



Research and development of medical products: opportunities and challenges

October 2010

A roundtable meeting with Dr Margaret Hamburg, Commissioner of Food and Drugs, US
Food and Drug Administration

The Academy of Medical Sciences

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Summary

In October 2010, the Academy of Medical Sciences FORUM with Industry convened a high-level roundtable meeting on 'Research and development of medical products: challenges and opportunities'. The meeting was chaired by the Academy's President, Professor Sir John Bell FRS HonFREng PMedSci and was attended by representatives from the pharmaceutical industry, medical research charities, academia and international regulatory bodies, including Dr Margaret Hamburg, Commissioner of Food and Drugs at the US Food and Drug Administration (FDA). Dr Hamburg later gave the Academy's 2010 FORUM Annual Lecture: 'The importance of regulatory science to the healthcare portfolio'.¹

The purpose of the meeting was to explore the current and future regulatory challenges facing the pharmaceutical industry, academia and regulators, and to discuss the opportunities for overcoming these challenges to ensure that new innovations benefit patients and that regulators have access to the most effective decision-making tools.

A central theme of these discussions was the need to improve tools that enable regulatory decision-making. The themes explored included: the need for more adaptable drug development and marketing dossier assessment processes, the desire to see greater regulatory transparency, the importance of global regulatory coordination, and the value of regulatory science to catalyse the development of new tools that enable product development and regulatory decision-making. Discussions frequently referred to emerging technologies and two examples were of particular interest: combination therapies (predominantly a pharmaceutical and a device) and companion diagnostics (used to help determine the best use of a pharmaceutical).

The key conclusions to emerge from discussions were that:

- The research and development landscape and the types of treatments emerging from it have changed, and will continue to change. Development and regulatory processes must be more flexible and adaptable to stimulate needed innovation while continuing to ensure that new innovations benefit patients.
- 'Regulatory science' can provide tools to improve product development and regulatory processes and consequently aid more effective translation of basic research into products that benefit patients. Increased resources and awareness within academia will be important in improving focus on and productivity in this field.
- Improved transparency of regulatory procedures and decision-making, with respect to both industry and the public, will help to improve the efficiency of product development and to raise confidence levels in regulatory processes.
- Partnership across the sectors will be of great value in improving regulation, particularly pre-competitively, so that the issues of emerging technologies can be discussed and regulatory strategies identified in an open forum.
- Regulators such as the FDA and the European Medicines Agency (EMA) should recognise their role as global leaders and the impact of their decision-making globally.

¹ For more information <http://www.acmedsci.ac.uk/p44evid156.html>

Introduction

The research and development (R&D) of medical products, including new pharmaceuticals, devices and diagnostics, is becoming increasingly challenging. Many factors are influencing this situation. Previously, industry identified numerous chemical compounds to treat diseases that affect large numbers of patients. However, as more of these drugs have come to market, fewer diseases with known pathogenesis with large patient populations remain without treatment possibilities, and expectations of the efficacy of novel treatments in these diseases have increased.² As a result, industry has been unable to identify new potentially 'blockbuster' agents and new business and scientific models are now required.

New products from novel technologies are, however, being developed. These emerging therapies are often more expensive and targeted at smaller patient populations. Consequently, a greater cost is spread amongst fewer people, and with lower returns for investors. In addition, regulatory processes, which are based in assessments of population effects, typically lack the flexibility to deal with these new developments, and efforts to address this challenge vary internationally between the different regulatory agencies. Industry thus faces difficult decisions over whether to invest when the financial returns are uncertain and the future regulatory framework is unclear. For example, combination therapies are increasingly recognised as the treatments of choice rather than traditional treatments for many conditions, but industry needs the incentives, both financial and regulatory, to invest in their development.

