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REGULATORY EXPECTATIONS AND RISK ASSESSMENT FOR BIOTHERAPEUTIC PRODUCTS

Scientific Principles to Consider

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed WHO document on *Regulatory Expectations and Risk Assessment for Biotherapeutic Products* to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text MUST be received by 12 March 2014 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Hye-Na Kang at email: kangh@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).

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1 **Background**

2 This document sets out scientific principles to be considered by national regulatory
3 authorities (NRAs) and manufacturers in the process of licensing biotherapeutic
4 products used in human medicine. It covers the regulatory expectations for innovative
5 biotherapeutic products, for so called copy products, as well as for similar biological
6 products. The document also considers the regulatory risk assessment needed for
7 dealing with situations where, for various historical reasons, products were licensed
8 under conditions which did not meet international regulatory expectations for these
9 biologicals as set out in this document, e.g. biotherapeutic products licensed through
10 generic approach/pathway. The International Conference of Drug Regulatory
11 Authorities (ICDRA) discussed such situations at its meeting in Singapore in 2010 (1)
12 and requested the WHO to assist in developing approaches to evaluating these already
13 licensed products according to WHO guidelines or for phasing them out in a
14 reasonable period of time.

15

16 Although this document deals primarily with biotherapeutic protein products, some
17 aspects are also relevant to polysaccharide based medicines, such as heparins.

18

19 **Regulatory Expectations for Biotherapeutic Products**

20 Special considerations apply to the production and control of biological medicines,
21 including biotherapeutics, which do not apply to chemical drugs. This is because of
22 the biological nature of the starting materials, the manufacturing processes and the test
23 methods needed to characterize batches of the product. For example, production of
24 many biotherapeutics involves the culture of cells and microorganisms. Others, such
25 as heparins, are isolated directly from biological materials. Also, biologicals are
26 highly complex products in molecular terms, sometimes derived using recombinant
27 DNA techniques. Even with the great progress made in the ability to purify and
28 characterize biologically active macromolecules with respect to their protein, lipid and
29 oligosaccharide components, it is still not possible to fully predict their biological
30 properties and clinical performance from their physicochemical characteristics alone.
31 Nonclinical and clinical evaluation are therefore key components of the regulatory
32 assessment of such biotherapeutics.

1 Furthermore, biological systems are known to be inherently variable, a feature which
2 has important consequences for the safety and efficacy of the resulting product.

3 Although comprehensive analytical characterization of the drug substance and/or drug
4 product is expected, considerable emphasis must also be given to the manufacturing
5 process, including process validation and in-process control. Understanding the
6 production process and monitoring consistency of production are, therefore, critical
7 since slight variations in the manufacturing process can impact the clinical safety and
8 efficacy of the product and occasionally lead to major adverse effects, such as
9 immunogenicity, with potentially serious safety implications. The demonstration that
10 batches of product do not differ from those of lots shown to be safe and effective in
11 clinical studies is a crucial component not only of product evaluation and licensing
12 but also of on-going regulatory oversight.

13 Regulatory expectations for biotherapeutic protein products can be found in the *WHO*
14 *Guidelines on the Quality, Safety and Efficacy of Biotherapeutic Protein Products*
15 *Prepared by Recombinant DNA Technology* which were adopted by the WHO Expert
16 Committee on Biological Standardization at its meeting in October 2013 (2). These
17 extensive guidelines provide NRAs and manufacturers with guidance on the quality,
18 safety and efficacy of biotherapeutic protein products prepared by recombinant DNA
19 technology and intended for use in humans. They are based on over three decades of
20 experience in this technically demanding field and replace “*Guidelines for assuring*
21 *the quality of pharmaceutical and biological products prepared by recombinant DNA*
22 *technology*” (WHO Technical Report Series 814, Annex 3, 59 – 70, 1991). They are
23 the result of several reviews and consultations during the period 2012-2013 and are
24 considered to be a replacement and not a revision of the original WHO guidelines.
25 This is because they contain new sections on nonclinical and clinical evaluation of
26 rDNA-derived protein biotherapeutics which were lacking in the original document.
27 In addition, a section on issues related to manufacturing changes both during
28 development and once the product is on the market also has been introduced. The
29 scope of products covered by these WHO Guidelines includes:

- 30 • All biologically active protein products used in the treatment of human
31 diseases and which are prepared by rDNA technology;
- 32 • Protein product used for *in vivo* diagnosis, such as monoclonal antibody
33 products used for imaging and products used for *ex vivo* treatment;

- 1 • Protein products intentionally modified by e.g. pegylation, conjugation with a
2 cytotoxic drug or modification of rDNA sequences.

