Annex 3

Regulatory assessment of approved rDNA-derived biotherapeutics

Addendum to Annex 4 of WHO Technical Report Series, No. 987

1. Introduction 134
2. Regulatory expectations for rDNA-derived biotherapeutics, including similar biotherapeutic products 134
3. Review of products on the market 135
4. Points to consider in a stepwise regulatory assessment 137
5. Regulatory actions 139
6. Authors and acknowledgements 140
7. References 144
Guidance documents published by WHO are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALIFAR</td>
<td>Asociación Latinoamericana de Industrias Farmacéuticas</td>
</tr>
<tr>
<td>DCVMN</td>
<td>Developing Countries Vaccine Manufacturers Network</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>EGA</td>
<td>European Generic Medicines Association</td>
</tr>
<tr>
<td>ICDRA</td>
<td>International Conference of Drug Regulatory Authorities</td>
</tr>
<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
</tr>
<tr>
<td>IGPA</td>
<td>International Generic Pharmaceutical Alliance</td>
</tr>
<tr>
<td>NRA</td>
<td>national regulatory authority</td>
</tr>
<tr>
<td>rDNA</td>
<td>recombinant DNA</td>
</tr>
<tr>
<td>RBP</td>
<td>reference biotherapeutic product</td>
</tr>
<tr>
<td>SBP</td>
<td>similar biotherapeutic product</td>
</tr>
</tbody>
</table>
1. Introduction

This WHO guidance document considers the regulatory assessment needed to address situations where, for various reasons, biotherapeutic protein products prepared by recombinant deoxyribonucleic acid (DNA) technology (rDNA-derived biotherapeutics) were licensed with data packages that do not follow current international regulatory standards for these biologicals. This includes, for example, biotherapeutic products licensed via a generic pathway or with limited analytical, nonclinical and/or clinical data (1, 2). At its 2010 meeting in Singapore (3) the International Conference of Drug Regulatory Authorities (ICDRA) discussed such situations and requested WHO assistance in developing approaches for evaluating these already-licensed products in accordance with current WHO guidelines. In May 2014 the Sixty-seventh World Health Assembly adopted two relevant resolutions: one on promoting access to biotherapeutic products and ensuring their quality, safety and efficacy (4) and the other on regulatory systems strengthening (5) in which WHO was requested to provide guidance, especially on dealing with increasingly complex biological products.

Although primarily addressing rDNA-derived biotherapeutic protein products, some aspects of this document may also be relevant to other biotherapeutics.

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

The regulatory expectations for rDNA-derived biotherapeutics can be found in the relevant WHO Guidelines adopted by the 2013 WHO Expert Committee on Biological Standardization (6). Following extensive consultation at the global level since 2004, WHO Guidelines on the evaluation of similar biotherapeutic products (SBPs) were adopted by the Committee in 2009 (7). These latter WHO Guidelines emphasize the need for a head-to-head demonstration of the “similarity” of such products 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 between a candidate SBP and an RBP 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 the safety and efficacy of the two products. It should be ensured that any differences that are detected have no clinically meaningful impact on product performance.
If a head-to-head comparison of the SBP with the RBP as outlined in the WHO Guidelines for SBPs (7) is not performed throughout the development process then 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.

3. Review of products on the market

Problems have been identified in some countries where, for various reasons, biotherapeutic products were licensed using data which no longer meet current WHO regulatory expectations – such as biotherapeutic products licensed as generics or as small-molecule drugs. In many cases pharmacovigilance systems in such countries are weak or even nonexistent, with the result that little is known about the safety and efficacy of individual products. In addition, the terminology used for such products is confusing and their traceability 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 both erythropoietin (12) and heparin (13). Some updating of national regulations has occurred to take account of the recognized difficulties and changes made 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:

1. First, NRAs should identify products that have been licensed with data which do not meet current WHO regulatory expectations.
2. Second, an assessment of identified products and gaps, based on the product-specific considerations listed below in section 4, should be carried out in order to decide upon the appropriate action needed to remedy the situation, and to determine the timelines for implementing this action. This will inevitably involve a risk–benefit assessment of the situation.
3. Third, manufacturers should submit a plan of action for dealing with the problem to the NRA within a defined – but short – period of time. 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.

