The Academy of Medical Sciences

Frameworks for the regulation of medicinal products: opportunities and challenges

March 2012

Report of Forum Annual Lecture delivered by Professor Sir Alasdair Breckenridge CBE FRSE FMedSci, Chairman of the Medicines and Healthcare products Regulatory Agency

The Academy of Medical Sciences

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All web references were accessed in March and April 2012.

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Introduction

The FORUM Lecture provides an opportunity for the Academy's FORUM members, Fellows and invited guests to hear from international leaders in biomedical science. The 2012 lecture, 'Frameworks for the regulation of medicinal products: opportunities and challenges', was delivered by Professor Sir Alasdair Breckenridge CBE FRSE FMedSci, Chairman of the Medicines and Healthcare products Regulatory Agency (MHRA). Sir Alasdair explored the future opportunities and challenges in the regulation of medicines and medical devices; particularly how improved regulation can support innovation. The lecture and subsequent discussion are summarised below, and contribute toward the Academy's ongoing work on the regulation and governance of health research.[1]

Frameworks for regulation

Sir Alasdair considered regulation of pharmaceuticals, medical devices and diagnostics within the context of three frameworks; law, science and public health. Addressing these three aspects of regulation is vital because although regulations are based on the law, they are driven by science and have no relevance unless they serve public health. Challenges that are common to the regulation of drugs, devices and diagnostics are:

- Regulation must follow scientific developments. Where science is developing fast it can be difficult for regulators to react quickly enough.
- Regulation must accommodate changing products.
- Regulatory science is at different stages in different countries.

The role of the MHRA was then outlined with respect to the three primary functions of a medicinal products regulator that Sir Alasdair defined as:

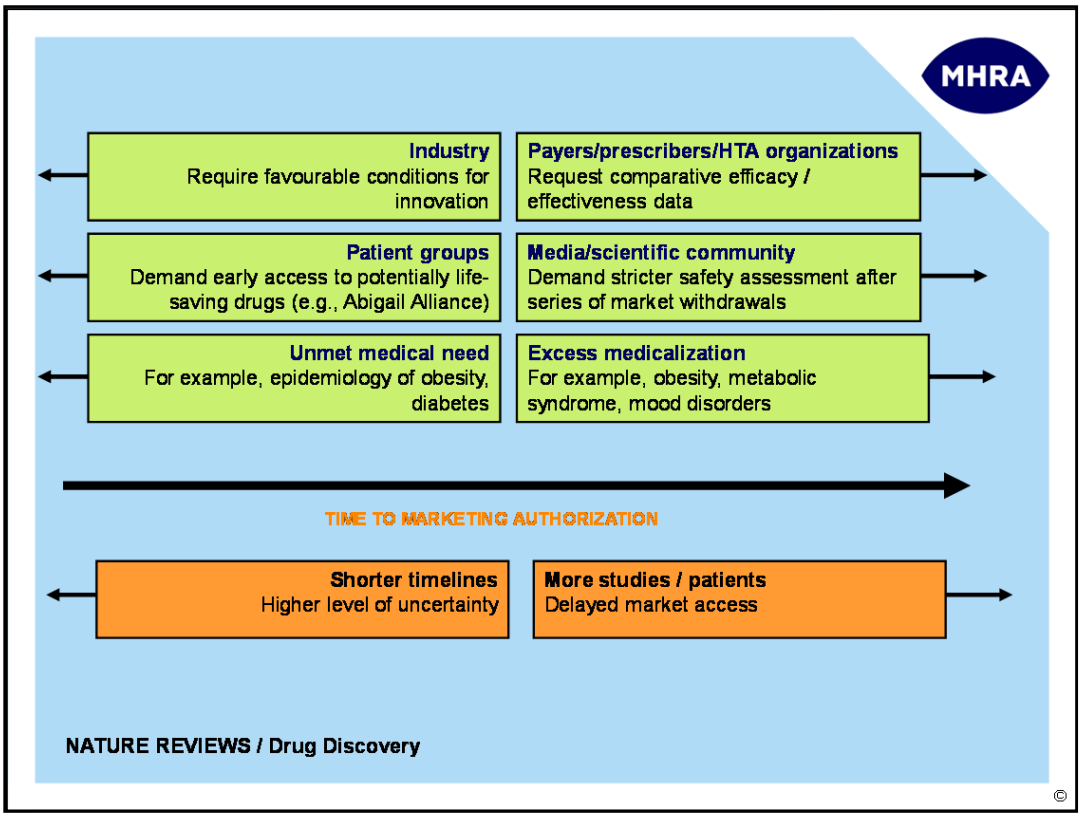
- Allowing to the market only products with an appropriate benefit-risk balance. Where this balance no longer exists, the regulator must take appropriate action.
- Communicating information to healthcare professionals and patients so that they can prescribe and use products appropriately.
- Encouraging innovation.

