

How drug regulatory authorities are adapting to new technologies

The past few years have seen the emergence of a number of new technologies. Some of these advances will have a significant effect on the nature of medicines and the way in which they are developed. This article discusses some of the significant changes in the regulatory oversight of drug development and licensing.

Many of the early advances in therapeutics were based on serendipity. As science developed, potential drug targets were identified in animal models of disease, and drug candidates identified by the exploration of molecules interacting with these targets¹. The technological advances now offer the opportunity to have a much greater understanding of the pathological processes in man. Genetic linkage and association studies enable particular diseases to be linked to particular genes or gene sequences².

As a consequence of genetic and bioinformatic advances, a greater number of targets have been identified. There have been advances in screening processes, lead identification and optimisation¹. New technologies such as gene therapy, cell therapy and xenotransplantation have emerged. Greater understanding of the pathological process will also lead to drugs targeted towards the disease rather than the symptoms. As understanding of the biological processes increase and drugs are more targeted towards specific human defects, it is likely that animal models of disease will become less relevant or non-existent. With developments in identification of patients most likely to respond to novel mechanism based drugs, smaller more effective clinical trials could be conducted, resulting in more rapid development times². All of these advances promise great changes for the future, however it should be noted that they have not yet resulted in a significant increase in the number of innovative products being launched each year. Indeed,

the number of new molecular entities first launched has remained static over the past decade.

As a consequence of these changes, the regulatory oversight of drug development and approval is evolving to remain relevant to the developing science. This article explores some of the ways in which regulatory authorities (with an emphasis on European authorities), are adapting to advances, particularly with respect to biological products where many of the greatest challenges lie.

Agencies involved in the regulatory oversight of medicinal products in Europe and the US

In the Europe Union, there are both national regulatory agencies in each country, such as the Medicines Control Agency in the UK, and a European agency – The European Agency for the Evaluation of Medicinal Products (EMA) and it is the nature of the product and the type of application that will determine to a large extent how any licence applications will be handled. In the US, the FDA is responsible for regulatory oversight of medicinal products.

European regulatory oversight of licensing of medicinal products

For the purpose of regulation of medicinal products in the European Union, a medicinal product is defined as “any substance or combination of substances presented for treating or preventing disease in human beings or animals. Any substance or

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Regulatory

combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological function in human beings or in animals is likewise considered a medicinal product³.

Both the EMEA and national agencies may be involved in assessing licence applications for medicinal products. However, the nature of the application may determine how the regulatory review is conducted. There are now two main processes for obtaining a licence to market a medicinal product across a number of countries within the European Union. One process is to obtain a national licence in a reference member state, the licence is subsequently recognised by other European countries via mutual recognition. The other process is the 'centralised procedure' whereby the application is made to the EMEA. When a product is handled by the centralised procedure it is considered by the EMEA's technical/scientific committee, the CPMP, who will allocate a rapporteur and co-rapporteur. The rapporteur and co-rapporteur arrange the technical assessment through their respective Member State's national agencies. The assessment is then circulated to other Member States and presented back to the CPMP who will make a scientific recommendation, which will be sent by the EMEA, to the Commission, who are responsible for granting a community licence valid in all EU Member States. The CPMP may establish specific expert groups involving external expert opinion to assist in the assessment of a licence application and hence in reaching a licensing recommendation, especially where there are specific, often complex issues. These expert groups provide expertise in addition to that which may be obtained by the national authorities acting as rapporteur/co-rapporteur.

The EU regulations stipulate that certain types of medicinal products must be handled via the centralised procedure, others may be handled by the centralised procedure, and others should be reviewed by national agencies. Those required to be handled by the centralised procedure of the EMEA include medicinal products developed by means of one of the following biotechnological processes:

- Recombinant DNA technology.
 - Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells.
 - Hybridoma and monoclonal antibody methods.
- There are a number of other categories of products which may be considered by the EU centralised pro-

cedure but which may also be considered by national agencies and by a process of mutual recognition, achieving registration in other Member States. These include: medicinal products developed by other biotechnological processes which, in the opinion of the agency, constitute a significant innovation; medicinal products administered by means of new delivery system, or for entirely new indications or derived from blood or plasma or employ processes which demonstrate a significant technical advance, or containing a new active substance⁴.