4. Fourth, NRAs should evaluate the plan of action proposed by the manufacturer and reach agreement with the manufacturer on the next steps for generating missing data and for their (possibly stepwise) submission to the NRA.

5. Fifth, NRAs should assess the submitted data (for example, quality/manufacturing, nonclinical and clinical data as needed) using a stepwise approach – possibly in several separate packages at different times – and decide upon the appropriate regulatory action to take based upon the assessment outcome.

The timeline for completing the overall review exercise will depend upon the time needed to generate and provide the missing information, taking into consideration the product-specific points outlined below in section 4. For example, in 2009 one NRA clarified the “appropriate regulatory pathway” for dealing with changes in the regulatory oversight of low molecular weight heparins1 to reflect the fact that in future they would be regulated in that country as biologicals and not as small-molecule pharmaceuticals (16). 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 report on how much of their licensed product was sold in the country per year following the official start date of the revised regulatory approach.

Similar transitional provisions have been made by other NRAs when updating the regulations for biotherapeutics, including biosimilars (15, 17).

---

1 Low molecular weight heparin is not an rDNA-derived biotherapeutic product but is highlighted here as an example of a reviewed product on the market. It is not considered to be a biological product in some countries.
4. 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 points when deciding upon the appropriate regulatory actions:

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

- 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 the relevant WHO Guidelines for rDNA-derived biotherapeutics (6) and in WHO 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 degree of confidence regarding product quality, safety and efficacy. In addition, it is 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 is also important to determine whether registration of the product in question has been rejected, cancelled or suspended by other experienced NRAs.

- It is also important to know the extent to which the registration dossier of the biotherapeutic product meets the recommendations set out in the above WHO Guidelines (6, 7). Attention should be paid to any key differences between national requirements and the WHO Guidelines – such as the lack of a head-to-head comparability exercise for an SBP. The NRA should provide manufacturers with a critical dataset for the 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.

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

- 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. Such effects might include cross-reactivity with native proteins caused by biotherapeutic products – such as pure red cell aplasia caused by erythropoietin (1).

- Consideration should also be given to the ability of the pharmacovigilance system in the country to detect and monitor any potential adverse reactions and/or efficacy problems (such as reduced clinical effectiveness) associated with the biotherapeutic product.

- Criteria for the evaluation of functional pharmacovigilance systems have been developed by WHO (18). Given the poor pharmacovigilance systems in many countries, as well as terminology difficulties, it may not be possible 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 in 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.

- The expertise and capacity of regulators responsible for licensing biotherapeutic products are critically important factors in 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).

- Consideration should be given to ensuring 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 provide an opportunity to request users to report any safety and/or efficacy issues.

5. Regulatory actions

On the basis of the outcomes of the regulatory assessment, the NRA should decide upon the appropriate actions to be taken. The decisions and actions of NRAs may differ depending upon the assessments made according the points listed above in section 4, 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 undergone further regulatory evaluation, and on condition that it was shown to have an acceptable risk–benefit profile.

Capacity-building will be needed where resources and expertise are considered inadequate. Where the number and level of experience of staff available to undertake an overall review are limited, consideration could be given to mentoring or to work-sharing arrangement amongst NRAs. In the case of mentoring, support could be provided through WHO from an experienced authority that uses well-established processes that accord with relevant WHO guidelines. In addition, the sharing of information between NRAs regarding the basis for regulatory decisions on biotherapeutic products (including SBPs) and the availability of publically available evaluation reports are considered important sources of support for regulatory authorities that are less experienced in dealing with these highly complex products, and may accelerate product assessment. Communicating the 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 promote confidence in biotherapeutic products. The summary basis of decision documents produced by some regulatory agencies, such as 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 document is flexible and designed to increase the accessibility of biotherapeutic products of assured quality, safety and efficacy, as called for in the relevant 2014 World Health Assembly resolutions (4, 5).

