



Regulating biotechnology products

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Biotechnology, including DNA technology, has opened up new and promising opportunities for the diagnosis, prevention and treatment of diseases through, for example, the provision of safe and effective drugs and vaccines, as well as sensitive diagnostic tools. However, the use of these biological substances raises concerns about safety and quality, resulting mainly from the novel processes used in manufacture and the complex structural and biological characteristics of the products themselves. It is therefore important to ensure that control measures are in place to ensure the quality of the manufacturing process and of its products and to safeguard recipients against possible adverse events.

This session looked at balancing the risks and benefits of biotechnology products through regulation based on international or global standards and norms, while not limiting development or use. Regulation that is comprehensive but simple to implement is particularly important for developing countries, where the technological base is limited and expertise may be less specific. Issues related to the comparability of biotechnology products, including those related to scale-up, were highlighted as needing particular attention.

Comparability of biotechnology products and cell substrates

Dr Takao Hayakawa, Japan

The problem we are facing is how to develop and establish rational concepts and approaches for assessing the comparability of protein

products derived from different biopharmaceutical manufacturing processes. Such an assessment is needed when a manufacturer claims that a product of a new manufacturing process Y is comparable to an existing product of manufacturing process X in terms of quality, safety and efficacy. A rational step-by-step approach, taking into account both product and process, is needed.

The essential first step is to establish whether the new product is comparable to the existing one in terms of both molecular and quality attributes. The criteria for molecular and quality comparability will depend on the nature or type of the product, e.g. the initial cell clone in the case of monoclonal antibody preparations.

It is also necessary to examine whether the new manufacturing process can ensure the consistent production of the active protein product as well as the elimination of potential impurities and contamination by infectious agents. The direct and indirect effects of any changes in the manufacturing process on the product should be considered and the modified process should be re-evaluated or validated as needed. It is also necessary to consider the suitability of available analytical methods.

Further assessment of preclinical and clinical comparability may be necessary in some cases. The extent and nature of preclinical and clinical studies should be determined on a case-by-case basis, taking into consideration various factors. These might include: the nature and extent of changes in the manufacturing process; the results of evaluation or validation studies on the new process, including the results of relevant in-process tests; the capabilities and limitations of tests used for any comparability studies; the extent of comparability of the candidate product with any existing counterpart with respect to molecular and quality attributes, including impurities; the nature of the product ; its intended clinical use; the availability of existing preclinical and clinical data; the extent of existing information and experiences pertaining to the product in question; and the stage of product development.

The types of documents to be submitted with a product application will depend on the nature of the case, including whether a product is

at preapproval stage, postapproval stage, or coming from the same manufacturer or different manufacturers. At present, there is no specific international guidance on assessing the comparability of biotechnology products. However, the regulatory authorities of Canada, the European Union, Japan and the USA have recently started to develop an international harmonized document on technical requirements for establishing comparability of biotechnology products. A fruitful outcome is expected in the near future.

Assessing biocomparability: a Canadian perspective **Dr Anthony Ridgway, Canada**

There is concern about biocomparability when a biological product is manufactured by two different processes, or possibly the same process at two different sites. The application of a comprehensive manufacturing control strategy is essential for any product but particularly for biologicals. Compliance with GMP, the application of process validation, a thorough characterization of the product and the setting of specifications are the main pillars of a control strategy that addresses the quality of the product by establishing and maintaining identity, purity, and potency. In concert with this in-process control strategy, the characterization of the material derived from the new manufacturing process conducted in parallel with a recharacterization of the original material, and comparative data on release specifications are the two main pillars in establishing comparability.

The extent of studies required will depend on factors such as the stage and extent of the changes being made, the impact of those changes on the product, the analytical capability available to evaluate the possible outcome of changes, and the link between quality criteria and safety and efficacy. Changes associated primarily with the drug substances include those involving changes in cell banks, the fermentation process, downstream purification or the location of the manufacturing site. For the drug product, the changes might relate to the formulation or dosage form, the container, or the filling site.

For manufacturing changes that affect the drug substance, the comparative data should be generated from analytical testing, i.e., function testing, from the drug substance specifications and possibly from pharmacological studies. For the drug product, comparative data should focus on the specifications, stability and pharmacokinetics.

The ICH guidelines provide valuable guidance on addressing the quality and safety of the products and are therefore relevant to the issue of comparability. For a change in the production of the drug substances, the ICH Q6B document on specifications is the most relevant. Other documents, such as Q5A, Q5B, and Q5D, are also important references. In the case of the drug product, Q6B is again useful, to be supplemented with Q5C and S6.

Biocomparability can be assessed by controlling product quality with regard to the characterization of the product conducted in parallel with a recharacterization of the earlier version of the product, a demonstration that all specifications are met, and validation of the process changes.