In addition to the expert groups mentioned above, set up to address specific issues and new developments, the CPMP and EMEA have established various groups such as the Biotechnology Working Party (BWP) and Efficacy Working Party (EWP)⁵. These groups consist of members from the national agencies and have been responsible for drafting various documents/guidelines which set the regulatory framework relevant to new technologies and new advances. These guidelines are designed to provide advice to industry and others defining requirements for licensing, taking account of new developments in science. For example, some of the recent papers produced by the BWP relevant to new technologies include the following⁵:

BWP: Concept papers

CPMP/BWP/1711/00 Concept Paper on the Development of a CPMP Points to Consider on the Use of Transgenic Plants in the Manufacture of biological Medicinal Products for Human Use.

CPMP/BWP/3326/99 Concept Paper on the Development of a CPMP Points to Consider on Xenogeneic Cell Therapy.

CPMP/BWP/1113/978 Concept Paper on the Development of a CPMP Guideline on Comparability of Biotechnology-derived Products.

BWP: Points to Consider

CPMP/BWP/41450/98 Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products.

Draft guidelines

CPMP/BWP/3207/00 Note for Guidance on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substance.

BWP: Adopted guidelines

CPMP/BWP/3088/99 Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products.

CPMP/BWP/328/99 Development Pharmaceuticals for Biotechnological and Biological Products –

Annex to Note for Guidance on Development Pharmaceuticals (CPMP/QWP/155/96).

CPMP/BWP/477/97 Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines, (CPMP adopted July 98).

CPMP/BWP/268/95 Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses (CPMP adopted Feb 96).

The BWP also provides specialist technical support to market authorisation dossier evaluation as required. The EWP has similarly produced a number of concept papers, point to consider, draft guidelines, adopted guidelines⁵. Many of these tend to be more disease associated in nature.

Both the BWP and EWP publish documents outlining their proposed workplans for the coming year⁵. For example, the BWP workplan lists, among many items, the following for this year:

- Note for guidance on the use of transgenic animals in the manufacture of biological medicinal products for human use (revision).
- Note for guidance on comparability r-DNA-derived medicinal products.
- Position paper on the use of oncogenic cell lines in the manufacture of medicinal products.
- BWP guidance on the assessment of viral safety data of r-DNA biotechnology products produced in mammalian cell lines.

It is evident, therefore, that at a European level, the regulatory authorities are adapting to new advances by ensuring that there are appropriate organisational capabilities and that, as science advances, regulation advances.

Effect of new technologies on national agencies

The impact of new technologies has resulted in changes in national agencies. Scientific assessments of licence applications are still performed at national level where, for example, a country is the rapporteur for a product being reviewed by the centralised route, or where the country is acting as reference member state in a mutual recognition procedure. The MCA in the UK has been nominated as the rapporteur country for a significant number of new applications being reviewed via the centralised procedure, or has acted as reference Member State frequently for products being licensed via the national/mutual recognition route. The MCA has therefore had to ensure appropriate expertise to enable a scientifically robust assessment of these applications. It has

Regulatory

achieved this in a number of ways. It has strengthened its biologicals/biotechnology unit and makes greater use of external scientific expertise to advise on specific aspects of applications. The MCA maintains a panel of external experts able to provide the agency with advice as appropriate. In addition, the Committee on Safety of Medicines, which reviews UK licence applications and advises the licensing authority in the UK, has strengthened its expertise in response to new technologies by establishing various sub-committees (eg biologicals sub-committee) and the greater use of additional expertise, to address specific issues.

MCA experts also contribute at a European level through, for example, membership of the CPMP or BWP. In addition to MCA experts contributing to these groups, external experts will also attend to ensure that, in considering an issue, the best scientific advice is obtained.