6. Authors and acknowledgements

The first draft of this guidance document was prepared by Dr E. Griffiths, Consultant, Kingston-upon-Thames, the United Kingdom; and Dr H-N. Kang and Dr I. Knezevic, World Health Organization, Switzerland.

Comments were then received from the following reviewers: Mrs A. Abas, Ministry of Health Malaysia, Malaysia; Dr W.S. Alhaqaish, Jordan Food and Drug Administration, Jordan; Dr N. Annibali, Asociación Latinoamericana de Industrias Farmacéuticas (ALIFAR), Argentina; Mrs J. Bernat (provided consolidated International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) comments), Switzerland; Dr B. Boonyapiwat, Ministry of Public Health, Thailand; Dr G. Castillero, Ministry of Health, Panama; Dr J.M. Cousiño, Federacion Latinoamericana de la Industria Farmacéutica, Chile; Dr F. Muñoz Espinoza, Instituto de Salud Pública de Chile, Chile; Dr M.T. Ibarz, Instituto Nacional de Higiene “Rafael Rangel”, Venezuela; Dr A. Klein, Health Canada, Canada; Dr C. Njue, Health Canada, Canada; Ms D. Pérez, Instituto Nacional de Higiene “Rafael Rangel”, Venezuela; Dr G.R. Soni, Ministry of Health and Family Welfare, India; Mr H. Vásquez, Dirección General de Medicamentos, Insumos y Drogas, Peru.

The second draft was prepared by Dr E. Griffiths, Consultant, Kingston-upon-Thames, the United Kingdom; and Dr H-N. Kang, World Health Organization, Switzerland taking into consideration comments received from the above reviewers as well as the discussions at the Second WHO Implementation Workshop on Quality Assessment of Similar Biotherapeutic Products held in Xiamen, China, 28–30 May 2012 and attended by: Mrs A. Abas, Ministry of Health Malaysia, Malaysia; Dr W.S. Alhaqaish, Jordan Food and Drug Administration, Jordan; Ms J. Archer (International Generic Pharmaceutical Alliance (IGPA) representative), Hospira, Australia; Dr B. Boonyapiwat, Ministry of Public Health, Thailand; Dr L. Gomes Castanheira, Agência Nacional de Vigilância Sanitária, Brazil; Dr R. Chakrabarti (United States Pharmacopeial Convention representative), United States Pharmacopeial Convention–India, India; Dr W. Chang, State Food and Drug Administration, China; Mr D. Cheng, Beijing Four Rings Bio-Pharmaceutical Co., Ltd, China; Dr Y. Choi, Korea Food and Drug Administration, Republic of Korea; Ms J. Dahlan, National Agency of Drug and Food Control, Indonesia; Mr G. Eich (IFPMA representative), Amgen Inc. Corporate Services/Global Regulatory Affairs & Safety, the USA; Dr K. Gao, National Institutes for Food and Drug Control, China; Mr T. Go, Health Sciences
Authority, Singapore; Dr E. Griffiths, Consultant, Kingston-upon-Thames, the United Kingdom; Dr L. Gu, Shenyang Sunshine Pharmaceutical Co., Ltd, China; Dr Z. Guo (Chinese Pharmacopoeia representative), Chinese Pharmacopoeia Commission, China; Dr N. Hassannia, Food and Drug Organization, the Islamic Republic of Iran; Dr K. Ho, Agence Nationale de Sécurité du Médicament et des Produits de Santé, France; Dr S. Hufton, National Institute for Biological Standards and Control, the United Kingdom; Mrs W. Jariyapan, Ministry of Public Health, Thailand; Mr R. Jian, Health Sciences Authority, Singapore; Dr J. Joung, Korea Food and Drug Administration, Republic of Korea; Dr Y. Kishioka (Japanese Pharmacopoeia representative), Pharmaceutical and Medical Devices Agency, Japan; Mr J. Leong, Health Sciences Authority, Singapore; Dr J. Li, Shanghai CP-Guojian Pharmaceutical Co., Ltd, China; Dr C. Liang, National Institutes for Food and Drug Control, China; Dr J. Luo, State Food and Drug Administration, China; Mrs V. Madrigal, Recepta Biopharma, Brazil; Dr C. Njue, Health Canada, Canada; Mrs Y. Hechavarria Nunez, Centro para el Control Estatal de la Calidad de los Medicamentos, Cuba; Dr P.H. Pan (Developing Countries Vaccine Manufacturers Network (DCVMN) representative), Innovax Biotech Co., Ltd, China; Dr R. Perez, Biotech Pharmaceutical Co., Ltd, China; Dr S. Pluschkell (IFPMA representative), Pfizer Inc., the USA; Professor C. Rao, National Institutes for Food and Drug Control, China; Dr M. Schiestl (IGPA representative), Sandoz GmbH, Austria; Dr T. Schreitmueller (IFPMA representative), F. Hoffmann-La Roche, Ltd, Switzerland; Dr S. Shani, Ministry of Health and Social Welfare, India; Dr Q. Shen, National Institutes for Food and Drug Control, China; Dr X. Shen, China Bio-Tech Group, China; Dr G.R. Soni, Ministry of Health and Family Welfare, India; Dr L. Sun, Xiamen Amoytop Biotech Co., Ltd, China; Dr R. Thorpe, National Institute for Biological Standards and Control, the United Kingdom; Mrs C. Ulm (European Generic Medicines Association (EGA) representative), Mylan GmbH, Switzerland; Dr A. Vallin, Centre of Molecular Immunology, Cuba; Dr J. Wang, Health Canada, Canada; Dr J. Wang, National Institutes for Food and Drug Control, China; Dr M. Xu, National Institutes for Food and Drug Control, China; Dr S. Zhang, State Food and Drug Administration, China; and Dr M.H. Friede, Dr H-N. Kang and Dr I. Knezevic, World Health Organization, Switzerland.