3

4 ***Regulatory Expectations for Copy Products***

5 As patents and data protection measures for innovative biotherapeutic products expire,
6 or near expiration, there has been considerable interest in producing copies of these
7 highly successful medicinal products. Indeed, copies of biotherapeutic protein
8 products have been produced in some developing countries even before patents had
9 expired globally. For example, under trade-related aspects of the Intellectual Property
10 Rights (TRIPS) Agreement of the World Trade Organization, the pre-1995 product
11 patents did not apply in India and this left many biological products that were
12 patented before 1995 marketable in India. Furthermore, innovators have not sought
13 patent protection for some drugs in India thereby creating an opportunity for Indian
14 companies to influence the huge domestic market and to supply other countries where
15 these products had not been patented (3). The emphasis of many Indian
16 pharmaceutical manufacturers has been directed more toward the development of
17 copies rather than original molecules because of much lower development costs
18 including reduced time to market (4).

19

20 Much of the interest in this pharmaceutical area has been driven by the possibility that
21 copy products would be more affordable than the innovative ones and thus improve
22 access to much needed biotherapeutic medicines globally. The major question that
23 arose was how copies of the innovator products should be licensed, and whether there
24 could be a reduction in the nonclinical and clinical package submitted, bearing in
25 mind that these medicines are highly complex products, manufactured by equally
26 complex and sophisticated processes, a situation compounded by the inherent problem
27 of biological variability. It was recognized that copying biologicals would be much
28 more complex than copying small molecules. Many biological molecules consist not
29 only of the amino acid sequence but also of various polysaccharides which are added
30 onto the polypeptide backbone during post-translational modification. Changes, such
31 as deamidation, oxidation or N- and C-terminal differences, can also occur in the
32 polypeptide chain. Details vary depending on the production process and may or may
33 not affect clinical performance. Particular attention also needs to be given to the

1 possible presence of adventitious viruses in biotherapeutics produced in mammalian
2 cells. Quite clearly some clinical data would be required for licensing such copy
3 biological products, and quite clearly too, a traditional generic pathway as used for
4 small molecule drugs would not be appropriate. The concept of “similar but not
5 identical biological products”, with a designated regulatory pathway, was then
6 developed by the WHO (5) and other countries, following the lead of the European
7 Medicines Agency (6).

8

9 ***Regulatory Evaluation of Similar Biotherapeutic Products***

10 Following considerable international consultations at the global level since 2004,
11 WHO *Guidelines on evaluation of similar biotherapeutic products* were published in
12 2010 (5). These rely on a head to head demonstration of the “similarity” of a
13 candidate biological product’s characteristics, with respect to both physicochemical
14 and biological activity to a defined and already licensed reference product in order to
15 justify a reduced non-clinical and clinical package for licensing the candidate product
16 which is expected to reduce overall development costs and time to market. Critically,
17 this head to head comparability exercise involves not only evaluation of quality
18 attributes but also of non-clinical and clinical aspects with the same reference
19 biological product throughout. The Guidelines emphasize the need for clinical studies
20 to be designed so as to specifically demonstrate comparable safety, efficacy and
21 immunogenicity between the products in sensitive populations in order for the
22 candidate product to be called a similar biotherapeutic product.

23

24 These WHO Guidelines are intended to provide a globally acceptable set of basic
25 principles regarding the evaluation of similar biotherapeutics although it was
26 recognized that, by themselves, they will not resolve all issues. Several countries or
27 jurisdictions have now developed their own guidelines but there are some differences
28 in detail between them. Furthermore, other regulatory pathways, such as a stand-alone
29 approach, may also be appropriate for licensing copy biologicals (7). However, it was
30 reaffirmed at a WHO Consultation in Seoul (7, 8) in 2010 that only copy biologicals
31 licensed on the basis of a full comparability package involving head to head
32 comparative evaluation of quality, nonclinical and clinical aspects with one defined
33 reference product should be called similar biological products. It was suggested that

1 copy products appropriately licensed by other pathways might be called “non-
2 innovative biological products” but this has not yet been universally accepted and
3 several names are being considered. Nevertheless, there is full agreement that the
4 approach to licensing small - molecule generic medicines, involving only product
5 analysis and the demonstration of bioequivalence to a reference product, is not
6 appropriate for the development, evaluation and authorization of copy biological
7 products. As already mentioned above, clinical performance of biologicals is highly
8 dependent on the manufacturing process and slight changes can lead to adverse
9 clinical effects. Some clinical studies are therefore essential to demonstrate the safety
10 and efficacy of copy biological products since it is still not possible to predict
11 biological properties and clinical performance from physicochemical characteristics
12 alone. Consistency of production is also critical since unintentional changes during
13 production may impact product performance.

