Regulatory Frameworks in Times of Uncertainty

Alasdair Breckenridge

Patient and public expectations on access to new types of medicines has changed the role of the regulator in granting marketing authorizations. Whether current regulatory frameworks can accommodate further advances in biomedical science remains a challenge, but suggestions are made as to how this may be possible.

I qualified in medicine in 1962 and practiced as a physician and clinical pharmacologist for 40 years until 2002. The medicines I prescribed were largely chemical-based small molecules; the diseases I treated were named according to the organ affected—such as heart failure, bronchial asthma, and while basic science was beginning to make great advances with the human genome unraveling in the 1990s and the World Wide Web being invented in the same era, their applications to medicine were not yet apparent or available.

Medicines were developed and regulated based on lessons learned from the thalidomide disaster and were largely dependent on clinical trials, which became increasingly long, large, and expensive. Regulation was a binary process, with approval granted or refused after phase III clinical trials and was a private process carried out between the developer and the regulator. Having said that, many of today’s medicines were brought to market under this regimen and have served us well.

In the succeeding 16 years, from 2002 until 2018, much has changed; important advances in therapeutics have largely been based on biopharmaceutical products, the taxonomy of disease has become increasingly based on genomic understanding of disease, and we have entered the digital age with the Internet.

The role of medicines regulation has changed too. Whereas its role had hitherto been to protect the public health by keeping “bad drugs off the market,” this has changed to protect the public health by encouraging “good drugs” to be available to the appropriate patient as soon as possible. This change has been largely due to the advent of biopharmaceutical products that could not only treat the symptoms but also the underlying cause of disease and cure several types of cancer, arrest the progress of diseases such as juvenile rheumatoid arthritis, and change acute lethal infections such as HIV-AIDS into chronic disorders with long life expectancy.

Not surprisingly, healthcare professionals and patients became increasingly unwilling to accept the length of time for regulatory approval of this new generation of medicines, demanding earlier access to them than could be afforded under the standard regulatory pathway.

Regulators have responded by introducing a series of novel procedures, leading to faster assessment or earlier access or both. Collectively called Facilitated Regulatory Pathways (FRPs), various names are given to these procedures by different regulatory authorities: the US Food and Drug Administration (FDA) has successively introduced Priority Review (1992), Accelerated Approval (1992), Fast Track approval (1997), and Breakthrough Therapy (2012), while in Europe, the European Medicines Agency has introduced Accelerated Assessment (2004), Conditional Marketing Authorisation (2006), Adaptive Licensing (2012), and PRIME (2016). The underlying conditions for these various schemes are the acceptance of increased uncertainty at the time of regulatory approval and the need for postauthorization evidence of safety and effectiveness.

FRPs are aimed at being used for serious debilitating diseases where there is unmet medical need that can be treated with promising new medicines (usually, but not always, biopharmaceuticals). FRPs may provide approval for limited patient groups with specific conditions, e.g., using the techniques of precision medicines and using surrogate rather than hard clinical endpoints while regulatory approval for subsequent indications can be obtained by iterative procedures.

The other important characteristic of FRPs is the involvement of other stakeholders beyond the company and the regulator in providing scientific advice to the developer. In Europe, where market access depends on not only regulatory approval but also positive health technology assessment (HTA) of cost and comparative clinical effectiveness, HTA experts may be invited to give scientific advice to the company alongside the regulator, as will patient representatives and healthcare professionals.

The conduct of postapproval studies of safety and effectiveness is contentious. While further conventional comparative
Clinical trials are possible, these are expensive and will have the well-known disadvantages of randomized controlled trials (RCTs), and thus increasing use is made of real-world data (RWD) that is clinical data or observations derived from the real world and obtained from means other than from clinical trials to provide real-world evidence (RWE), which is the relevance of these data to the real world. The FDA has already used RWD in the approval of diseases in inborn errors of metabolism where insufficient numbers of patients exist to conduct standard clinical trials and in calculating appropriate dosing regimens for rabies vaccines, and for repurposing old drugs for neglected tropical diseases (CURE-NTD). In Europe, RWD is being used in proactive safety assessment of the safety of pertussis vaccines in pregnancy and in investigating the possible relationship between influenza vaccines and narcolepsy.