The resulting draft document was posted on the WHO Biologicals website for the first round of public consultation from 11 February to 12 March 2014. The draft document was also discussed at the First WHO Implementation Workshop on Evaluation of Biotherapeutic Products held in Seoul, Republic of Korea, 13–14 May 2014.

The third draft was prepared by Dr E. Griffiths, Consultant, Kingston-upon-Thames, the United Kingdom; and Dr H-N. Kang, World Health Organization, Switzerland, taking into account comments received from following reviewers: Mrs A. Abas, Ministry of Health Malaysia, Malaysia;
ALIFAR, Argentina; Mrs J. Bernat (provided consolidated IFPMA comments), Switzerland; Dr B. Boonyapiwat, Ministry of Public Health, Thailand; Dr Y. Choi, Ministry of Food and Drug Safety, Republic of Korea; Dr F. Muñoz Espinoza, Instituto de Salud Pública de Chile, Chile; Dr H-K. Heim, Bundesinstitut für Arzneimittel und Medizinprodukte, Germany; Dr J. Joung, Ministry of Food and Drug Safety, Republic of Korea; Dr Y. Kishioka, Pharmaceutical and Medical Devices Agency, Japan; Dr A. Klein, Health Canada, Canada; Ms S. Kox (provided consolidated EGA comments), Belgium; Dr P. Kurki, Finnish Medicines Agency, Finland; Mrs V. Madrigal, Recepta Biopharma, Brazil; Dr C. Njue, Health Canada, Canada; Mrs Y. Hechavarria Nunez, Centro para el Control Estatal de la Calidad de los Medicamentos, Cuba; Dr J. Shin, WHO Regional Office for the Western Pacific, Philippines; Dr W. Tan, Genzume Singapore, Singapore; Dr R. Thorpe, Consultant, Welwyn, the United Kingdom; Dr J. Wang, Health Canada, Canada; Dr M. Weise, Bundesinstitut für Arzneimittel und Medizinprodukte, Germany; Dr S. Xie, China Food and Drug Administration, China.

The draft document was then posted on the WHO Biologicals website for the second round of public consultation from 16 December 2014 to 30 January 2015.