Without unambiguous, effective regulation that reflects the changes to R&D and the nature of these innovations, the delivery of effective treatments to patients will be slowed. Regulatory decision-making processes should facilitate innovation that improves health and ensure that promising new technologies reach patients. The Academy has highlighted the need to create a more proportionate, risk-based regulatory framework for medical research involving patients.^{3,4} However, the participants at this roundtable also identified the kinds of regulatory challenges that exist during the development of products and at the regulatory marketing dossier assessment stage for new products. The Academy's mission is to ensure better healthcare through the rapid application of research to the practice of medicine and efficient product development and assessment processes, that are nonetheless scientifically robust, prevent biases, and protect the safety and interest of patients, are central to achieving this objective.

² Cooksey (2006). *A review of UK health research funding*. <http://www.official-documents.gov.uk/document/other/0118404881/0118404881.pdf>

³ Academy of Medical Sciences (2010). *Reaping the rewards: a vision for UK medical science*. <http://www.acmedsci.ac.uk/p48prid78.html>

⁴ Since the roundtable meeting, the Academy has published 'A new pathway for the regulation and governance of health research'. For more information <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88>

Emerging technologies/approaches

New products using novel technologies are being rapidly developed across areas such as healthcare IT, clinical decision support, companion diagnostics and combination therapies. The latter two were discussed in particular detail at the meeting and Box 1 provides further detail on these innovations. Technologies develop more rapidly than medical practice and regulatory practice. The pace of technological development in these fields demands that product developers and regulators both pay close attention and they must work together on issues of knowledge development about potential drug targets and medical product development, as well as regulatory strategies.

Many participants felt that the regulation of diagnostic tests in many jurisdictions is creating a significant constraint on the sector. There is a perception that some existing regulatory frameworks are ill-equipped to deal with diagnostics and IT solutions that are likely to be crucial for the evolution of healthcare to a more personalised, rather than population, model. For example, concerns were expressed that new diagnostic capabilities that will arise from next generation sequencing might not be efficiently and well managed within the current framework even though they are likely to be widely used in managing diseases such as cancer. The concern was raised that certain regulatory frameworks could risk driving molecular diagnostics into an unregulated environment. These problems are compounded by the need to use companion diagnostics to successfully advance more targeted or stratified medicines. Because of differences in authorisation standards of such products, two years after authorisation in certain jurisdictions, there are still no approved tests for k-ras or epidermal growth factor receptor (EGFR) as companion diagnostics for cancer therapies in others. Many participants thought that a more flexible approach to the regulation of companion diagnostics should therefore be a priority and it was suggested that a more risk-based, yet still evidence-based, approach would be helpful.

Participants stated that current regulation is designed to promote the development of separate therapeutic agents, but combination pharmaceuticals (as opposed here to combination products) are emerging as potentially more effective in many cases, for example for treating HIV, hepatitis C and many cancers. They emphasised the importance of enabling the co-development of two or more novel agents that together could be more efficacious in particular diseases without the need to complete development programs with each agent as monotherapy first. The approach of developing a particular combination of agents as that combination, rather than on an individual basis, was seen as preferable.⁵

⁵ Since the meeting, the FDA has issued new draft guidance for the codevelopment of two or more unmarketed investigational drugs for use in combination. For further information <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf>.

Box 1 Emerging technologies/approaches***Combination therapies***

Combination therapy describes the simultaneous use of more than one medication (*combination pharmaceuticals*) or other type of product (e.g. a device with a pharmaceutical: a *combination product*) to treat a single disease. This approach is becoming increasingly popular in medicine, for example in cancer, but the developmental requirements and marketing dossier assessment standards for these various combination therapies are not well established in all jurisdiction. Determining whether a combination therapy works and its key benefits is central to establishing the health value of the product and thus gaining regulatory authorisation.

Infectious disease is a field in which combination pharmaceuticals have been successfully developed and authorised; initiatives, for example in tuberculosis and AIDS, continue this work. It is clear that this field has benefited from relatively straightforward *in vitro* assay development, which has enabled early assessment of potential benefits.

Participants felt that combination pharmaceuticals might be extended to other diseases, including immune and inflammatory conditions, and diabetes. The challenge is designing informative pre-clinical assays for these conditions, the results of which would provide a foundation for developing clinical trials. Participants felt this was achievable and inflammatory diseases were highlighted as particularly promising, given the numerous cytokines and chemokines that have been identified in disease pathogenesis.