Sources of RWD include drug registries, routine clinical databases such as electronic health records (EHRs), research clinical data bases such as SENTINEL in the US, and the Clinical Research Datalink (CPRD) in the UK and pharmacy databases such as PHARMO in the Netherlands. Such data may be used to conduct observational studies or pragmatic clinical trials such as the Salford Lung Study. It remains to be seen whether in the future social media data can also be used to provide RWE for regulatory purposes, for 10% of all social media relates to healthcare issues and may become a valuable data source once technical problems can be solved. Pragmatic clinical trials should not be considered as an abandonment of the scientific methods that have led to countless breakthroughs, nor do they take away from basic science or diminish the importance of RCTs—we need a balance, for no clinical trial is completely explanatory or pragmatic. RCTs and pragmatic clinical trials exist on a continuum.

But for FRPs to become workable entities, regulators should encourage companies to conduct clinical trials with outcomes which measure value, and which would be of importance to HTAs, payers, and patients. Further, regulators should emphasize the importance of ensuring patient compliance in FRP clinical studies where regulatory approval will depend on limited clinical data. Applicants for marketing authorization should answer the question “Which reliable method did you use in this clinical trial to ensure adherence?” Regulators should also ensure that postauthorization studies required as part of accelerated approval are carried out to completion and in a timely fashion. Finally, if a new medicine approved under FRP guidelines does not fulfill its initial expectations, strategies should exist to withdraw it from the market.

EHRs may prove to be the most valuable source of RWD, but many EHR systems were designed for commercial, i.e., billing purposes, rather than research uses, and the many various EHR systems have found difficulty in communicating with each other. However, networks such as the Electronic Medical Records and Genomic (eMERGE) Network, show that EHRs may become an important source of RWD.

The question remains whether the situation as described above will be sufficient to fulfill the expectations of the public and accommodate the current rate of change in biomedical sciences. One adaptation of these paradigms that may help make regulatory science capable of meeting public health demands is to combine clinical databases with DNA Biobanks. In genome-wide association studies (GWAS), the genotypes or the exons of the genomes of a cohort with a phenotype such as a rare disease or an unusual adverse drug reaction can be systematically examined for single nucleotide polymorphisms (SNPs) and compared with the genomes of a cohort without the phenotype.

CONCLUSION
The advent of biopharmaceutical medicines has stimulated regulators to create a series of new frameworks allowing earlier patient access and quicker assessment than hitherto. The price is greater uncertainty at market authorization and the means of addressing this increasingly depend on the use of real-world data.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST
The author reports no conflicts of interest.

© 2018 The Authors. Clinical Pharmacology & Therapeutics published by Wiley Periodicals, Inc. on behalf of American Society for Clinical Pharmacology and Therapeutics

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

1. Lumpkin, M.M. et al. Advancing the science of medicines regulation; the role of the 21st century medicines regulator. Clin. Pharmacol. Ther. 92, 486–493 (2012).
2. Liberti, L. et al. Adaptive licensing and facilitated regulatory pathways. Clin. Pharmacol. Ther. 98, 477–479 (2015).
3. Robertson, A. et al. The impact of US priority review vouchers on private sector investment in global health research and development. PLoS Negl. Trop. Dis. 6, e1750 (2012).
4. Bakerley, N.D. et al. The Salford Lung Study Protocol. Resp. Res. 16, 101 (2015).
5. Gottesman, O. Electronic Medical Records and Genomics (eMERGE) network. Genet. Med. 15, 761–771 (2013).
6. Denny J.C. et al. The influence of big (clinical) data and genomics on precision medicine and drug development. Clin. Pharmacol. Ther. 103, 409–419 (2018)