The document WHO/BS/2015.2251 was prepared by Dr E. Griffiths, Consultant, Kingston-upon-Thames, the United Kingdom; and Dr H-N. Kang, World Health Organization, Switzerland taking into account comments received from the following reviewers: Dr R. Aaron, Tanzania Food and Drugs Authority, United Republic of Tanzania; Mrs A. Abas, Ministry of Health Malaysia, Malaysia; Dr A. Abdelaziz, Jordan Food And Drug Administration, Jordan; Dr R. Abete (provided consolidated ALIFAR comments), Argentina; Dr M. Aboulwafa, National Organization for Research and Control of Biological Products, Egypt; Mrs J. Bernat (provided consolidated IFPMA comments), Switzerland; Dr Y. Choi, Ministry of Food and Drug Safety, Republic of Korea; Dr J. Gangakhedkar, Central Drugs Standard Control Organization, India; Dr K. Gao, National Institutes for Food and Drug Control, China; Ms C. Gongora Torres (provided consolidated comments), Ministry of Health and Social Protection, Colombia; Dr T. Guo, National Institutes for Food and Drug Control, China; Dr H. Hamedifar, CinnaGen Co., the Islamic Republic of Iran; Dr H-K. Heim, Bundesinstitut für Arzneimittel und Medizinprodukte, Germany; Dr J. Joung, Ministry of Food and Drug Safety, Republic of Korea; Dr B. Kim, Ministry of Food and Drug Safety, Republic of Korea; Dr Y. Kishioka, Pharmaceutical and Medical Devices Agency, Japan; Ms S. Kox (provided consolidated EGA comments), Belgium; Dr P. Kurki, Finnish Medicines Agency, Finland; Dr C. Liang, National Institutes for Food and Drug Control, China; Dr N. Lyoko, Zambia Medicines Regulatory Authority, Zambia; Mr R. Mezzasalma (provided consolidated European Association for
BioIndustries comments), Belgium; Dr R. Mody, United States Pharmacopeial Convention–India, India; Mr F. Montes de Oca, (provided consolidated Argentine Association of Industrial Pharmacy and Biochemistry comments), Argentina; Dr V. Murthy, Apotex Inc., Canada; Dr C. Njue, Health Canada, Canada; Dr D. Pathankar, United States Pharmacopeial Convention–India, India; Dr Z. Sauna, United States Food and Drug Administration, the USA; Dr T. Schreitmüller (provided consolidated Federación Latinoamericana de la Industria Farmacéutica comments), Mexico; Dr M. Seigelchifer, United States Pharmacopeial Convention–India, India; Ms J. Shim (provided consolidated Korea Biomedicine Industry Association comments), Republic of Korea; Dr J. Southern (Developing Country Vaccine Regulators’ Network representative), South Africa; Dr S. Suh, Ministry of Food and Drug Safety, Republic of Korea; Dr M. Wadhwa, National Institute for Biological Standards and Control, the United Kingdom; Dr J. Wang, Health Canada, Canada.

