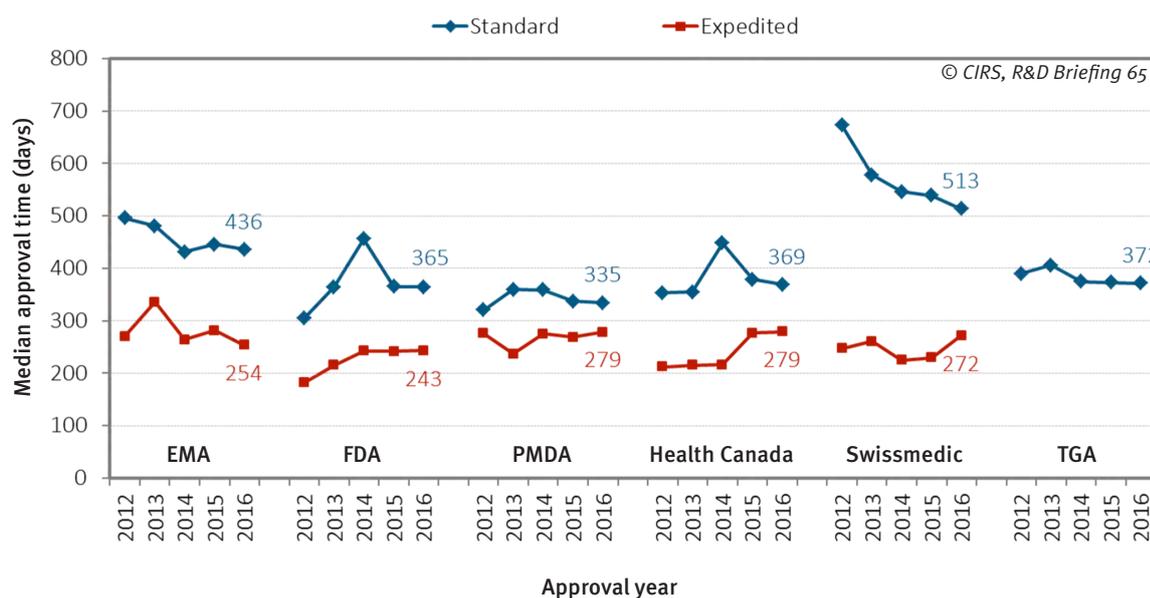
'Expedited review' refers to the European Medicines Agency (EMA) 'Accelerated Assessment' and FDA/PMDA/Health Canada/Swissmedic 'Priority Review'. Australia's TGA introduced an expedited (priority) review programme in 2017. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

to identify the key aspects of making these respective decisions. Using the concepts of regulatory science, Donelan *et al*[12] developed the multifactorial Quality of Decision-Making Orientation Scheme (QoDoS) instrument. This approach focuses on the quality of the decision-making process used by individuals and organisations with the underlying premise that the consistent use of a structured approach results overall, in more effective and appropriate outcomes (see Figure 1).

A survey of 14 regulatory agencies and 25 multinational companies found the need to further characterise and assess the practices and behaviours of individuals and organisations. All of the companies and 90% of the agencies believed that decision-making at their organisations could be improved.[13] Although both stakeholders were found to some extent to have already implemented frameworks and various methodologies, these are often informal and unsystematic.

As with any other culture-change process, barriers to quality decision-making were observed. These were primarily related to overcoming the influence of biases, and could be addressed by developing the general principles of a formal quality decision framework and identifying quality decision-making practices to ensure that structured decisions are made throughout the lifecycle of medicines.

The development of good regulatory practices (GRPs) is an important component of quality decision-making driven by regulatory science. These harmonised tools to conduct various regulatory activities allow standardisation of practices, increased transparency, and informed decision-making processes. Among these activities are good review practices (GRevP).

Underscoring the importance of GRevP in expediting the regulation

of critical new medicines, the FDA developed a procedure entitled "Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics" (MAPP 6025.6). This procedure was designed to expedite the development and review of these therapies by guiding how to address an efficient drug development programme, assign a cross-disciplinary review team, and to ensure an organisational commitment to involve senior management in the review.