Companion diagnostics

The emerging field of companion diagnostics involves techniques, including genetic or histopathological tests, biomarkers and imaging tools, being used to determine whether a pharmaceutical will be effective or safe in a particular patient or to establish the optimal drug dose. Identifying stratified patient populations in this way will improve the efficacy and safety of treatments by enabling greater targeting towards these specific groups. The benefits of this move towards targeting more homogeneous populations are widely recognised by industry, regulators, and clinical medicine. Additionally, more effective and safer medical treatments offer clear economic benefits to governments. This has fuelled a desire to develop processes that develop, assess and authorise both the therapeutic and diagnostic simultaneously.

Towards greater transparency

Regulatory transparency

Participants agreed that a greater degree of transparency around certain regulatory processes would be helpful for product developers, other regulators, and the general public. However, they acknowledged that determining the most appropriate degree of openness is challenging, given the competing societal values regarding open government, personal privacy, and commercial confidentiality.

From the perspective of industry, a lack of transparency of regulators results in more unpredictable processes, which is perceived to hinder efforts to gain authorisation. Many participants stated that a greater degree of dialogue with regulators during the marketing dossier assessment process would be welcomed by industry and identified the EMA's system of allocating a 'rapporteur', who communicates with the product sponsor, as a positive move towards greater, more helpful transparency within the European central system. Creating more targeted review teams, as the FDA does, was suggested as another mechanism by which certain regulators might achieve deeper, earlier and more consistent engagement with sponsors, which would help to define and clarify the regulator's expectations of them.

Where the public is concerned, industry and regulators have unique concerns, particularly with respect to commercially confidential information and the legal issues that surround it. Defining what counts as commercially confidential data will be key to deciding on the correct level of transparency with respect to the public, and participants stated that decisions around the timing of the release of clinical data presents a particular challenge. It was reported that some regulators are concluding that clinical data are not commercially confidential. Other concerns expressed include opening up large quantities of data in ways that allow analyses to be conducted by any individual into any phenomenon, which is likely to produce numerous 'false signals' in addition to more useful findings. Clarity is thus being sought on whether increased accessibility should include the information contained in databases. Participants acknowledged that transparency initiatives evolve and are improved with time and experience and agreed that it is important that any model of transparency, while increasing trust in process, should not inadvertently create more confusion than clarity.

Patient data

Participants also raised the issue of the availability of patient records. Once new therapies have been authorised, using electronic patient records combined with other data, e.g. from genetic studies, could provide large datasets from which patient subsets that most benefit from a particular therapy might be identified more effectively. However, current attitudes towards electronic records may hinder efforts to perform this kind of analysis, particularly in the UK where the role of electronic patient records has not yet been realised as a tool for improving healthcare. Some participants questioned the value of

patient data on its own, stressing that multiple variables exist within patient populations, such as disease severity and duration, drug compliance and patient pharmacokinetics.

A more adaptable clinical development and marketing authorisation process

Much investment in the pharmaceutical industry currently goes into drugs that fail during phase II or III clinical trials. The clinical development process is historically a sequential framework, designed as a set of steps to collect and study incremental knowledge regarding the safety and efficacy of the product in the intended population, and that, if demonstrated benefits continue to outweigh known risks, the product will succeed and reach the market. However, market authorisation is the fate of very few products that start the clinical development process. Participants at the roundtable therefore stressed the importance of exploring the possibilities for more flexible and adaptable methods of evaluation and authorisation, voicing concern that without such flexibility, drugs may not in future reach the smaller, more stratified populations for which they must be targeted. Participants agreed that regulators should seek a more adaptable regulatory development and authorisation framework that is responsive to emerging data and new areas of science, and which is more able to take on appropriate levels of risk assessment to keep meaningful innovation flowing.