Innovation was placed as a centrepiece of the Goverenment's growth agenda by The Life Sciences Strategy, the NHS Innovation Strategy and the Innovation and Research Strategy.[2,3,4] While the regulator's role with respect to innovation is expanding, the definition of 'innovation' varies depending on the stakeholder and the stage of

[1] For further information: http://www.acmedsci.ac.uk/p47prid88.html
[2] Department for Business, Innovation and Skills (2011). *Strategy for UK Life Sciences.* http://www.bis.gov.uk/assets/biscore/innovation/docs/s/11-1429-strategy-for-uk-life-sciences.pdf
[3] Department of Health (2011). *Innovation Health and Wealth, Accelerating Adoption and Diffusion in the NHS.* http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131784.pdf
[4] Department for Business, Innovation and Skills (2011). *Innovation and Research Strategy for Growth.* http://www.bis.gov.uk/assets/biscore/innovation/docs/i/11-1387-innovation-and-research-strategy-for-growth.pdf

development of a product. For example, patient groups and industry often see innovation as bringing products to the market faster, while regulators and researchers might perceive innovation as the increased understanding of the mechanisms and safety of drugs. Although the differing interpretations of innovation are not mutually exclusive, they can present challenges to the regulator in balancing many different concerns in the development of new medicinal products. Furthermore, as medical science progresses, regulation must accommodate changes in the nature of products being developed.

Figure 1 The concerns and drive to innovation by different stakeholders can increase or decrease the time to product marketisation. The regulator must balance these concerns.[5]



Pharmaceuticals

The regulator plays an active role in promoting innovation of pharmaceuticals by offering scientific advice to the manufacturer, in granting marketing authorisation, and in post-marketing surveillance of both safety and effectiveness to better understand benefit-risk balance.

The current model of drug development faces a number of emerging challenges that need to be appropriately addressed. The number of new chemical agents put on to the market has also dramatically decreased in recent years and there are increasing costs associated

[5] Eichler H, *et al*. (2008). *Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma.* Nature Reviews Drug Discovery **7**, 818-826

with developing biopharmaceutical agents (also known as 'biologics') over that of new chemical agents.[6] Biopharmaceutical agents are less likely to be used to treat a large number of patients, but may treat the causes of the disease rather than just the symptoms, dramatically improving patient outcome and reducing adverse reactions. Novel biopharmaceutical agents may therefore lend themselves to being brought to the market earlier, which requires adaptive licensing. While it is recognised that decreasing the time to market and increasing patient access to novel products will also produce favourable conditions to industry to innovate, this has to be balanced by concerns for patient safety (see figure 1). One way to address this issue is to put greater emphasis on post-marketing assessment of safety and effectiveness, and improving benefit-risk assessments by taking into account how these are valued by patients and carers. This would allow better weighting of benefits and risks that could inform regulation and the comparison of products.

Devices

The regulation of medical devices in Europe is a devolved system, with device approval overseen by a governmental body called a National Competent Authority (NCA) in each EU country. These competent authorities apply a series of EU directives that outline the requirements under which medical devices (as well as other commercial goods) can be designated with a Conformity European (CE) mark. Importantly, once a CE mark is designated to a device in any one EU country, this device can be marketed across all EU countries. In the UK this function is undertaken by the MHRA. The MHRA conducts inspections to confirm manufacturing standards, oversees approval of the lowest risk devices, collects post-marketing safety reports, and designates Notified Bodies (NB) to oversee approval of more complex devices. NBs are independent commercial organisations that evaluate the performance and reliability of many products including medical devices. The specific requirements for pre-marketing clinical studies are poorly defined and although clinical data is required for more complex devices, the nature of these studies is not binding on manufacturers or NBs, and is not made available to the public. An additional layer of regulation is also present in the post-marketing phase, where manufacturers must report all serious adverse events to the competent authority.