More broadly, GRevP have been the focus of the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC), as part of the implementation of the "2020 Good Review Practices (GRevP) Roadmap".[14]

To ensure the integration of GRevP into everyday decision-making, APEC has conducted a series of ongoing workshops for regulatory representatives from more than 20 economies. Workshops have been designed to address the fundamental elements of a well-designed regulatory review system, to provide training modules for GRevP and to exchange and use product assessment reports between regulatory authorities. The goals of aligned GRevP are to promote regulatory efficiencies and best practices. While APEC has noted that the adoption of GRevP is key to building trust between agencies, each economy should address its needs and adopt its own best practices based on its resources and environment. Collaboration involves developing a framework for the development of a GRevP best-practice document.

In 2015, informed by the work being conducted by APEC and others, the World Health Organization developed "Good review practices: guidelines for national and regional regulatory authorities".[15] The WHO noted that implementation of GRevP helps agencies to achieve timely reviews with high quality outcomes,

Figure 3. Risk-stratification reliance approval pathways to reduce overall review times.
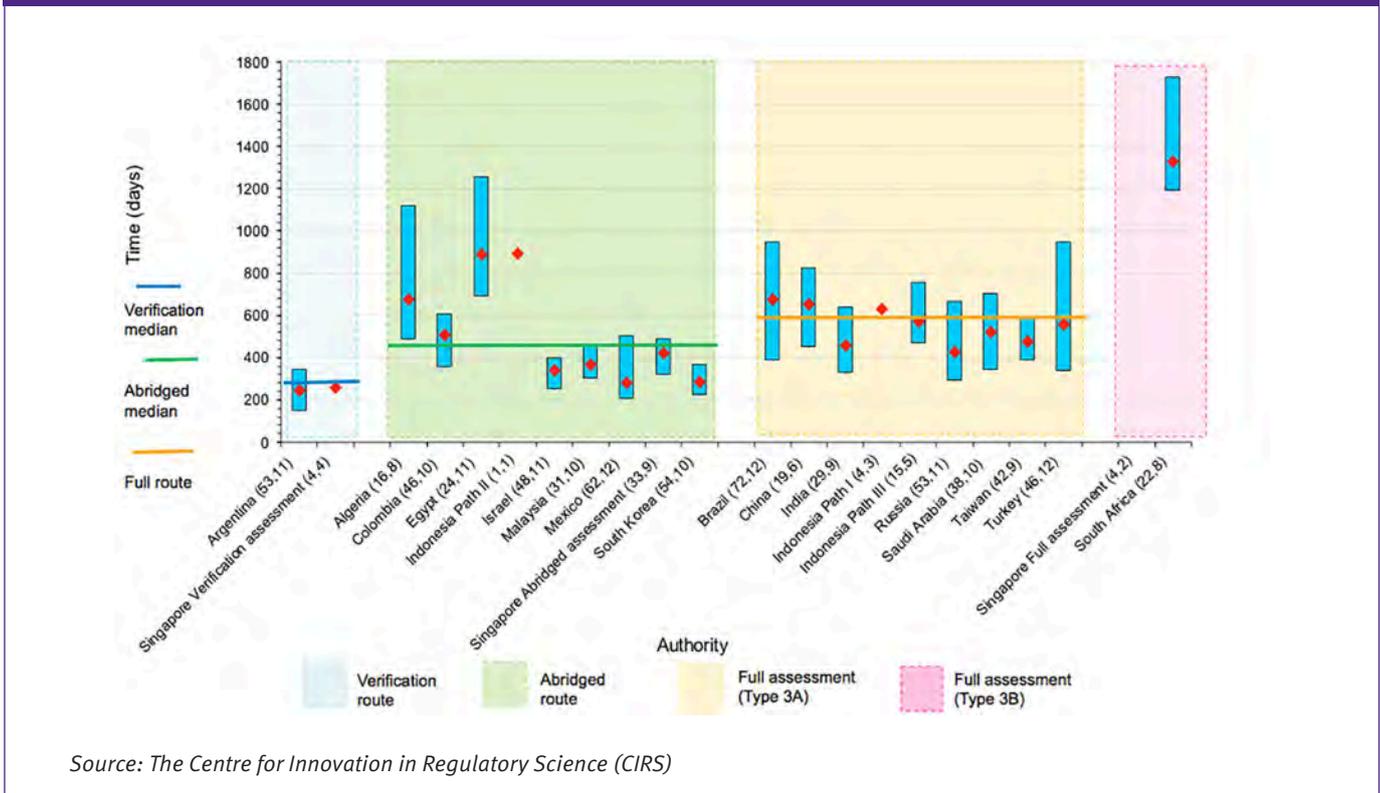
Source: The Centre for Innovation in Regulatory Science (CIRS)