The purpose of process validation is to establish, with a high degree of assurance, that a specific process will consistently produce a product conforming to the predetermined specifications and quality characteristics. Compliance with the specifications can ensure that the process is consistent, that product quality is maintained, and that the product is safe and effective.

In the characterization of biological products it is important to provide a comprehensive picture of the chemical structure, where known, physical and biological properties, impurity profile and degradation pathways of the drug substance.

The ICH Q6B provides important guidance on the characterization of biological products. There are provisions on the control of the chemical structure, physicochemical properties, biological activity, purity and impurity profiles, and protein quantity. The structural confirmation should involve looking at, for example, the amino acid sequence and composition, while typical physicochemical properties

include relative molecular mass, isoform pattern, etc. Biological activity can be determined in a variety of ways, including animal-based, cell-culture-based and biochemical assays. It is also important to look at product-related and process-related impurities and potential contaminants.

Furthermore, one should also consider including additional tests that are specifically directed at evaluating the impact of the change on the products and process assays at the manufacturing steps most likely to be affected. In some circumstances a clinical trial may be required.

The globalization of the pharmaceutical industry and the modern regulatory environment present considerable challenges to industry. The increasing number of manufacturing processes and facilities lead to an expanding inventory of biotechnology products, more new facilities, facility changes, etc. There are also direct and indirect costs associated with making manufacturing changes in a global marketplace, for example, the cost to keeping up to date with national and regional requirements.

There are wider consequences of delays in implementing manufacturing changes, since patients may have to wait longer for access to improved quality or less expensive products. Manufacturers may be discouraged by such delays from implementing improvements to a process.

The new ICH Q5E guidelines address the issue of industry costs and delays associated with meeting region-specific requirements. They propose harmonization of data packages to support manufacturing changes or variations.

It is agreed that there are no generic biological products, and subsequent-entry products will be examined on a case-by-case basis. New clinical data are required in some circumstances, but the extent of the data required should be agreed between the manufacturer and the National Regulatory Authority on a case by case basis.

Regulatory aspects of nucleic acid vaccines

Dr Johannes Löwer, Germany

DNA vaccines are considered to be gene transfer products. Gene transfer medicinal products usually consist of genetically modified autologous, allogeneic or xenogeneic cells, or products targeted at genetically modifying human somatic cells, and which are used for the treatment, diagnosis or prevention of disease in humans or animals.

DNA vaccines are more similar to attenuated vaccines than to simple antigens. The antigens encoded by the DNA are expressed inside the body and this is advantageous to the mounting of an appropriate immune response. With DNA vaccines, the antigenicity of expressed viral antigens is similar to that observed during natural infection, and it is possible to express multiple combined antigens in the sense that several antigen genes can be combined on the same piece of DNA.

Possible applications of DNA vaccines include products to deal with viral, bacterial and parasitic diseases. Naked DNA alone is not very effective, but DNA immunization followed by boosting is better. DNA vaccines provide several benefits but they also may have disadvantages, e.g. the synthesis of antigen is considered to be relatively easy, and transport and storage simple; there is no risk of infection but there is a risk of inducing tolerance; they induce cellular and humoral immune responses but there is a risk of inducing autoimmune disease.

One difficulty in the preclinical studies was the move from laboratory rodents to human beings. DNA vaccination worked very well in mice but in humans a large amount of DNA is needed to obtain a reasonable response. As DNA alone is not so effective in humans, it can be combined with an immunostimulating agent such as a cytokine, or with a vector carrying the gene for such a cytokine. A number of clinical trials are currently under way to study the immune response to various infective agents, e.g., the malaria parasite and influenza virus.

The special safety considerations associated with DNA vaccines which need to be addressed include the possible induction of tumours or tolerance and adverse reactions and immunopathology due to the coadministration of cytokine and/or immuno-stimulatory genes. Other concerns include the appearance of systemic lupus erythematosus due to the rise in anti-DNA antibodies, and possible adverse reactions due to the biological activity of the expressed antigen itself.

Tumour induction might result from chromosomal integration. Integration could occur in various tissues and vary with formulation, sequence, route of administration, type of tissue, and quality of the DNA. The question is what tests are needed to look for chromosome integration and what might be the regulatory requirement?

The European regulations and guidelines in “Notes for Guidance on the Quality, Pre-clinical and Clinical Aspects of Gene Transfer Medicinal Products” provide useful information. There are provisions on quality and safety evaluations, toxicity studies, and biological monitoring.

Scientific advice on gene transfer medicinal products is sought according to the EMEA centralized evaluation procedures. Expert authorities and central ethics committees in various member states are being consulted. Furthermore, regulations related to the initiation of clinical gene therapy/DNA vaccine trials in Europe will be implemented in 2003.