The European database EUDAMED (EUropean Database on MEdical Devices) is available to store data on manufacturers, clinical studies, adverse events and details of post-marketing events that are collected during the course of regulation. However, this database is extremely variable in terms of content and is therefore of limited value.

Sir Alasdair identified a number of ways in which this regulation could be improved to increase the innovation of safe and effective medical devices, including:

- Increasing the capability and standard of NCAs across the EU.
- Improving and unifying the performance of NBs, decreasing their number, and ensuring they have the necessary expertise.

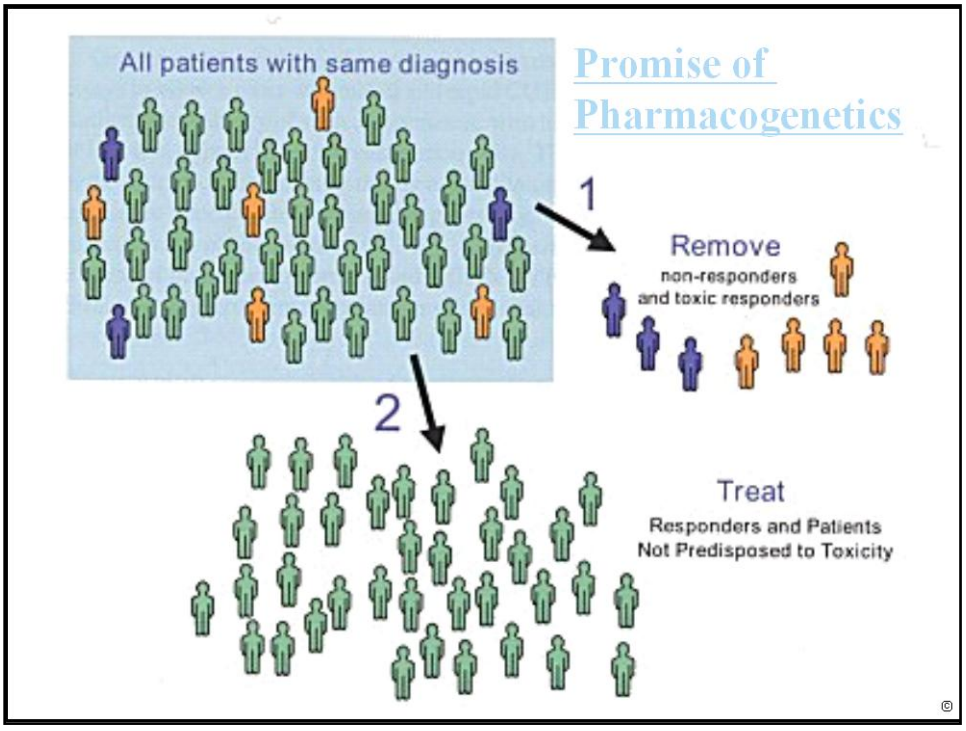
[6] Biologics or biopharmaceuticals are biological products such as products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

- Improving post-marketing surveillance by NCAs and ensuring that reports are accessible across Europe.
- Empowering patients and healthcare providers to report events.
- Creating a viable European register of devices.
- Increasing transparency.

Diagnostics

The promise of pharmacogenomics or stratified medicine is that by selecting for treatment only those patients who are known to respond to the medicine, or who will not suffer an adverse reaction, the therapeutic result will be optimised (see figure 2). However, this selection requires diagnostic tests, such as for genomic biomarkers, which are currently regulated not as a medicine but as a medical device under the In Vitro Diagnostic Medical Devices Directive (98/79/EC). This regulation does not require data about the clinical usefulness of the test, but merely its specificity and sensitivity. Unless the clinical applicability of the diagnostic test can be validated, its value remains uncertain. Close collaboration between the respective regulators is therefore required to overcome this difficulty and allow appropriate regulation of medicines with companion diagnostics.

