8. New approaches to promoting innovation

8.2 Regulatory structures to support pharmaceutical innovation

See Background Paper 8.2 (BP8_2regulatory.pdf)

The regulatory system for market authorisation is a critical factor in the development of new medicines. This system has to take into consideration the protection of public health while, at the same time, ensuring that patients have timely access to medicines including those that address unmet medical needs. Overall, the system has been successful in ensuring that many valuable medicines with a positive benefit-risk profile have reached the market. However, there are important challenges to be met if the regulatory system is to ensure a continuous flow of the new medicines most needed by society.

In order to function optimally the regulatory system has to find the right balance in three key areas:

- **Cautiousness**: It can be overly or insufficiently cautious, for example, by not granting marketing approval for a medicine with a favourable benefit-risk profile or by allowing unsafe or ineffective medicines on the market.
- **Incentive structure**: It can lack incentives for pharmaceutical innovation, or incentivize innovations that do not address public health needs.
- **Comprehensiveness**: It can add undue regulatory burden through redundant regulation or have regulatory gaps.

This search for the right balance is especially pertinent in the ‘adaptive’ approaches to marketing authorization that have been proposed and discussed since the 2004 Report. Such approaches are known under various names (including staggered approval, adaptive approval, progressive authorization and adaptive licensing) and have been proposed by key opinion leaders in the EU and the United States. These adaptive approaches are all based on the premise that knowledge about medicines is not binary but continues to evolve over time. The proposal is to replace the single transition from non-approval to approval with a series of approval stages with iterative phases of evidence gathering and regulatory evaluation. The use of adaptive approaches, which also incorporate elements of existing pathways, should be seen as a holistic option in the future regulatory system.

Although the concept of adaptive approaches is attractive, these approaches face a number of challenges. For example, when medicines are initially approved for a restricted population (based on specific evidence for this subpopulation), the process of appropriately defining, targeting and learning from this population during the initial phases would require efforts to monitor the utilization of medicines as well as interventions to ensure their appropriate use, including patient adherence. These actions would need to be strong enough to influence the behaviour of actors such as patients, pharmacists and physicians, and provide sufficient information for policy makers.
The 2004 Report emphasized that “every aspect of the regulatory process should be re-examined” and that “the evidence base for regulatory practices should be critically analysed using modern methodologies.” Over recent years, numerous studies have been conducted on different elements of the regulatory system such as evidence generation for initial marketing approval and the benefit-risk assessment. In addition, various new trial designs and analysis techniques are being piloted. Meanwhile, initiatives such as NEWDIGS, CASMI and The Escher Project have created networks for analysis of regulatory practices and information sharing in Europe (see Background Paper 8.2).

Another issue that was highlighted in the 2004 Report was the need for communication between stakeholders. An overview of recent discussions shows that this field has progressed considerably in recent years. For example, there is now widespread interest in how regulators and industry can further improve communication and most productively engage in an early dialogue in the drug development process and in how changes in regulations impact on product development.

The 2004 Report highlighted two weaknesses in the regulatory process: the critical role of patients and the need for an increased focus on post-marketing activities. Various regulatory authorities now accept the changing role of patients and that they should be involved in the regulatory process. However, more information is needed about what patients can add at the different stages of decision making. In addition, the optimal tools for patient involvement have not yet been identified (see Chapter 8.5 and the related Background Paper). With regard to post-marketing activities, the strengthening of the pharmacovigilance legislation and discussion about adaptive licensing are important drivers for an increasing role for post-marketing studies. While 10 years ago it was not uncommon for important policy documents to exclude the post-marketing phase, today this is rarely seen, and the role of post-marketing (safety) surveillance is well entrenched. Nevertheless, there are still important challenges, such as the post-marketing surveillance for medicines used exclusively in low- and middle-income countries (e.g. antiretroviral medicines for children or new antimalarials). Less well established is the role of post-marketing effectiveness evaluation. As such, the appropriate use of real-life data (see Chapter 8.4) is critical for the future.

Although these changes are welcome, a number of key priorities for research have been identified. In particular, tools are needed to: enable regulators to release medicines on to the market with confidence, including in cases where more limited evidence is available than is customary at the market authorization stage; and to collect and analyse evidence proactively over time after release. In an adaptive approach, a medicine’s regulatory status (authorization and indication) is likely to change over time. This could have implications for pricing and reimbursement decisions, especially when value-based pricing is fully implemented.

In line with this, when the 2004 Report was published, the traditional randomized controlled trial was still seen as the gold standard for measuring efficacy. In 2013, this is increasingly being challenged, based on the need to move from efficacy based on limited clinical trials to real-world effectiveness, with broadening of indications,
repurposing of medicines and demands for comparative effectiveness data. There is a clear need for more research in this area.

**Research priorities**

Four research priorities have been identified:

**Continue to develop and pilot new methods for evidence generation and benefit-risk assessment**

Additional research is needed on alternative instruments (such as the use of surrogate and other clinical outcome measures and adaptive study designs) to optimize regulatory requirements for initial marketing approval. In addition, the increased use of post-marketing observational studies for effectiveness and safety should be explored. In line with the adaptive licensing proposals, effectiveness studies would also be needed to make better assessments for the (future) real-world effectiveness of medicines under development based on trial efficacy. Improving this kind of learning could help to achieve an adequate level of (safety and efficacy) knowledge while requiring less data to be collected before the medicines are approved.