Report on WHO Monitoring Group on Gene Therapy Dr Hongki Min, WHO

In 2002 the WHO Expert Committee on Biological Standardization (ECBS) recommended that the WHO secretariat monitor progress and consider developing guidelines for gene therapy products, along the lines of the existing guidelines for assuring the quality of DNA vaccines.

In response, a WHO Monitoring Group on Gene Therapy was formed with the objectives: to monitor developments in gene therapy and assess the need for international reference materials; to consider

nomenclature of gene therapy products and to provide advice to the WHO Committee on International Nonproprietary Names; to consider development of appropriate guidelines.

The Group proposed that it be renamed as the WHO Clinical Gene Transfer Medicinal Products Monitoring Group, and that it should deal with all such products currently being developed for use in or on humans either for therapeutic purposes or for prophylaxis. In order to understand better the needs of countries outside Europe and the USA, it was recommended that WHO convene a meeting on the state of development of gene therapy products and regulatory oversight, with participants from all regions.

Future action will include monitoring the development of gene therapy products and developing guidelines for assuring their quality, safety and efficacy in harmony with existing guidelines and requirements. Standards, reference materials and assays for relevant products should be developed, and educational sessions organized for scientists and regulators in clinical gene transfer.

Regulating biotechnology products: Cuban experience Mr Rolando Dominguez, Cuba

CECMED, the Cuban national regulatory authority, comprises five main technical departments, including one that regulates biologicals (e.g. vaccines, biotechnology products, blood derivatives and monoclonal antibodies). The structure of an application for a marketing authorization in Cuba is similar to those in other countries, and the documents required mainly provide chemical and biological information.

In Cuba, there are quite a variety of biological products on the market. All of them are manufactured in local facilities which are subject to GMP inspection every year.

The Center for Genetic Engineering and Biotechnology (CIGB) is the leading centre for biotechnology drugs in Cuba. It manufactures a wide variety of products such as recombinant proteins and vaccines. Another important centre is CIM, which produces monoclonal

antibodies, recombinant proteins and anticancer vaccines. Thirdly, the Finlay Institute is the leading institute producing meningococcal, tetanus, leptospirosis and polysaccharide typhoid vaccines.

At present, the current requirements for marketing authorization do not fully address the issue of variations. For this reason, CECMED has been working on a regulation on “Changes to an Approved Application: changes to manufacturing process. Comparability of biologicals”. This regulation is now undergoing final review with the local industry.

The regulation requires the approval of changes in the manufacturing process, control methods, manufacturing facilities and equipment, key personnel or the product itself (e.g. stability), and aims to ascertain the safety and efficacy of the new product.

Positive outcomes expected include more flexibility in the implementation of changes to approved products and a more dynamic regulatory process.

Regulation of products derived from recombinant DNA technology in China

Professor Haijun Zhou, China

The major difference between recombinant DNA products and other pharmaceutical products is that biotechnology makes use of genetically modified living organism to produce proteins and peptides, whereas other pharmaceutical products are derived from naturally occurring substances, or by chemical synthesis. However, biotechnology products are no different from other biological products after the process of protein purification. For this reason, the requirements for process validation, environmental control, aseptic manufacturing and quality assurance are fundamentally similar. However, the complexity of the system is greater for biotechnology products because their production requires highly developed cell propagation processes and complicated purification methods.

The following principles underlie the regulation of r-DNA products in China:

- Specific concerns about particular products should be raised with the appropriate specialists on a case-by-case basis.
- A new licence application is required even if the active ingredient is identical in molecular structure to a naturally occurring or previously approved product.
- Differences can arise at different production stages. Because ability to characterize the identity and structure and to measure the activity of the clinically active components is limited, emphasis has to be put on the control of the manufacturing process.

The following need to be considered during the evaluation process:

- the different vector and host cells used in constructing the engineered cell;
- the specificity of different kinds of r-DNA products in different animals;
- the different usage and frequency of administration of specific products and their implications for the acceptable levels of impurities;
- the need for special attention to modified moieties;
- possible contamination with potentially hazardous impurities if the purification process is not capable of eliminating them;
- unintended variability in the culture, which may lead to differences in impurities and inconsistencies in the product itself.

In ensuring the quality of r-DNA products, controls must cover:

- Source materials: expression of vector and host cells, sequence of the cloned gene, and the measures used to promote and control the expression of the cloned gene.

- Manufacturing process: master cell bank, consistency of yield product from full-scale culture, criteria for rejection of the culture lots, etc.
- Final product: physicochemical characterization, biological tests for identity and potency, tests for contaminants.
- Preclinical toxicity evaluation.
- Clinical trials.