Figure 2 Utilising diagnostic tests for genetic biomarkers presents opportunities for the development of stratified medicines



Discussion

The lecture was followed by a vibrant discussion that began by considering the value of the regulator giving scientific research advice given the considerable uncertainty around research outcomes. For example, a company might seek advice about the type of studies that might be conducted with respect to endpoints chosen or type of study. Sir Alasdair explained that this advice is welcomed and valued by industry and researchers. Regulators first entered into such discussions with researchers in the 1990s, which have since expanded in the UK to include input with the payer via the Health Technology Assessment (HTA) programme. These tripartite meetings are often requested by industry, suggesting that they are helpful in informing innovative research. It was noted that in some cases, where there are multiple payers and HTA-equivalents, this relationship would be more difficult.

The discussion then moved on to the role of the patient in the regulation process. In particular it was stressed that patients, patient groups and carers might be prepared to accept a relatively high level of risk or side effects if efficacy was high. Sir Alasdair noted that historically the European Medicines Agency and MHRA have relied on advisory committees containing lay members to inform many regulatory decisions. However, lay committee members quickly became 'experts' and often tried to advise on matters beyond their expertise and remit. Increasingly, patient groups are being included in these advisory committees. This will enable risk to be more appropriately balanced against the value of the benefits from the use of new medicinal products.

Government's proposals to give patients earlier access to drugs for conditions that do not currently have effective treatment (i.e. adaptive licensing) was welcomed by a number of attendees. Post-marketing surveillance of safety and effectiveness will be even more important in these adaptive licensing situations and will help inform clinicians about how to prescribe these medicines appropriately. Concerns were expressed that clinicians did not always take into account the evidence provided by this post-marketing surveillance, preferring to use their own judgement. Much harm can be done by inappropriate prescribing but the MHRA does not regulate clinicians so this may need to be addressed through restricting the licensing of the drug.

There was a detailed discussion on the importance of health informatics in supporting regulation. The new Clinical Practice Research Datalink (CPRD) in England was welcomed as a step in the right direction.[7] It was suggested that there was a need to automate the collection of outcomes to ensure that it wasn't reliant on information being inputted by the patient, operator, manufacturer or prescriber. In the case of medical devices, post-marketing surveillance is in its infancy but recent problems with breast implants and all-metal hip implants have highlighted the importance of monitoring durability and having a register of devices. For both drugs and devices, the variability in quantity and quality of safety and efficacy information available from other European countries is a problem.

Returning to Sir Alasdair's point about the challenges for regulators in keeping pace with scientific developments, one attendee raised the case of 'biologics' that may be neither a

[7] For further information please see: http://www.cprd.com/intro.asp

drug nor a device. This is an emerging area where regulators and sponsors are working together to ensure a risk-based approach to regulation.

The lecture and discussion were brought to a close by Professor Sir John Tooke PMedSci, who thanked Sir Alasdair for a thoughtful, considered and science-focused analysis of a very complex area.

Annex I Lecture delegates

Dr Dipti Amin	Faculty of Pharmaceutical Medicine
Dr Rajiv Bhalla Radiochemistry Specialist	GE Healthcare
Dr David Blowers	Faculty of Pharmaceutical Medicine
Dr Helen Bodmer Head, MRC and Health Research Team, Research Funding Unit	Department for Business Innovation & Skills
Rachel Bosworth Director of Communications	Medicines and Healthcare Products Regulatory Agency
Dr Keith Bragman	Faculty of Pharmaceutical Medicine
Professor Sir Alasdair Breckenridge CBE FRSE FMedSci Chairman	Medicines and Healthcare Products Regulatory Agency
Daniel Bridge Policy Adviser	Cancer Research UK
Phil Brown	Association of the British Pharmaceutical Industry
Dr Miles Carroll Interim Director and Head of Research	Health Protection Agency Centre for Emergency Preparedness & Response
Dr Tim Cave Medical Director	Novartis UK
Sir David Cooksey GBE FMedSci Chairman	UK Financial Investments
Professor Charles Craddock Consultant Haematologist and Translational Director of Birmingham Health Partners	University of Birmingham
Peter Donelan Press Officer	Medicines and Healthcare Products Regulatory Agency
Sir Gordon Duff FRSE FMedSci Chair	Commission on Human Medicines
Dr Hans-Georg Eichler Senior Medical Officer	European Medicines Agency
Catherine Elliott Head of Clinical Research Support and Ethics	Medical Research Council
Dr Robin Fears Biosciences Programme Secretary	European Academies Science Advisory Council
Professor Barry Furr OBE FMedSci Consultant	Llangarth Ltd
Dr Alasdair Gaw Lead Specialist, Stratified Medicine	Technology Strategy Board
John Gillespie Policy Intern	Academy of Medical Sciences
Professor Sir Malcolm Green FMedSci Emeritus Professor of Respiratory Medicine, National Heart & Lung Institute	Imperial College London

