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REGULATORY ASSESSMENT OF APPROVED rDNA-DERIVED BIOThERAPEUTICS


Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology

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This appendix considers the regulatory assessment needed for dealing with situations where, for various reasons, rDNA-derived biotherapeutic products were licensed with data packages that do not follow current international regulatory standards for these biologicals – for instance, biotherapeutic products licensed by a generic pathway or with limited analytical, nonclinical and/or clinical data (1, 2). The International Conference of Drug Regulatory Authorities (ICDRA) discussed such situations at its meeting in Singapore in 2010 (3) and requested WHO to assist in developing approaches for evaluating these already-licensed products according to current WHO guidelines. In 2014 the Sixty-seventh World Health Assembly adopted two relevant resolutions: one on critical needs in the biotherapeutics area, aiming to promote access to these products as well as to ensure their quality, safety and efficacy (4), and the other on strengthening of regulatory systems, whereby WHO is requested to provide guidance on strengthening regulatory systems, and especially those dealing with increasingly complex biological products (5).

Although this appendix deals primarily with rDNA-derived biotherapeutic protein products, some aspects may also be relevant to other biotherapeutics.

1. Regulatory expectations for rDNA-derived biotherapeutics, including similar biotherapeutic products

Regulatory expectations for rDNA-derived biotherapeutic protein products are found in the main text of these guidelines which were adopted by the WHO Expert Committee on Biological Standardization (ECBS) at its meeting in October 2013 (6). Following considerable international consultation at the global level since 2004, the Guidelines on evaluation of similar biotherapeutic products were adopted by the ECBS in 2009 (7). These guidelines emphasize the need for a head-to-head demonstration of the “similarity” to reference biotherapeutic products (RBPs) of assured quality, safety and efficacy that have been licensed on the basis of a full licensing dossier. A head-to-head comparability exercise of a candidate similar biotherapeutic product (SBP) with a reference biotherapeutic product is essential to justify a reduced nonclinical and clinical package for licensing (7). Studies should be designed to demonstrate comparability and to detect any potential difference in quality, nonclinical and clinical attributes between the SBP and RBP rather than simply to confirm safety and efficacy of the two products. It should be ensured that any detected differences have no clinically meaningful impact on product performance.

If a head-to-head comparison of the SBP with the RBP is not performed throughout the development process as outlined in WHO’s guidelines for SBPs (7), the final product should not be referred to as an SBP (8, 9). SBPs are not “generic medicines” and the approval process used for small molecule generics is not applicable.

2. Review of products on the market

Problems have been identified in some countries where, for various reasons, biotherapeutic products were licensed using data which do not now meet current WHO regulatory expectations – such as biotherapeutics licensed as generics or as small molecule drugs. Often little is known about the safety and efficacy of the individual products since, in many cases, pharmacovigilance in the countries concerned is weak and sometimes nonexistent. In addition, the terminology used for these products is confusing and their traceability is poor (10, 11). In some countries, the coexistence on the market of these products and SBPs, as well as rDNA-derived biotherapeutics
licensed with full data packages, is a matter of concern. This was the situation for erythropoietin (12) and similarly for heparin (13). Some updating of national regulations has occurred to take account of recognized difficulties and there have also been changes in international regulatory expectations (14–17). Special considerations apply to the production and control of biological medicines, including biotherapeutics, which do not apply to chemical drugs. This is because of the biological nature of the starting materials, the manufacturing processes and the test methods needed to characterize batches of the product as well as the highly complex molecular structure of products themselves. Nonclinical and clinical evaluations are key components of the regulatory assessment of all biotherapeutics. Products already approved under the pre-existing regulations will need to be reassessed to ensure that they meet the new requirements.

National regulatory authorities (NRAs) should undertake a stepwise regulatory review of all biotherapeutic products already authorized for marketing, as follows:

- First, NRAs should identify products that have been licensed with data which do not meet current WHO regulatory expectations.
- Second, an assessment of identified products and gaps, based on the product-specific considerations listed in section 3, should be carried out in order to decide the appropriate action to remedy the situation and the timelines for implementing this action. This will inevitably involve a risk–benefit assessment of the situation.
- Third, manufacturers should submit to the NRA within a defined – but short – period of time a plan of action for dealing with the problem. The plan of action should consist of an analysis of available and missing data in accordance with WHO guidelines (6, 7), as well as a description of measures, which may include interim assessments, and proposed timelines needed to address the identified gaps.
- Fourth, NRAs should evaluate the plan of action proposed by the manufacturer and agree with the manufacturer on the next steps for generating missing data and their (possibly stepwise) submission to the NRA.
- Fifth, NRAs should assess in a stepwise approach the data (e.g. quality/manufacturing, nonclinical and clinical data as needed) that have been submitted – possibly in several separate packages at different times – and on the basis of the outcome should decide on appropriate regulatory action.

The timeline for completing the overall review exercise will depend on the time needed to generate and provide the missing information, taking into consideration the product-specific points outlined in section 3. For example, in 2009 one NRA clarified the “appropriate regulatory pathway” for dealing with changes in the regulatory oversight of low molecular weight heparins to reflect the fact that in future they would be regulated in that country as biologicals and not as small molecule pharmaceuticals. In addition, it was announced that any biosimilar heparin submissions should follow the regulatory framework for biosimilars and not the generic pathway. A transition period of 12 months was set to allow manufacturers to update their files to reflect the data required for biologicals. Manufacturers were also required to identify immediately after

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1 Low molecular weight heparin is not an rDNA-derived biotherapeutic product but provided as an example of reviewed products on the market. It is not considered a biological product in some countries.
the official date of transfer of regulatory authority how much of their licensed product was sold in that country per year (16).
Similar transitional provisions have been made by other NRAs when updating regulations for biotherapeutics including biosimilars (15, 17).