Also taken into consideration were comments and advice provided during a WHO informal consultation on regulatory risk assessment for biotherapeutic products held in Geneva, Switzerland, 29–30 April 2015 and attended by: Mrs A. Abas, Ministry of Health Malaysia, Malaysia; Dr A. Abdelaziz, Jordan Food and Drug Administration, Jordan; Dr K. Bangarurajan, Central Drug Standards Control Organization, India; Mrs J. Bernat (provided consolidated IFPMA comments), Switzerland; Dr B. Boonyapitwat, Ministry of Public Health, Thailand; Ms J. Dahlan, National Agency of Drug and Food Control, Indonesia; Mrs D. Darko, Food and Drug Authority, Ghana; Mr D. Goryachev, Ministry of Health, Russia; Dr E. Griffiths, Consultant, Kingston-upon-Thames, the United Kingdom; Dr K. Heidenreich (IFPMA representative), Novartis International AG, Switzerland; Dr H-K. Heim, Federal Institute for Drugs and Medical Devices, Germany; Dr C. Ilonze, National Agency for Food and Drug Administration and Control, Nigeria; Mr R. Ivanov, Biocad, Russia; Mrs W. Jariyapan, Ministry of Public Health, Thailand; Dr J. Joung, Ministry of Food and Drug Safety, Republic of Korea; Dr D. Khokal, Health Sciences Authority, Singapore; Dr P. Kurki (European Medicines Agency Biosimilar Medicinal Products Working Party representative), Finnish Medicines Agency, Finland; Ms S. Kox (provided consolidated EGA comments), Belgium; Ms I. Lyadova, Ministry of Health, Russia; Ms S. Marlina, National Agency of Drug and Food Control, Indonesia; Dr J. Meriakol, Ministry of Health, Kenya; Mr K. Nam, Ministry of Food and Drug Safety, Republic of Korea; Dr C. Njue, Health Canada, Canada; Mrs Y. Nunez, Centro para el Control Estatal de la Calidad de los Medicamentos, Cuba; Ms H. Pedersen, WHO Regional Office for Europe, Denmark; Dr M. Pombo, Pan American Health Organization, the USA; Dr A. Qu (DCVMN representative), Shanghai Institute of Biological Products Co., Ltd, China; Dr S. Ramanan (IFPMA representative), Amgen Inc., the USA; Dr M. Schiestl (EGA representative), Sandoz GmbH, Austria; Dr E. Spitzer (ALIFAR
representative), Argentina; Ms I. Susanti (DCVMN representative), PT Bio Farma, Indonesia; Dr R. Thorpe, Consultant, Welwyn, the United Kingdom; Dr C. Vaca Gonzalez, Ministry of Health and Social Protection, Colombia; Ms B. Valente, Agência Nacional de Vigilância Sanitária, Brazil; Ms N. Vergel, Instituto Nacional de Vigilancia de Medicamentos y Alimentos, Colombia; Dr M. Wadhwa, National Institute for Biological Standards and Control, the United Kingdom; Dr J. Wang, Health Canada, Canada; Dr J. Wang, National Institutes for Food and Drug Control, China; Dr L. Wang, National Institutes for Food and Drug Control, China; Dr K. Watson (IFPMA representative), AbbVie, Ltd, the United Kingdom; Dr C. Webster (EGA representative), Baxter Healthcare Corporation, the United Kingdom; Dr S. Xie, China Food and Drug Administration, China; Dr T. Yamaguchi, Pharmaceuticals and Medical Devices Agency, Japan; Dr A. Zhang (DCVMN representative), China National Biotec Group Co., Ltd, China; and Dr K. Gao, Dr H-N. Kang and Dr I. Knezevic, World Health Organization, Switzerland.

The document WHO/BS/2015.2251 was then posted on the WHO Biologicals website for the third round of public consultation from 3 July to 14 September 2015, and comments were received from the following reviewers: Mrs J. Bernat (provided consolidated IFPMA comments), Switzerland; Dr S. Creekmore, National Institutes of Health, the USA; Dr R. Domínguez Morales, Centro para el Control Estatal de la Calidad de los Medicamentos, Cuba; Mr F. Fon Mendez (provided consolidated Asociación Mexicana de Industrias de Investigación Farmacéutica comments), Mexico; Dr E.P. Fuenterr, Consultant, Argentina; Ms K. Holcombe, Bio, the USA; Dr J. Joung, Korea Ministry of Food and Drug Safety, Republic of Korea; Dr D. Khokal, Health Sciences Authority, Singapore; Ms S. Kox (provided consolidated EGA comments), Belgium; Dr Z. Kusynova (provided consolidated International Pharmaceutical Federation comments), Netherlands; Mr M.A. Maito, (provided consolidated ALIFAR comments), Argentina; Dr J. Wang, Health Canada, Canada; Dr K. Zoon, National Institutes of Health, the USA.

Further changes were subsequently made to document WHO/BS/2015.2251 by the WHO Expert Committee on Biological Standardization.

7. References