with a significant impact on public health, for example in terms of patients' access to important medical products, and costs to both government and applicants. GRevP also facilitate progress towards regulatory convergence through the exchange of review reports and better mutual understanding among agencies. This is a significant benefit as the use of reviews and decisions reached by other agencies is expected to become increasingly important in achieving review efficiencies in the face of pressures on resources.

Advancing the efficient use of accelerated frameworks

Earlier it was noted that the IMI initiative recognised the importance of regulatory science in investigating new licensing/authorisation approaches to expedite the development of safe and effective medicine and that the WHO is placing increasing emphasis on the use of prior reviews. Consequently, significant work has been made in understanding the laws, regulations and scientific basis for new streamlined regulatory approaches that continue to ensure the approval of safe and effective medicines while using the most up-to-date methodologies to inform these accelerated pathways. At a workshop conducted by CIRS in 2014, industry and regulatory participants identified what they felt to be the key elements of an efficient regulatory system. Notably they indicated that all agencies should have accelerated/priority and risk-based pathways available.

It is beyond the scope of this manuscript to review all of the opportunities now available for expedited pathways. Accelerated pathways in mature agencies have been reviewed in detail by Baird *et al*[16] and Liberti *et al*[17] among others. And a comprehensive integrated overview of a proposed way to integrate numerous

accelerated pathways available to the international community (collectively termed "facilitated regulatory pathways" [FRPs]) has been assessed in work conducted by the Utrecht University Institute for Pharmaceutical Sciences and The Centre for Innovation in Regulatory Science (*www.offpage.nl/ebooks/2017_lliberti/*).

FRPs, therefore, can fall into two distinct categories: primary FRPs and secondary FRPs. Primary FRPs are those used by an agency (usually a stringent regulatory authority [SRA] or reference agency) to speed the development and initial review of a product (eg, breakthrough therapy designation, priority review, PRIME, SAKIGAKE). Figure 2 indicates that the median time for products to undergo an accelerated review utilising a primary FRP (accelerated) pathway is relevantly shorter than a standard review.[18]

Secondary FRPs are those used by national regulatory authorities (NRAs) or regional regulatory initiatives (RRIs) wherein their decisions can be expedited by the reliance on or recognition of prior reviews.[19] Reliance refers to the act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision. Recognition refers to the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that the evidence of conformity with the regulatory requirements of one country is sufficient to meet the regulatory requirements of another.

Secondary FRPs usually involve a verification or abridged review process and are applied when the quality of the product under review has been verified to an appropriate standard. Secondary FRPs are applied when the quality of the product under review has been verified to an appropriate standard. When considering the review

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of a marketing authorisation application, an agency must clearly define how its activity "adds value" especially when prior reviews have been conducted with positive recommendations by SRAs or reference agencies. To address this issue, a risk-stratification approach has been implemented by some agencies to guide the use of secondary FRPs. However, there is no common or single approach to this stratification process. However, there appear to be benefits to risk stratification. In our experience (see Figure 3), from data provided by the multinational industry, overall median approval times (comprising both agency and company times) are shortest for products that undergo a simple verification review, slightly longer for those that use an abridged route and longest for those that undergo a complete dossier review. These data support the move toward the use of secondary FRPs (abridged and verification assessments) to improve the efficient use of resources and expedite the access to important medicines.

More recently, countries including Mexico, Brazil, Saudi Arabia and Jordan have implemented accelerated pathways that can in part be based on reliance mechanisms.

Implications for industry and regulators

Regulatory science forms the basis of all critical activities involved in the development, assessment and lifecycle management of medicinal products. In this context, this article has focused on how this science underpins activities related to benefit–risk assessment, quality decision-making, and the use of efficient, expedited pathways to accelerate patient access to safe and effective medicines.