In addition, various collaborative initiatives have been proposed in order to develop more structured benefit-risk assessments, based on qualitative and quantitative instruments. The aim is to increase the consistency and transparency of benefit-risk assessments and thereby the predictability of the marketing authorization procedure. Examples of collaborative initiatives are the Unified Methodologies for Benefit-Risk Assessment (UMBRA) initiative of the Centre for Innovation in Regulatory Science (CIRS), the IMI PROTECT work package on benefit-risk integration and representation and EMA’s Benefit Risk Methodology Project. However, as with the proposals for adaptive evidence requirements, introducing structured qualitative and quantitative instruments for benefit-risk assessment requires substantial changes in a regulator’s way of decision-making and in the way companies prepare submission documents. At present, little evidence exists as to how quantitative instruments affect the quality of regulatory decision-making or public health. Additional field studies should identify practical limitations and test optimal ways of data visualization. In addition, these field studies of quantitative benefit-risk instruments could gain insight into uncertainties in benefit-risk assessments and demonstrate how robust decisions are in relation to different perspectives about clinical relevance (e.g. by patients or prescribers) and how (new) real-world data would affect the balance.

**Clearly identify expectations and key performance indicators for new regulations and set up prospective studies**

Measuring the success and cost (effectiveness) of regulatory policies is often difficult. In order to evaluate and improve existing regulations and to base new incentives on best practices, expectations should be made explicit and performance indicators should be defined and reported on.
European Union regulatory incentives for pharmaceutical innovation for special disease areas, special populations and special products may not always take into account all the factors involved in successfully bringing a medicine to the market. In the case of the orphan drug regulation the market exclusivity incentive has, without doubt, yielded an increase in the number of potential drug candidates for rare diseases. However, some instruments, such as free protocol assistance, may not be a key driver for generating more innovative medicines. Other incentives, such as the significant investments by governments in research into rare diseases, or the market exclusivity period may play a far more important role. The paediatric regulation could be looked at in a similar manner. Future research could establish which incentives provide added value from a societal perspective and help to achieve public health goals.

The 2012 EU pharmacovigilance legislation will enforce post-marketing obligations and complement the current conditional approval regulation. In implementing the newly established pharmacovigilance legislation, European regulators explicitly defined measures of impact such as change of behaviour in prescribing, dispensing and consumption and outcomes such as mortality, morbidity and quality of life. Formulating expectations by qualitative and quantitative performance indicators, and monitoring them through carefully designed studies could stimulate timely adjustments in the regulations and provide evidence for new policies. For this purpose, the effective use of electronic health record (EHR) databases and real-life data is of critical importance (see also Chapter 8.4).

**Establish constructive collaborations and dialogues with key actors**

Many actors are involved in the marketing authorization of medicines. Collaboration and dialogue between all these parties is essential for an effective regulatory process and should be supported at multiple levels. Creating such dialogues and collaborations is not easy. Often, it is not part of the tradition of the parties involved. As a result, different actors speak different languages.

First, both regulators and pharmaceutical companies should be encouraged to have a dialogue at an early stage of drug development (e.g. in the preclinical phase or during Phase I), especially for those products using innovative approaches for development. Scientific advice is one of the key tools for this.

Second, involving Health Technology Assessment and Pricing and Reimbursement bodies in such a scientific dialogue is important to harmonize requirements and post-marketing authorization obligations.

Third, involving patients and prescribers could better adjust benefit-risk assessment to their preferences or risk perceptions. Although networks of patients have been established (e.g. in the EMA Patients and Consumers Working Party), there is a need to determine how patients can most effectively contribute to decision making. At present, little is known about how best to involve patients in decision making and at what stage they can most effectively contribute (see Chapter 8.5).
Invest in sharing and analysis of regulatory datasets for system evaluation

In order to support evidence-based improvements of the regulatory system and to test and explore new methods for drug development and regulatory decision-making, close collaboration is needed between regulatory agencies and academia, as well as input from companies. For the purpose of regulatory science, regulatory databases should be examined to learn from previous marketing authorization procedures and to evaluate tools and regulations as discussed in this paper.

The EMA publishes the European Assessment Reports of approved, non-approved and withdrawn products on its website. Although to some extent this offers the opportunity to evaluate previous marketing authorization procedures, certain informative documents that could add to the learning process, such as the objections made during the marketing authorization procedure, also provide insight into the priorities and perspectives of the regulator. More detailed data on outcome measures and confidence intervals are also needed in order to validate quantitative benefit-risk instruments.

Regulations play a critical role in balancing people’s expectations for new medicines to address unmet medical needs against the need to ensure that medicines are efficacious and have a positive benefit-risk ratio. For regulators and companies to adapt to a changing world, research on the regulatory process is needed.

In conclusion, there has been real progress since 2004, which has created controversies and challenges, but regulators have shown willingness to be involved in stimulating innovation. Regulatory science has not been a research priority, but many forms of drug innovation need to be supported by research in regulatory science in order to be able to move forward in the most effective way.

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