The marketing authorisation process

Traditional regulatory processes seek to determine both the efficacy and safety of a product using methods primarily designed to establish efficacy (i.e. the trials are designed to test an efficacy hypothesis, not a safety hypothesis). The design of such trials is often one of significant cost, in both time and financial resources, to the study sponsor. For example, efficacy hypothesis testing is ideally carried out in an unconfounded population, which is both hard to define and difficult to gather together. A new approach was proposed involving a two-stage process (described below), which separates efficacy from safety, meaning that safety could be explored in a more easily assembled group and potentially in both the pre- and the post-authorisation phase, where patient populations are more rigorously followed up using electronic patient records. This could ultimately shorten the process of determining whether a drug is efficacious and then answer the safety question more adequately, quickly and perhaps more cheaply.⁶

A new model

While the direction of drug development is towards smaller patient populations, the central question for any new treatment remains: 'Does it work?'. Participants expressed a desire to see a regulatory model that allows industry to answer this question more efficiently, so that failure (i.e., not being efficacious) is discovered more quickly and at a lower cost. Such a model could reflect the two objectives of the drug discovery process, in which:

- Stage 1 would involve experimental medicine, with the aim of establishing whether a new product has putative biological efficacy in patients.
- Stage 2 would be formal marketing authorisation, consisting of the safety assessment with which we are familiar.

⁶ The NEWDIGS group at the Massachusetts Institute of Technology and the Athenaeum Group in the UK are exploring alternative approaches product development using these principles.

Thus, a product would be 'expected to fail' in the first stage and only progress to Stage 2 once evidence has been gathered to demonstrate its efficacy.

Flexible licensing

Participants also discussed earlier 'conditional licensing' of drugs as another possible mechanism for a more adaptable marketing authorisation process, as highlighted previously in Sir David Cooksey's 2006 report, 'A review of UK health research funding'.⁷ This would allow more target evaluation of the efficacy and toxicity of novel entities, for example, in responder populations. If this kind of approach is not pursued, several participants warned that the products are likely to be authorised elsewhere, under less scientific conditions, and subsequently distributed globally from sources that some regulators would consider unsafe.

Parallel authorisations – market access and reimbursement

Sequentially reviewing drug safety/efficacy/manufacturing quality, followed by cost-effectiveness (for reimbursement purposes), is time consuming and impacts both industry and patients. In addition, the remit of the organisations involved in these activities was seen as ambiguous and often overlapping, and thus must in future be clearly defined within a more efficient system. Most participants stressed that decisions about market access authorisation and cost-effectiveness/reimbursement should be separate, but considered how parallel review by the relevant agencies might work to shorten the overall authorisation processes; they were encouraged by regulators' efforts to create a more efficient system. Participants highlighted that this will impact on processes within pharmaceutical companies as both applications will be made simultaneously, increasing the importance of regulatory transparency (by both types of agencies) because companies must understand what kind of information they are expected to provide. Participants stated that a significant challenge is finding a suitable way in which to deliver joint scientific advice (i.e. from both types of agencies) to product sponsors so that product development programmes can be devised to most efficiently provide the information needed by both types of agency.

⁷ Cooksey (2006). *A review of UK health research funding*. <http://www.official-documents.gov.uk/document/other/0118404881/0118404881.pdf>

Global coordination and leadership

Coordination between regulatory agencies is helpful in data analysis and interpretation, and subsequently in translating conclusions into recommendations. Participants agreed that regulators such as the FDA and EMA must acknowledge their role as global leaders, but recognised that it is a difficult job balancing an agency's statutory mandate to perform its role in the context of the benefit to the public health of its own jurisdiction while knowing that its decisions often have global influence. Other regulators, for example in developing economies, often look to these agencies for leadership on particular issues and participants questioned how regulators might deal with differences in risk-benefit analyses between countries.

Rotavirus vaccines, which are used to prevent rotavirus gastroenteritis, provide a helpful example. After market authorisation of RotaShield rotavirus vaccine in the late 1990's, a rare, but significant risk of intussusception was detected through post-authorisation surveillance activities. Given the fact that rotavirus infection was generally treatable without significant detrimental outcome in most western health care systems, the benefit of the vaccine was reappraised as not outweighing the risk of intussusception. Thus the product was withdrawn from their markets by western regulators. However, the striking difference in risk-benefit in developing countries, where gastroenteritis causes a greater number of deaths, demonstrates an important problem. Regulators in these countries were faced with the difficult task of deciding whether to allow a product on their market despite the fact that it "was not deemed safe for western markets."