As seen from the collaborative efforts of the FDA, APEC, the WHO and many other organisations, the successful implementation and adherence to activities driven by the strengths of regulatory science require an international collaborative effort across key stakeholders. Alignment of expectations, supported by consistent approaches to training and implementation, based on the precepts of regulatory science will continue to drive innovation and efficiencies. ■

References

1. A A Moghissi, S R Straja, B R Love *et al*. 'Innovation in Regulatory Science: Evolution of a new scientific discipline', *Technology and Innovation*, 2014:16(2):155–165 doi:10.3727/19498241 4X14096821477027.
2. M Goldman, N Seigneuret, H-G Eichler. 'The Innovative Medicines Initiative: an engine for regulatory science', *Nature Reviews Drug Discovery,* 2015:14;1–2 doi:10.1038/nrd4520.
3. M M Lumpkin, H-G Eichler, A Breckenridge *et al*. 'Advancing the science of medicines regulation: The role of the 21st-century medicines regulator', *Clin Pharmacol Ther*, 2012:92(4);486–93. doi: 10.1038/clpt.2012.146. Epub 5 September 2012.
4. P-L Lezotre. 'International cooperation. Convergence and harmonization of pharmaceutical regulations, a global perspective', *Elsevier Inc*, 2014. Available at: www.elsevier.com/books/international-cooperation-convergence-and-harmonization-of-pharmaceutical-regulations/lezotre/978-0-12-800053-3
5. US FDA. 'Advancing Regulatory Science for Public Health', October 2010. Available at: www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM228444.pdf
6. B M Psaty, S N Goodman, A Breckenridge. 'Advances in regulatory science at the Food and Drug Administration', *JAMA*, 2013:309(20);2103-2104.
7. US FDA. 'Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making Draft PDUFA V Implementation Plan – February 2013 Fiscal Years 2013-2017', February 2013. Available at: www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf
8. J Leong, N McAuslane, S Walker, S Salek. 'Is there a need for a universal benefit–risk assessment framework for medicines? Regulatory and industry perspectives', *Pharmacoepidemiol Drug Saf*, 2013:22(9);1004-12. doi: 10.1002/pds.3464.
9. S Walker, N M McAuslane, L Liberti *et al*. 'A universal framework for the benefit-risk assessment of medicines: Is this the way forward?', *Therapeutic Innovation Regulatory Science*, 2015:49(1);17–25.
10. N McAuslane, J Leong, L Liberti, S Walker. 'The benefit-risk assessment of medicines: experience of a consortium of medium-sized regulatory authorities', *Therapeutic Innovation Regulatory Science,* 2017, Vol 51(5) 635–644.
11. D Kahneman. 'Thinking Fast and Slow', Farrar, Straus and Giroux, New York, NY, 2011.
12. R Donelan, S Walker, S Salek. 'The development and validation of a generic instrument, QoDoS, for assessing the quality of decision making', *Front Pharmacol*, 13 July 2016. Available at: https://doi.org/10.3389/fphar.2016.00180.
13. M Bujar, N McAuslane, S Salek, S Walker. 'Quality of regulatory decision-making practices: Issues facing companies and agencies', *Therapeutic Innovation & Regulatory Science,* 2016:487–495.
14. H-Y Lin, S Jun-Yi Chen, C-S Gau, L L Liu. 'APEC Workshop Report of Good Review Practices on Medical Products', *Therapeutic Innovation Regulatory Science,* 2015:49(4);483–492.
15. World Health Organization Drug Information. 'Good review practices: guidelines for national and regional regulatory authorities', 2015;29(1).
16. L G Baird, R Banken, H-G Eichler *et al*. 'Accelerated access to innovative medicines for patients in need', *Clin Pharmacol Ther,* 2014:96(5);559–571.
17. L Liberti, M Bujar, A B Breckenridge, J Hoekman *et al*. 'FDA Facilitated Regulatory Pathways: Visualizing their characteristics, development, and authorization timelines', *Front Pharmacol*, 3 April 2017. Available at: https://doi.org/10.3389/fphar.2017.00161
18. M Bujar, N McAuslane, L Liberti. 'New drug approvals in six major authorities 2007–2016: Focus on the internationalisation of medicines', Centre for Innovation in Regulatory Science, London, UK, *R&D Briefing 65*, 2017.
19. World Health Organization. 'QAS/16.686 Draft Guidance. Good regulatory practices: guidelines for national regulatory authorities for medical products', October 2016. Available at: www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf?ua=1