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## Regulatory challenges of new technologies

### **Moderator: Dr John Lim, Singapore**

In recent years there has been much research and development in the use of new technologies — such as biotechnology and combination products as therapeutic agents. There are approximately 200 biotechnology products on the market and more than 350 in the late development stage. These products include recombinant peptides and proteins, modified proteins, monoclonal antibodies and related products, gene transfer products, cell-based therapies and engineered tissue products.

Research and development in biotechnology will continue to grow. Regulatory agencies worldwide have a vital role to play in safeguarding public health and in the continued development of such products. Biotechnology products differ from traditional synthetic chemical medicines in several important aspects, including immunogenicity, the inherent greater variability of the manufacturing process, the more limited applicability of animal models, and a greater potential for microbial contamination and the transmission of disease.

The history of clinical use of therapeutic biologicals is extremely short. Sharing and exchange of information between regulatory agencies worldwide will be extremely beneficial in the process of developing new regulations and guidelines. The challenge to both regulators and industry will be to remain vigilant in designing new approaches to risk management and risk communication to ensure the safe use of these products without unduly hampering the development of these exciting technologies.

## The EU regulatory system in the international environment Mr Thomas Lönngren, EMEA

In the European Union regulatory system, there are 15 harmonized member states. In recent years, there has been intense cooperation with the Central and Eastern European countries. Within the framework of ICH, standards are being set through bilateral agreements and discussions with the United States, Japan and others. The EU has also extended its cooperation and attention to other international partners.

The European system has two licensing routes: a centralized procedure, and mutual recognition between national authorities. The EMEA is the focal point in this system. Currently there are a number of initiatives in preparation:

- Review of the European regulatory system in order to have one harmonized standard for new medicines.
- A high-level group on innovation and provision of medicines to improve competitiveness of European companies.
- Regulation and harmonization of all clinical trials in the European Union by 2004.
- Proposal on the development of paediatric medicines.
- Building of a robust electronic regulatory system for the EU.
- Enlargement of the EU.

In recent years, research in genetics and genomics led to the development of many innovative new technologies in the production of medicines, such as gene transfer techniques, cell manipulation, DNA vaccines, therapeutic cancer vaccines and transgenic animals. Such innovations provide many new therapeutic choices and opportunities in terms of prevention, diagnosis, and treatment.

Drug development in this area is likely to generate an unprecedented amount of information for target identification and screening. Some of these data could lead to quicker development of effective medicines and faster solutions for emerging diseases, with shorter and more focused development time. Early-phase pharmacovigilance, postmarketing studies and long-term follow-up should be in place to confirm safety. Classic scientific evaluation of quality, safety and efficacy may need to be complemented by considerations of risk

perception, risk management, and societal, economic, traditional, ethical and environmental concerns. Drug regulatory authorities may face pressure to approve new therapies quickly and increasing expectations from patients to be involved in the process.

Regulatory authorities should be prepared for challenges, such as keeping up to date with scientific progress and its potential benefit for public health, keeping the expertise for scientific review, and being flexible in integrating different disciplines and regulatory frameworks to tackle this new challenge. Our rules cannot stand still: regulatory requirements must reflect scientific progress, not define scientific pathways. There should be new ways of ensuring compliance in a changing environment with greater regulatory transparency. In order to take into account different interests, common rules need to be established through international cooperation. This is not an issue for Europe or the United States alone, but is rather a worldwide issue and we, as regulators, need to decide how to handle these new therapies.

In 1995, the EMEA published the first guidelines on gene and cell therapy. The EMEA expert groups are looking at new guidelines and reviewing the existing guidelines. A multidisciplinary team, the EMEA task force on innovation, is also looking at ways of adapting the current regulatory framework to the innovations. EMEA also aims to take a proactive role in international cooperation with organizations like ICH, FDA, etc.

Last, but not least, here are some perspectives for the future:

- New technologies and therapies have the potential to bring significant benefits to patients, but when will they actually appear?
- What is the relevance of the target diseases selected by industry and which patients will benefit?
- Will the high cost of new therapies limit patient access and range of target diseases?

- Standards should be developed through international cooperation, not through a country-by-country response.