Will Greenacre Policy Officer	Wellcome Trust
Emma Greenwood Policy Manager	Cancer Research UK
Dr Jonathan Hafferty Clinical Advisor to the Chief Executive	Medicines and Healthcare Products Regulatory Agency
Alison Hall Senior Policy Adviser	PHG Foundation
Dr Bassam Hallis General Project Manager	Health Protection Agency
Dr Russell Hamilton Deputy Director of Research and Development	Department of Health
Dr Esteban Herrero-Martinez Regulatory Manager and Interim Joint Lead of the Medical and Innovation Department	Association of the British Pharmaceutical Industry
Dr David Heymann CBE FMedSci Chairman of the Board	Health Protection Agency
Professor Raymond Hill FMedSci President	British Pharmacological Society
Professor Susan Iversen CBE FMedSci Emeritus Professor of Psychology	University of Oxford
Andrew Jack Journalist	Financial Times
Dr Ian Laws Vice President, Global Regulatory Affairs	GlaxoSmithKline
Dr Louise Leong Head of R&D and interim joint lead of the Medical and Innovation Department	Association of the British Pharmaceutical Industry
Thomas Lönngren Strategic Advisor	NDA Advisory Service
Joanna Maitland-Smith Director of Regulatory Affairs	Merck Sharp & Dohme
Professor Sir Alexander Markham FMedSci Professor of Medicine	University of Leeds
Brian Matthews Clinical Manager	BUPA
Nathan Moore Head of Office for Strategic Coordination of Health Research	Department of Health
Alan Morrison Vice President of Regulatory Affairs	Amgen
Sharmila Nebhrajani Chief Executive	The Association of Medical Research Charities
Professor Mahesh Parmar Director of Clinical Trials Unit	Medical Research Council
Professor Sir Keith Peters FRS FMedSci Past President	Academy of Medical Sciences
Professor Jack Price Professor of Developmental Neurobiology	Institute of Psychiatry

Becky Purvis Head of Policy	The Association of Medical Research Charities
Dr Rachel Quinn Director of Medical Science Policy	Academy of Medical Sciences
Dr Frances Rawle Head of Corporate Governance and Policy	Medical Research Council
Dr Paul Robinson Medical Director	Merck Sharp & Dohme
Graeme Sandell Assistant Director (Health, Social Care & Pharmaceuticals)	Department for Business, Innovation and Skills
Professor Caroline Savage FMedSci Professor of Nephrology	University of Birmingham
Lesley Sims Interim Executive Director	Academy of Medical Sciences
Sir John Skehel FRS Former Director	MRC National Institute for Medical Research
Laurie Smith Medical Science Policy Manager	Academy of Medical Sciences
Professor Robert Souhami CBE FMedSci Emeritus Professor of Medicine	University College London
Nick Sykes Director, European Regulatory Policy	Pfizer
Professor Paul Peter Tak Senior Vice President and Head of Therapy Area ImmunoInflammation	GlaxoSmithKline
Dr Janette Thomas Programmes Director	Integrated Medicines
Dr Beth Thompson Policy Adviser	Wellcome Trust
Professor Sir John Tooke PMedSci President	Academy of Medical Sciences
Dr Lincoln Tsang Partner, Life Sciences focus	Arnold and Porter
Professor Jonathan Weber FMedSci Director of Research, Faculty of Medicine	Imperial College London
Dr Tony Whitehead Medical Director	Sanofi-Aventis
Doris-Ann Williams MBE Chief Executive	British In Vitro Diagnostics Association
Dr John Williams Head of Clinical/Neuroscience	Wellcome Trust
Professor Sir Kent Woods FMedSci Chief Executive	Medicines and Healthcare Products Regulatory Agency

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