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WHO/KFDA joint workshop on implementing WHO guidelines on evaluating similar biotherapeutic products, Seoul, Republic of Korea 24–26 August, 2010

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ABSTRACT

In August 2010, the World Health Organization and the Korea Food & Drug Administration jointly organized the first implementation workshop of WHO guidelines on evaluating similar biotherapeutic products (SBPs) at the global level. The objective of the Workshop was to facilitate implementation of the newly adopted WHO Guidelines into the practice of national regulatory authorities (NRAs). WHO Guidelines were recognized by the workshop participants as a tool for harmonizing regulatory requirements worldwide. By reviewing and practicing several case studies, better understanding and consensus on the principles of clinical trial designs were reached. However, variations in terms of the national requirements for quality, safety and efficacy of these products revealed diversity in the regulatory expectations in different countries and regions. In addition, lack of terminology for the products developed as copy products (so called "me too" products) with a partial comparability to an RBP, led to a great diversity in evaluating as well as naming these products. The workshop participants proposed the following actions: a) NRAs should make efforts to build their capacities for regulation of SBPs; b) WHO should revise WHO Guidelines for assuring the quality of products prepared by recombinant DNA technology (WHO TRS 814) and continue monitoring progress with the implementation of the Guidelines on evaluating SBPs. Publication of the outcome of the Workshop was recognized as another action that WHO should coordinate.

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1. Introduction

Dr Yun-Hong Noh, the commissioner of Korea Food and Drug Administration (KFDA) opened the workshop with a welcome address which highlighted the importance of biosimilar medicines in the global market. On behalf of WHO, Dr Ivana Knezevic (WHO, IVB, QSS) welcomed all the participants, chairperson and rapporteurs and explained that the objective of the workshop was to review the current situation with the regulation of biosimilar products and to define next steps towards better access to biotherapeutics of assured quality. Focus of the workshop was the application of the principles defined in the WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) into regulatory and manufacturers' practices worldwide [1]. She added that the outcome of the workshop would be reported to the Expert Committee on Biological Standardization (ECBS) in October 2010 and to the International Conference of Drug Regulatory Authorities (ICDRA) in November 2010 for further considerations and advice. Dr Knezevic invited all participants to share their experience and to contribute to the discussion as well as to the preparation of a publication reflecting the proceedings and outcome of the workshop afterwards.

The workshop organized jointly by the WHO and KFDA was attended by participants from regulatory agencies from various countries, clinical and scientific experts and representatives from industry. Dr Elwyn Griffiths (Health Canada, Canada) was appointed the chairperson and Dr Robin Thorpe (NIBSC, UK) and Dr Meenu Wadhwa (NIBSC, UK) served as rapporteurs.

Following a self-introduction by all participants, the chairperson commented briefly on the intense interest from governments worldwide in biosimilar products and thanked the WHO team for their resilience in forging ahead amid much controversy with the very difficult task of producing the Guidelines on SBPs and their adoption finally in October 2009. He mentioned that the guidelines enabled harmonization of key principles for evaluation of quality, safety and efficacy of biosimilar products and the main objective for the WHO team, therefore, was to facilitate global implementation of the guidelines and to identify any problems or issues that the various regions are facing with implementing the principles outlined in the guidelines.

Dr Ivana Knezevic briefly described the WHO Biological standardisation program which includes provision of both written (guidelines and recommendations for production, quality control and evaluation of biologicals) and measurement standards (International Standards and Reference Preparations); the latter served as physical potency standards for calibration of biologicals worldwide. Following a brief overview of the background on the development of WHO guidelines on SBPs (mandated by the ICDRA, 2006 [2] and the ECBS, 2007) and the consultations which enabled the formulation and the final adoption of the WHO SBP guidelines by the ECBS (at the 60th meeting) [3], she emphasized that the key principles for evaluation of SBPs highlighted in the guideline provide a basis for different regulatory authorities to set national requirements for licensure of these products. She explained the scope and important key definitions such as SBP, reference biotherapeutic products (RBP) and the importance of using appropriate terminology. The guideline advocates the principle of a step-wise comparability approach for SBP evaluation - similarity of the SBP to RBP in terms of quality is a prerequisite for reduction of non-clinical and clinical data required for approval. Additionally, comparative efficacy data showing equivalence or non-inferiority in adequately powered, randomized trials and comparative safety data are required to demonstrate biosimilarity of the SBP with RBP, which if shown may allow extrapolation to other indications of the RBP for the SBP. The need for pharmacovigilance and the use of appropriate method(s) for

identification of the administered product, along with post-marketing commitments and risk minimization strategies were stressed. She concluded that for an effective regulatory oversight of SBPs in various countries, the involvement of various stakeholders (e.g. industry, regulators, WHO) is critical to ensure implementation of guidelines. While some progress towards implementation and/or development of guidance documents in various countries had been made, there were many challenges which need to be addressed for global harmonization of the regulatory framework for licensure of biotherapeutics.

Dr Jinho Shin (WHO) gave an overview of WHO's International Nonproprietary Name (INN) policy including its naming schemes and use with specific examples for a number of biotherapeutics. The INN facilitates the identification of active pharmaceutical substances in a medicinal product and is intended for use in pharmacopoeias, labelling, product information, advertising, drug regulation and scientific literature, and as a basis for product names, e.g. for generics. For generic drugs, the same INN as the innovator product is assigned. In 2006, an informal WHO consultation on INN policy for biosimilars discussed how INNs should be assigned to biosimilar products and concluded that INNs for all biological products should be based on molecular characteristics and pharmacological class and not on regulatory route used for licensure [4]. There should be no change in policy and no distinctive INN designation for biosimilar products and decisions regarding product interchangeability should be based on appropriate scientific and clinical data as decided by the national regulatory authority, not on INNs.