The MCA has also established close links with other UK bodies in order to ensure appropriate expertise is available as necessary. These may include groups such as the Gene Therapy Advisory Committee (GTAC) which deals with ethical issues surrounding gene therapy (whereas the MCA regulates clinical trials and licence applications). GTAC's terms of reference⁶ are to consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks. GTAC also provides advice to United Kingdom Health Ministers on developments in gene therapy research and their implications. One of GTAC's particularly important initiatives is a proposal for long term monitoring of patients in gene therapy studies⁷. The rationale behind this proposal is the recognition that, while gene therapy is a novel approach to treating disease and it is hoped that it will eventually lead to effective and safer medical treatments, the long-term effects of gene therapy treatments are unknown. Patients will be monitored via their health records. This will allow GTAC to monitor the health of both participants and their children up to the age of 16 years.

In addition, the MCA has established close links with other bodies such as the Human Fertilisation and Embryology Body who are involved in the regulation of stem cell research, the National Institute for Biological Standards and Control, who have a very active programme of research and continue to define new standards for biological products relevant to emerging technologies, Department of Health Research and Development Branch and the Medical Research Council, thereby allowing appropriate expertise to be called upon where necessary.

Clinical trials regulation in Europe

Clinical trials in Europe are regulated at a national level. Greater regulatory harmonisation and oversight will be achieved with the implementation, by 2004, of the Clinical Trials Directive (published on May 1, 2001⁸). This directive covers five main areas, approval of clinical trials including normal volunteer studies (which are currently outside the scope of regulation in some Member States), manufacture and importation of investigational medicinal products, inspection to verify compliance with GCP and GMP, pharmacovigilance and procedures concerning ethics committees. While national agencies in Europe currently have procedures in place to review and grant permission for clinical trials, the directive will, in general, extend the scope of regulation in this area. The Directive is designed to afford the participants in clinical trials appropriate protection as well as enhancing regulatory oversight. Ensuring appropriate protection to such participants is critically important to all trials. However for trials involving new technologies new issues will become apparent and it is appropriate that these trials receive the necessary regulatory scrutiny and oversight.

Scientific advice during development

In addition to advice given by national agencies to companies during the development phase, the EMEA has a mechanism whereby applicants can obtain scientific advice on questions relevant to development issues from the CPMP via its Scientific Advice Review Group (SciARG)⁵. Membership of the SciARG is by nomination from the individual member states. The scientific advice process is particularly relevant to new technologies, where complex issues have not previously been addressed. Following an application for scientific advice, co-ordinators are appointed by the group and advice is prepared, generally via the national authorities, and presented back to the SciARG and CPMP, and once endorsed, given to the applicant.

US regulatory oversight of medicinal products

In the US, the regulatory oversight for new technologies involving biological products falls to the Centre for Biologics Evaluation and Research (CBER), which is one of five centres within the FDA⁹. CBER's regulation of biological products has been expanded in recent years to include a wider variety of new products such as biotechnology products, somatic cell therapy and gene therapy. Recognising the importance of new technologies to

drug development and licensing, they have set among their priority initiatives for 2001, development of capabilities in genomics, proteomics, transgenics and tissue, cellular and gene transfer products. In addition, there are a number of other reinvention initiatives currently ongoing. One such is the Tissue Action Plan, implemented in March 1998, which develops policies, regulation and guidance documents, inspection and compliance, and co-ordination of scientific and regulatory policy, with respect to cellular and tissue-based products. Another is the xenotransplantation action plan, initiated in response to the recognition that transplantation of non-human live cells could, as well as providing many potential benefits, present a risk of introducing infectious diseases into the human population. The purpose is to provide a comprehensive approach for the regulation of xenotransplantation that addresses the potential public health safety issues associated with xenotransplantation and to provide guidance to sponsors, manufacturers and investigators regarding xenotransplantation product safety and clinical trial design and monitoring.