More recently, a similar challenge emerged when the Rotarix vaccine was suspended due to an incidental finding that suggested the vaccine was contaminated with porcine circovirus 1 (PCV1). Although the risks were small, the FDA recommended that an alternative product (available in the US) be used while the findings were investigated further. However, a different decision might be judged appropriate elsewhere (e.g. where an alternative product was not available), such as in a developing economy, which raises broader social and ethical challenges because it could be perceived as effectively comparing the value of the lives of individuals in these different countries.

Regulators are increasingly considering how they support their counterparts in other countries, for example by clearly setting their advice in context. In the Rotarix case, the FDA tried to emphasise that its decision was unique to US circumstances and that it would not recommend such a decision elsewhere, especially where the burden of disease was much higher.

Participants identified that there was a need to improve the science of risk-benefit analysis and how to apply it. Clinical trials data provides information about the risks and benefits of a product. It does not provide a risk-benefit judgement as this depends on the local context and to determine this, regulators must consider the risk tolerance of the particular community into which the risk is being introduced. However, there is an added political risk, which accompanies authorising a treatment, not approved in another country, for one's own country. Regulators such as the FDA and EMA can provide guidance in deciding what clinical trials data say about risks and benefits, but decisions

over the risk tolerance of a population can only be made by governments who understand the local context and whether the benefits outweigh the risks within the local environment. Initiatives such as inviting individuals from other regulatory agencies to join the scientific discussions of those such as the FDA or EMA are helping to move towards more effective mentoring, leveraging and sharing, based on principles of risk and benefit, as well as the recognition of national sovereignty and that differences exist in local medical practices and risk perceptions and tolerances.

The group emphasised the need for effective dialogue to advance discussions on how the regulatory framework for drugs and diagnostics might be modified to make the process more efficient and transparent. There is an important role for academic scientists to participate in this dialogue, which has historically involved only regulators and industry. Academic groups should contribute to both the underlying science of regulation and its application (see 'The value of regulatory science').⁸

⁸ Since the roundtable meeting, the US National Institutes of Health Scientific Management Review Board has recommended that a new Centre for Translational Medicine and Therapeutics should be established. For more information: http://smrb.od.nih.gov/documents/reports/TMAT_122010.pdf

The value of regulatory science

A central theme of the discussions was the need to reduce barriers to product development and facilitate clear, consistent regulatory decision-making. It was widely recognised that the tools that provide data to inform such activities need to be improved. The Academy has previously stressed the importance of efficiently translating scientific advances into benefits for patients and society.^{9,10} Developing more innovative approaches to product development and regulatory review to catalyse knowledge generation in new ways would help to ensure, for example, that the new drugs being developed for smaller patient populations are able to reach patients. There is a relationship between the way regulators address questions about product efficacy and manage uncertainty and risk, and the ability of the industry to truly innovate. Thus, improving the tools with which regulator and product developers must make decisions could stimulate innovation.

Participants identified a gap in the academic research agenda from which these novel tools and methodologies might emerge. Dr Hamburg has referred to the science that bridges this gap as 'regulatory science', acknowledging the difficulty of labelling it with a specific title, but emphasising the need to focus industry, regulatory, and academic resources to this area.

Participants agreed that there is a need for greater investment in this field and highlighted the importance of raising its profile within the academic research community. Many felt that the level of resources being invested into the EU Innovative Medicines Initiative (IMI) has provided a greater incentive and been helpful in drawing attention to the field.¹¹ Encouraging and enabling collaboration between scientists from across the sectors will be central to increasing productivity in this field, but progress is likely to be gradual.

Participants discussed examples of novel tools and methodologies that could aid product development and regulatory decision-making and ultimately benefit both industry and patients. This included:

- Identifying and characterising biomarkers that help to identify patient sub-populations.
- Developing new clinical trial analysis techniques that enable studies to be quicker and more targeted.
- Exploring ways to use smaller numbers of patients to gather adequate data for decision-making.