14

15 ***Regulatory Capacity Needs***

16 Although discussions on how best to license copy biotherapeutics on the basis of a
17 reduced nonclinical and clinical data package continues, there is increasing alignment
18 between jurisdictions on key issues (see 9). Since the publication of the WHO
19 *Guidelines on evaluation of similar biotherapeutic products* (5), several activities
20 have been undertaken by the WHO at both global and regional levels. It has become
21 clear that much investment in the development of biosimilar and copy biotherapeutic
22 products is taking place worldwide, including in countries with emerging economies.
23 It is also becoming clear that the regulatory agencies of many countries need to be
24 strengthened with respect to their regulatory oversight of biotherapeutic products in
25 general and biosimilars and copy products in particular. The expertise of regulators
26 responsible for licensing is critically important for the appropriate evaluation of these
27 often sophisticated products which should be understood to be biologicals and which
28 may include proteins, polysaccharides and DNA molecules. Regional initiatives to
29 improve the awareness of countries concerning these issues are already well underway
30 in some areas, for example in PAHO (10, 11), but needs may differ from region to
31 region.

32

1 ***Risk Assessment Considerations***

2 A serious problem has been identified in some countries where, for historical reasons,
3 biotherapeutic products have been licensed on data which did not meet international
4 regulatory expectations regarding quality, nonclinical and clinical data. Sometimes,
5 copy products have even been licensed as simple generics (12). Generally, little is
6 known about the safety and efficacy of the individual products, since in most cases
7 pharmacovigilance in the countries concerned is weak. In addition, the nomenclature
8 for these products is confusing and traceability poor (13). In some countries, the
9 coexistence on the market at the same time of inappropriately licensed copy products
10 and true biosimilars is a matter of concern. The lack of terminology for products
11 developed as copy products with only partial comparability to a reference product has
12 compounded the problem and led to a great diversity in evaluating as well as naming
13 these products (8)

14 Slight differences between the biotherapeutic product of one manufacturer and that of
15 another, or between an innovator and copy biotherapeutic product, could have
16 unintentional effects on their clinical performance and safety and need to be handled
17 carefully from a regulatory perspective. NRAs should consider undertaking a
18 regulatory risk assessment of biotherapeutic products already on the market but
19 known to have been licensed with data which do not meet international regulatory
20 expectations. A risk based approach to dealing with this problem would allow
21 licensed biotherapeutic products to remain on the market for a specified period during
22 which time manufacturers would be required to submit first a Risk Management Plan
23 for regulatory approval and subsequently appropriate quality, nonclinical and clinical
24 data, as necessary, for regulatory evaluation to support the continuation of the license.
25 The timeline for completing such a review exercise would depend on the risk
26 assessment of each individual product on the market. Products from manufacturers
27 who did not submit a Risk Management Plan or appropriate data, or submitted data
28 which were considered insufficient to support continued licensing, would be
29 automatically removed from the market.

30 In adopting a risk based approach, product supply would not be compromised and
31 authorization would be regularized after the defined time period when all products
32 would have undergone further regulatory evaluation and found to meet internationally
33 accepted standards of quality, safety and efficacy. Should a problem be identified with

1 a particular product before the end of the specified time period, the implicated
2 product's license could be withdrawn immediately or the labelling modified as
3 appropriate. A product claimed to be a similar biotherapeutic but failing to meet
4 WHO Guidelines (5) could be given the opportunity to be re-submitted as a stand
5 alone product or the labelling modified as appropriate.

6 Traceability is a key element in monitoring the performance of biotherapeutic
7 products since some problems maybe batch related. An adequate nomenclature system
8 is essential to ensure specific identification. This should include not only the
9 International Non-proprietary Name (INN) but also other important indicators such as
10 brand (proprietary) name, manufacturer's name, country of origin and, critically, the
11 lot number.