3. Points to consider in a stepwise regulatory assessment

A particular licensed product should be allowed to remain on the market during the review process unless specific causes or events lead the NRA to make its own judgment to suspend market availability of the product during the review process. Consideration should be given to the following in deciding appropriate regulatory actions:

a) NRAs should consider: 1) the number of products on the market which have been licensed without adequate quality, nonclinical and/or clinical data; and 2) the availability of alternative therapeutics on that market licensed locally with an adequate data package and/or also by an experienced NRA, meeting the standards of the relevant WHO guidelines (see b, below).

b) It is important to find out if the product in question is manufactured and licensed in a country with a jurisdiction which has, and follows, well-established regulatory frameworks, including, as appropriate, all the principles set out in these guidelines for biotherapeutic products (6) and, in WHO’s guidelines for SBPs (7). Account should also be taken of whether the jurisdiction concerned has considerable experience in the evaluation of biotherapeutic products including SBPs and post-marketing surveillance activities. If a product is manufactured and/or licensed in a country with considerable experience in these areas, then this provides some confidence regarding quality, safety and efficacy. In addition, it would be important to ascertain whether the actual product authorized in the country with limited regulatory experience is comparable – with respect to manufacturing process and controls, recent good manufacturing practices inspection and labelling – to the product licensed, supplied and used in the manufacturing country with the more experienced jurisdiction. It would also be important to see whether registration of the product in question has been rejected, cancelled or suspended by other stringent NRAs.

c) It is also important to know the extent to which the registration dossier of the biotherapeutic product meets the recommendations of WHO’s Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology and Guidelines on evaluation of similar biotherapeutic products (6, 7). Attention should be paid to key differences between national requirements and WHO guidelines – such as the lack of a head-to-head comparability exercise for an SBP. The NRA should recommend a critical dataset for re-registration of such products. Changes in regulatory requirements may be needed, as well as amendments to the legal framework of the country concerned, to enable such new requirements to be implemented.

d) The extent of the use of a biotherapeutic product as well as availability of alternative products if any should be ascertained. For example, this includes whether the product is essential for treating certain patients and what the clinical outcomes would be if the product was taken off the market. This assessment should cover: the disease that is being treated, whether the condition is life-threatening, the consequences of treating or not treating or stopping treatment in patients already using the product, the risk of switching
between therapeutic alternatives, the likelihood (and potential consequences, if any) of supply problems on clinical outcomes should the product be taken off the market, and the type of patient population (for example, paediatric, adult, older persons).

e) The seriousness of a potential lack of efficacy should be considered, as should possible safety issues (including higher efficacy) that may result from the continued use of the product under review. This should include an assessment of the severity of the potential impact on a patient of an immunogenic effect arising from the use of the product and an assessment of any adverse effects, for example biotherapeutic products that may cause cross-reactivity with native proteins (e.g. pure red cell aplasia caused by erythropoietin (1)).

f) The ability of the pharmacovigilance system in the country should be considered to monitor and determine adverse reactions and/or efficacy problems (such as reduced clinical effectiveness) associated with the biotherapeutic product, should they exist. Criteria for the evaluation of functional pharmacovigilance systems can be found in WHO’s document *The safety of medicines in public health programs: pharmacovigilance an essential tool* (18). With poor pharmacovigilance systems in many countries, as well as terminology difficulties, it may be impossible to obtain sufficient data to demonstrate that a particular product was the cause of an adverse reaction or that patients may be at risk from the use of products that are clinically untested or were tested with inadequately designed studies. Traceability is a key element in monitoring the safety and efficacy of biologicals as it enables pharmacovigilance measures to be put in place.

g) The expertise and capacity of regulators responsible for licensing biotherapeutic products is critically important for the appropriate evaluation of these products. Collaboration between NRAs, including work-sharing agreements and joint reviews with other NRAs, should also be explored (for example, see 2, 19, 20).

h) Consideration should be given to transparency with respect to informing health-care professionals, pharmacists and patients of the review process and its timelines. This could be done through website posting (16), via a symbol and some text in the product information, or any other means the NRA is allowed to use, highlighting the need to align the licensing process with current international expectations. This could also be an opportunity to request users to report any safety and/or efficacy issues.

### 4. Regulatory actions

On the basis of the outcomes of the regulatory assessment, the NRA should make decisions on appropriate actions to be taken. The decisions and actions of NRAs may differ depending on the assessments made according the points listed in section 3, which will be jurisdiction-specific. In a stepwise approach, product supply would not be compromised and authorization might be regularized after the defined time period during which the product would have been undergone further regulatory evaluation and so long as it is shown to have an acceptable benefit-risk profile. Capacity-building will be needed where resources and expertise are considered inadequate. Where the number and experience of persons available to undertake an overall review is limited, consideration could be given to mentoring, through WHO, of the NRA needing support by an experienced authority that has established processes which follow relevant WHO guidelines, or by work sharing arrangement amongst NRAs. The sharing of information between NRAs regarding the basis for regulatory decisions on biotherapeutic products, including SBPs and the
availability of publicly available evaluation reports are considered an important support for regulatory authorities that are less experienced in dealing with these highly complex products and may accelerate the assessment of the products. Communicating details of what information was reviewed and how it was incorporated into decision-making is also important for prescribers, patients and other stakeholders and can help them gain confidence in biotherapeutic products. The summary basis of decision documents of Health Canada, the European Medicines Agency and the United States Food and Drug Administration are examples of informative documents. The stepwise regulatory assessment approach outlined in this addendum is flexible and is designed to support the accessibility of biotherapeutic products of assured quality, safety and efficacy, as requested in two resolutions of the Sixty-seventh World Health Assembly in 2014 (4, 5).
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