Companion diagnostics will allow more targeted data to be collected and important new insights for product developers, regulators, and clinicians on the specific benefits of a treatment for particular patient groups. Improving our ability to stratify populations in this way could in turn inform further developments in regulatory science, product

⁹ Academy of Medical Sciences (2003). *Strengthening clinical research*.
<http://www.acmedsci.ac.uk/p48prid18.html>

¹⁰ Academy of Medical Sciences (2010). *Reaping the rewards: a vision for UK medical science*.
<http://www.acmedsci.ac.uk/p48prid78.html>

¹¹ For more information <http://www.imi.europa.eu/>

development and medical care. For example, a particular drug may be most effective in a specific subset of patients with a particular genetic polymorphism, but the existence of such a phenomenon may not emerge from trials conducted in a heterogeneous population; it is essential that we are able to identify the patients who will benefit. Participants felt that the European and US regulatory agencies should take a leadership role in setting this specific agenda so that industry is provided with a more predictable regulatory landscape, in which it can invest, and regulators are provided with the kind of targeted data that supports more focused decision-making.

Participants agreed that work to define a field, and thus also a framework, for regulatory science must progress alongside ongoing work to identify critical issues and to develop and pilot new methods. Regulatory science exists at the intersection of multiple fields, including those in basic, clinical and epidemiological research, as well as informatics.¹² Defining the research agenda within a wider framework will help to make sense of individual findings. For example, work in academia, e.g. on biomarkers, may not be specifically targeted at a regulatory application, but understanding it within the context of an overarching structure may aid its development into such an application. Participants stated the importance of partnership here, in sharing experiences and knowledge from which others can learn.

Participants agreed that pre-competitive partnerships across the sectors would be of great value in laying out the issues and identifying possible strategies to address them. It was suggested that organisations such as the Academy could provide a forum for discussing such strategies.

¹² Dr Hamburg outlined her views on the importance of regulatory science in the Academy's FORUM Annual Lecture, which followed the roundtable meeting. For more information <http://www.acmedsci.ac.uk/index.php?pid=44&evid=156>

Appendix I: Meeting attendees

Professor Sir John Bell FRS HonFREng PMedSci, President, Academy of Medical Sciences

Dr Richard Barker, Director General, Association of the British Pharmaceutical Industry

Sir Alasdair Breckenridge CBE FRSE FMedSci, Chairman, Medicines and Healthcare Products Regulatory Agency

Sir David Cooksey GBE FMedSci, Chairman, UK Financial Investments

Dr Moira Daniels, Vice President Regulatory Policy, Intelligence and Labelling, AstraZeneca

Mr John Dineen, President and CEO, GE Healthcare

Sir Colin Dollery FMedSci, Senior Consultant, GlaxoSmithKline

Dr Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency

Dr Margaret Hamburg, Commissioner of Food and Drugs, US Food and Drug Administration

Professor Jonathan Knowles, Vice Chairman, Caris Life Sciences

Dr Harpal Kumar, Chief Executive Officer, Cancer Research UK

Dr Murray Lumpkin, Deputy Commissioner for International Programs, US Food and Drug Administration

Mr Alan Morrison, Vice President International Regulatory Affairs and Safety, Amgen

Professor Sir Michael Rawlins FMedSci, Chairman, National Institute for Health and Clinical Excellence

Dr David Roblin, Senior Vice-President Worldwide R&D, Pfizer

Dr Alan Smith CBE FRS, Senior Vice President, Research and Chief Scientific Officer, Genzyme

Professor Patrick Vallance FMedSci, Senior Vice-President, Drug Discovery, GlaxoSmithKline

Sir Mark Walport FMedSci, Director, Wellcome Trust

Professor Kent Woods FMedSci, Chief Executive, Medicines and Healthcare Products Regulatory Agency



Academy of Medical Sciences
41 Portland Place
London, W1B 1QH
Tel: +44(0)20 3176 2150

Email: info@acmedsci.ac.uk
Web: www.acmedsci.ac.uk
Registered Charity No. 1070618
Registered Company No. 3520281