12 13 ***Points to Consider in a Stepwise Risk Based Assessment***

14 A stepwise risk-benefit assessment, based on product-specific considerations, should
15 be carried out in order to decide the appropriate action and the time a particular
16 inappropriately licensed product should be allowed to remain on the market prior to
17 finalization of the review. This will depend upon the time needed to generate and
18 provide the missing information, the risk associated with removing the product from
19 the market and the risk of keeping the product on the market, and could be between
20 say 6 months and 4 years. However, manufacturers should first be required to submit
21 a Risk Management Plan to the NRA within a short time period detailing their
22 proposals for dealing with the situation including the generation and provision of
23 quality, non-clinical and clinical data as appropriate. An example of a risk based plan
24 for dealing with a particular regulatory situation can be found in the actions of Health
25 Canada. In 2009, Health Canada initiated a risk based plan of action to deal with
26 changes in the regulatory oversight of heparins to reflect the fact that in future they
27 would be regulated in Canada as biologics and not pharmaceutical drugs. While both
28 unfractionated heparins and low molecular weight heparins are administratively
29 controlled as drugs in some administrations, they are essentially biologicals and the
30 importance of their biological origin is increasingly recognized by the global
31 regulatory community. Health Canada set a 12 month transition period to allow
32 manufacturers to update their files to reflect data required for biological drugs.
33 Manufacturers were also required to identify immediately after the official date of

1 transfer of regulatory authority how much of their licensed product was sold in
2 Canada per year. In addition Health Canada announced that any biosimilar heparin
3 submissions should follow Health Canada's regulatory framework for subsequent
4 entry biologics and not the generic pathway used for small molecule drugs (14).

5
6 Consideration should be given to the following in deciding appropriate actions:

- 7 a) The number of inappropriately licensed products on the market and whether
8 there are any alternatives on the market which have been licensed also by an
9 experienced NRA (see b, below).
- 10 b) Whether the product in question is manufactured and licensed in a country
11 with a jurisdiction which has well established regulatory frameworks and
12 principles, as well as considerable experience in the evaluation of
13 biotherapeutic products, and post marketing surveillance activities. If a
14 product is manufactured and licensed in such a country, then this provides
15 confidence regarding its quality, safety and efficacy. However, it would be
16 important to ascertain whether the product on the market but inappropriately
17 licensed in the country with limited regulatory experience is identical,
18 including site of manufacture, to that licensed, supplied and used in the
19 manufacturing country with the more experienced jurisdiction;
- 20 c) The extent to which the registration dossier of the biotherapeutic product
21 meets the recommendations of the *WHO Guidelines on the Quality, Safety and*
22 *Efficacy of Biotherapeutic Protein Products Prepared by Recombinant DNA*
23 *Technology* and the *WHO Guidelines on evaluation of similar biotherapeutic*
24 *products* (2, 5). Attention should be paid to any important differences between
25 national requirements and WHO Guidelines, such as mandatory requirement
26 for viral validation and human immunogenicity studies and data needed to
27 allow extrapolation of biosimilars to other indications (4)
- 28 d) The level of actual use of the biotherapeutic product in the clinic (market share
29 or number of patients impacted);
- 30 e) Whether the product is essential for treating certain patients. This assessment
31 should cover: What is the disease being treated?; Is the condition life-
32 threatening?; What are the consequences of treating or not treating?; What is
33 the nature of the affected patient population (paediatric, adult, senior/elderly);

- 1 f) The expected severity of the consequences of supply problems on clinical
2 outcomes should the product be taken off the market;
- 3 g) The seriousness of a potential lack of efficacy, as well as possible safety
4 issues that may result from the continued use of the product under review.
5 This should include an assessment of the severity of the potential impact on a
6 patient of an immunogenic effect arising from the use of the product;
- 7 h) The ability of the pharmacovigilance system in place in the country to monitor
8 and determine adverse reactions and / or efficacy problems, such as reduced
9 clinical effectiveness, associated with the biotherapeutic product, should they
10 exist. With poor pharmacovigilance systems in many countries, as well as
11 nomenclature difficulties, it may be impossible to obtain sufficient data to
12 demonstrate that a particular product was the cause of an adverse reaction or
13 that patients may be at risk from the use of clinically inadequate products.
14 Traceability through appropriate labelling is a key element in monitoring the
15 performance of biologicals.
- 16 i) As already mentioned, the expertise and capacity of regulators responsible for
17 licensing biotherapeutic products is critically important for the appropriate
18 evaluation of these products. Capacity building will be needed where
19 resources and expertise is considered inadequate. Where the number and
20 experience of persons available to undertake an overall review is limited,
21 consideration could be given to the possible mentoring of the NRA needing
22 support by an experienced authority through the WHO.
- 23 j) Consideration should be given to transparency with respect to informing
24 healthcare professionals, pharmacists and patients of the review process and
25 its time lines. This could be done through website posting, as in Canada (14),
26 and referring to the need to align the licensing process with current
27 international expectations.

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27

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