Regulation of biotechnology products in the Republic of Korea

Dr Won Shin, Republic of Korea

The Korean Food and Drug Administration (KFDA) regulates biotechnology and medicinal products in the Republic of Korea. KFDA has three subsidiary institutes that are involved in the control of biologicals:

- The Pharmaceutical Safety Bureau handles all the administrative and regulatory processing of submissions, new drug applications, postmarketing surveillance, GMP inspections, and all compliance actions, such as product recall, issuance of regulatory letters, and revocation of product licences.
- The Biologics Evaluation Department evaluates the chemistry, manufacture and construction of application dossiers, does post-GMP inspections, performs official laboratory release tests of biologicals, and conducts laboratory searches to facilitate the scientific review process.
- The National Institute of Toxicological Research evaluates the pharmacology, toxicology and clinical data section of the application and conducts laboratory work in its areas of expertise.

There are regulations relating to registration of biologicals: GLP, GCP, and GMP apply to all product development; and manufacturers should have a manufacturing licence for their production facilities. They, as well as the importers, should obtain product licences after

the KFDA's evaluation of safety, efficacy and quality. There is also postmarketing surveillance, an adverse reaction monitoring system and an annual programme of sampling and testing of products on the market.

In conclusion, KFDA tries to implement science-based regulations compatible with ICH and global standards, and also to facilitate domestic and global drug development.

Regulation of biotechnology products in Indonesia

Dr Lucky S. Slamet, Indonesia

One of the advantages of biotechnology, including DNA technology, is that it allows the production of large quantities of therapeutic products that are difficult to prepare from natural sources using a conventional approach, or that are otherwise unavailable. The development implies a potentially limitless supply of drugs and vaccines.

Biotechnology products are probably the best purified and characterized biological medicines in clinical use. Their nature and production are highly sophisticated and must comply with international guidelines on standardization and control. However, the quality, efficacy and safety of such biological medicines in humans still needs to be ensured through regulation, such as premarketing approval and licensing, and postmarketing inspection. Considerable emphasis must also be given to "in-process" controls on the starting material and the manufacturing process, as much as to the analysis of the final product. Data are needed on quality and purity of cell culture and on the effectiveness of purification and test methods. Furthermore, the ability of the purification process to remove unwanted materials, such as DNA and potential viral contamination, must also be validated.

The existing international guidelines on the production and control of biotechnology products have helped the Indonesian authority to regulate these products before and after marketing. Regulation covers the critical functions needed to ensure the quality of biologicals, i.e., a published set of requirements for licensing,

surveillance, system of lot release, laboratory testing, regular inspection for GMP, and evaluation of clinical performance.

For licensing, the basic criteria for evaluation cover the main aspects of safety, efficacy, relevance to actual needs, quality, and compliance with GMP. Confirmation of safety and efficacy is based on review of preclinical and clinical data. For quality, evaluation covers control of the manufacturing process, from starting materials to final product. However, with the increased production capacity for biotechnology products, not only in developed but also in developing countries, regulatory measures as well as the authority's scientific capacity for premarketing evaluation needs to be strengthened, including the capacity to oversee clinical trials, ensure compliance with GMP, and carry out postmarket quality assurance and safety monitoring of such products.

Recommendations

The need to make optimal use of the products of new biotechnologies in the prevention, diagnosis and treatment of diseases that are the major causes of morbidity and mortality throughout the world, especially in developing countries, was recognized. However, it was emphasized that these are highly complex products, often manufactured using novel biotechnologies, and the need for careful evaluation and regulation was vital. Issues relating to the comparability of biotechnology products, including those of scale-up, were highlighted as needing particular attention.

Rapid growth of the biotechnology industry in a number of developing countries was noted, as was the science-based regulatory oversight already in place in some instances. However, effective regulatory oversight, as well as adequate resources to deal with biotechnology products, was still needed in the majority of developing countries. Full support was expressed for the application of biotechnology to the development of vaccines, therapeutic biologicals and diagnostics for the prevention, treatment or diagnosis of disease.

1. Given the rapid advances in biotechnology and the challenge of balancing the risks and benefits, WHO, in collaboration with regulatory authorities, should monitor developments and continue to provide clear guidelines on issues relating to quality, safety and efficacy of biotechnology-derived medicinal products, including biocomparability. Rapid dissemination of this advice is crucial and WHO should strive to improve awareness of available guidance.
2. Regulatory authorities lacking experience in the regulation of biotechnology-derived products should be strengthened through education, training and updating, as appropriate. They should draw upon the knowledge and skills of regulatory authorities already experienced in this area, with the collaboration of WHO. Regulatory authorities should recognize the need to support the participation of officials at scientific and related meetings dealing with the regulation of this fast-developing field.
3. Regulatory authorities with limited experience should identify sources of expertise within their countries, such as in academia, to assist in the review of applications for clinical trials and for marketing authorizations. Where these are lacking, the support of experts from more experienced regulatory authorities should be explored, with the assistance of WHO, as a means of obtaining the necessary skills and knowledge.
4. WHO should continue development of International biological reference materials that can serve as reference standards for new products.
5. Progress should be reported back to the ICDRA.