## **FDA/CBER regulation of emerging therapies**

### **Mr Mark A. Elengold, United States of America**

The regulation of products by the Food and Drug Administration (FDA) in the USA is based on sound science, law and public health impact. Biological products are regulated by the Center for Biologics Evaluation and Research (CBER). The cornerstone for our regulatory efforts is research. We serve the functions of both evaluator, enforcement authority, and standards and control authority over biological products in the United States. In order to do that, we have a robust mission-related research programme that allows us to learn about these cutting-edge products, and at the same time retain high-quality staff, which is key to regulating these emerging technologies.

The aim of research and development is to shepherd the production of safe and effective products from bench to bedside, and ultimately to the marketplace, based on safety and quality. In 2000, the Pharmaceutical Research and Manufacturers Association estimated that there were 369 products resulting from developments in biotechnology. Cancer and related conditions are the number one target for this research. The US human genome project began in 1990 with a short-term goal of diagnosis and prevention of diseases. In the long run, the study of the gene may lead to the development of drugs such as small-molecular drugs, therapeutic protein drugs, and pharmacogenomics. In the USA, new offices are being set up to regulate various new tissues, cells and related therapies such as:

- conventional bank tissues for transplantation,
- gene therapy,
- reproductive cells for assisted reproductive therapy,
- human reproductive and therapeutic cloning,
- somatic cell therapies, e.g. stem cells,
- xenotransplantation.

Control of human reproductive cloning presents a great challenge to FDA. Regenerative medical techniques, such as stem cell manipulation and tissue engineering, raise public expectation that, in time, many human parts — heart, lungs, eyes, skin, etc. — will be available. CBER's proposed approach to human cellular and tissue-based products is a risk-based stratified approach. Most tissue-based products are regulated solely under the Public Health Service Act Sec:361, the primary purpose of which is to prevent disease transmission. Such cellular and tissue-based products include musculoskeletal, ocular and cellular products, haematopoietic stem cells, reproductive tissue, heart valves, dura mater, etc.

“Kicked-up” products that do not meet the criteria of PHS Act Sec:361, but that raise concerns about safety and/or effectiveness other than those associated with conventional use of tissues, will be regulated as drugs, biologicals or devices. In relation to xenotransplantation, the following initiatives have been taken:

- Xenotransplantation Action Plan,
- Secretary's Advisory Committee on Xeno (SACX), second meeting, July 2001,
- Xeno Sub-Committee of the Biological Response Modifiers Advisory Committee,
- National Xenotransplantation Registry and Database-Pilot Phase,
- Xenotransplantation and Gene Therapy Disclosure, published 18 January 2001.

Transgenics is another promising area that raises regulatory issues that are only now becoming apparent. Plants and animals are being used to make products such as vaccines, monoclonal antibodies and therapeutic proteins. New techniques, including recombinant DNA technology, open up exciting prospects for developing a range of new vaccines such as DNA vaccines, tumour vaccines and new live attenuated vaccines. New technology has led to advances in genomics, proteomics, metabonomics, cellonomics and bioinformatics. The

microarray technology promises to bring about a better understanding of the complex causes of hitherto unconquered human diseases. Research in these new technologies contributes to the discovery of innovative medicines, vaccines and the provision of new diagnostic tests.

Oligonucleotide microchips can be used for surveillance or detection of both naturally occurring pathogens and those that might be used in biological warfare. The microchips can also be used in vaccine quality control and vaccine development.

There are some potential impacts of proteomics. Research is likely to lead to the development of new disease markers for early detection, new therapeutic targets, and new markers for therapeutic efficacy and for toxicity. New regulations will therefore need to take into account the new target pool, new markers for toxicity, new endpoints for efficacy, new endpoints for potency, and new bioassays for, e.g. identity and purity.

Last, but not least, here are some challenges for the future:

- New discoveries through biomedical research and technology:
  - gene therapy,
  - stem cell products,
  - genomics and proteomics,
  - transgenic plants and animals,
  - xenotransplantation,
  - new vaccines.
  
- New analytical methods:
  - three-dimensional nuclear magnetic resonance,
  - microarray technology,
  - proteomics,
  - fluorescent cell imaging,
  - MALDI-TOF spectroscopy,
  - PERT assays.