The FDA also has extensive links with other US bodies and scientific experts⁹. It has various expert committees providing advice. For example, in the area of gene therapy, the FDA receives advice from its Biological Response Modifier Advisory Committee. The FDA also works closely with the NIH. In the area of gene therapy, the FDA's remit is to ensure that manufacturers produce high quality and safe gene therapy products, and these are properly studied in human subjects, whereas the NIH's primary job is to evaluate the quality of the science involved in human gene therapy research, and provide funding for the scientific developments. The NIH also has a public advisory committee which holds regular meetings on gene transfer research, focussing on scientific, safety and ethics issues .

Thus it is clear, that, like the situation in Europe, the FDA is also ensuring appropriate organisational capabilities for new technological advances, regulation develops as science evolves, and appropriate scientific advice is available to contribute to the development of regulatory systems.

ICH

The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 as a joint regulatory/industry project to improve, through harmonisation, the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the

Regulatory

References

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- 8 Directive 2001/20/EC of the European Parliament and of the Council of April 4, 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use.
- 9 Centre for Biologics Evaluation and Research website: www.fda.gov/cber/
- 10 International conference on harmonisation website: www.ifpma.org/ich7.html
- 11 European Commission Enterprise DG Pharmaceutical and Cosmetics website: <http://dg3.eudra.org/F2/review/index.htm>

United States, in order to make these products available to patients with a minimum of delay. The six parties to ICH represent the regulatory bodies and research-based industry in the three regions, Europe, Japan and the US, where the vast majority of new medicines are currently developed.

The ICH process has achieved success because it is based on scientific consensus developed between industry and regulatory experts and because of the commitment of the regulatory parties to implement the ICH tripartite, harmonised guidelines and recommendations.

ICH has considered a number of new technologies over recent meetings. At the Brussels July 2000 steering committee, a report was presented from a 'brainstorming' meeting, in which the development of an ICH topic on 'gene therapy' was discussed. In view of the interest expressed by all parties in this topic, it was agreed that this should be further explored.

At the May 2001 ICH meeting, a satellite on Biotechnology and Gene Therapy Products was held. During this meeting, it was agreed that the scientific principles for the regulation of gene therapy or gene therapy products are currently harmonised in the three regions. And it was also agreed that there was a need to continue to foster the exchange of information under the auspices of ICH in relation to emerging scientific information on such products. Many areas of scientific importance were identified among which three topics were prioritised for discussion under ICH: dose definition and standardisation, virus shedding and germ-line integration. A workshop was recommended in Washington in Spring 2002 to take forward the discussions on technical issues related to dose definition and standardisation.

Future changes: European 2001 review

In Europe, the European Commission has recently proposed a number of changes to the legislation governing regulation of medicines¹¹. These proposals will need to be passed by the European Parliament before becoming law, and therefore may be liable to change and may take some time before coming into effect. Some of the goals of the review of legislation have been the need to continue to guarantee a high level of public health protection for European citizens, rationalisation and simplification of the regulatory process with a view towards better procedures and decision-making and preparation for an enlarged Europe. The proposals include allowing more products access to the centralised procedure (and making it mandatory for new active substances), extending the scope of scientific advice, introducing a fast-track regis-

tration procedure for products of significant therapeutic interest, introducing a conditional marketing authorisation, in particular cases when there is a specific and identified patient need. There are also changes proposed to the Mutual Recognition procedure with consultation with other Member States prior to issue of the first licence in the RMS, and greater use of an arbitration procedure in the event of proposed withdrawals from a Concerned Member State, and greater definition of what constitutes a public health concern¹¹.

Conclusions

The regulatory oversight of drug development and licensing is undergoing significant changes, in both Europe and the US, adapting to a number of factors including the emergence of new technologies. Regulatory agencies are working closely with industry and many other expert bodies in the development of regulations relevant to these new technologies. Appropriate guidance is being produced in many areas, helping industry develop innovative products. Appropriate organisational structures are in place or are being developed enabling appropriate technical expertise to be available for technical assessments of licence applications involving new technologies.

Regulation of medicinal products is designed to protect public health, as well as to provide the framework for development and licensing of new products of appropriate safety, quality and efficacy. It is hoped that the ongoing revolution in drug discovery and development will ultimately translate into safer, more effective medicines thereby improving public health.

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