2. Updating region/country situations on evaluating SBPs

Dr Maria Luz Pombo (WHO, Pan American Health Organization, PAHO region) mentioned that a previous survey (2008) conducted in the PAHO region had shown that most of the Latin American and Caribbean countries had regulations for biological products [5]. Some countries have licensed non-innovator copy products but no clear definition or process for approval is often in place. Based on the interest shown by the PAHO countries for harmonized documents and mechanisms for licensing biotechnology products, a technical working group on biotechnology products with participants from various countries had been established. This group aims to promote information exchange among regulatory authorities in terms of regulations, identify guidelines and issues and develop tools and training programs for harmonization of effective regulatory oversight of biotechnology products within the region.

Dr Adnan Badwan (AUPAM, Jordan) provided an overview of the diverse activities of Arab Union of the Manufacturers of Pharmaceuticals and Medical Appliances (AUPAM) and the situation and practices in the Arab region in evaluating SBPs. He mentioned that biotherapeutic products, including biosimilars, are imported from several countries; a majority of these are repackaged imported products. Two licensed non-innovator products, erythropoietin from Argentina and insulin produced by a regional manufacturer are available in Egypt. More recently, biotherapeutic product manufacturing has been initiated within the region but the manufacturing is not well-controlled and unified as products are manufactured at different sites depending on the development stage and then formulated in yet another site/country. The reasons for this are the lack of expertise in assessment of biotechnology products including biosimilars and inexperience with regulatory processes. Consequently, there is a need for WHO intervention in increasing training for product testing of SBPs and awareness of regulation in the region.

Dr Hemant Malhotra (clinician, Jaipur, India) mentioned that the lower costs of 'copy' products had increased access of these

products to the larger population of the country. India has many marketed copy products; these products are also available in less regulated countries but the approval process for these is not clear. Quality, non-clinical and clinical evaluations of the product are conducted as per the national regulations but they are not done in a comparative manner. More likely, non-comparative clinical trial data showing similarity to published data on the reference product were used for approval. Guidance for Industry for biological products has become available since 2009, but significant resource constraints (skill shortage, training) mean that significant progress towards implementation of the WHO guideline in the near future is unlikely.

Ms. Jalene Poh (HSA, Singapore) explained that Singapore's biosimilar guidance is mainly based on EU's biosimilar guidelines with consideration of Singapore's local regulatory environment [6–9]. The prerequisite for submission of a biosimilar product is that it has to be evaluated and approved as a biosimilar product by at least one of HSA's reference agencies (*i.e.* US FDA, Health Canada, EMA, or Therapeutic Goods Administration). A complete quality, non-clinical and clinical data package demonstrating comparability between the biosimilar and reference product is needed for submission. The conditions of use of the biosimilar product are those defined for the reference product registered in Singapore (and not for other indications which may be approved elsewhere). Interchangeability is allowed but not substitutability and the product leaflet requires a warning statement regarding substitutability. To date, there is one approved biosimilar Growth Hormone product, SciTropin A (Omnitrope, Sandoz) based on the reference product, Genotropin (Pfizer).

3. Exchanging the experiences with comparability studies/RBPs

Dr Rania D. Hadaddin (JFDA, Jordan) provided a brief overview of the regulatory framework for registration of biosimilar products and EMA specific guidelines until specific guidelines for registration of biological and biosimilar products are released. Prior to 2006, few biosimilars were registered using the process applied to generic drugs. Licensing of RBP in Jordan is not a prerequisite for using RBP in the comparability studies and the first product registered internationally with a particular active ingredient is considered as the RBP. In the example that Dr Haddadin presented, the originator was licensed in USA. In the same example, she discussed the clinical comparability studies submitted for approval. A post-marketing surveillance study is requested after a biosimilar product is authorized.

Dr Younjoo Park (KFDA, Republic of Korea) mentioned that guidance for biosimilar products, developed in July 2009 [10], follow the principles for evaluation of biosimilar products as described in WHO and EMA Guidelines. She also presented an abbreviated pathway which only requires the demonstration of clinical comparability to RBP. In the latter approach, there is no comparison with the RBP in terms of quality and approval is based on a full quality assessment of the product followed by a reduced data package for non-clinical studies. Both pathways co-exist, but only the products which are approved through the biosimilar pathway described in their guidelines can be called 'biosimilars'. No biosimilars have been approved.

4. Challenges raised by reviewers

Dr Hans-Karl Heim (BfArM, Germany) briefly described the EU biosimilar approach and the requirements of the product specific guidelines, which form the basis for the non-clinical evaluation for biosimilars [9,11–14]. Study design should be sufficient to detect

differences in pharmacological and toxicological response between the SBP and reference medicinal product and not just the response *per se*, and is tailored to the specific product on a case-by-case basis, with justification. He reviewed the non-clinical study data submitted for approval of some biosimilar products (*e.g.* growth hormone, G-CSF, erythropoietin) currently licensed in EU and commented that, in some cases, there are deviations in the studies from the guidelines as guidelines were not available when the products were in development. However, future applications for biosimilars are expected to adhere closely to the approaches recommended in the guidelines.

Dr Cheng Gang Liang (NICPBP, China) stated that there is neither definition nor specific regulations for biosimilars. Products are registered according to the national drug registration regulations. Several marketed products are available *e.g.* insulin and growth hormone approved using a stand-alone approach which requires a comprehensive evaluation of product quality but reduced preclinical data (not comparatively assured). In practice, principles of WHO SBP guidelines are partly followed and the regulatory authorities are working towards strengthening of documentary requirements and guidelines for SBPs.

Dr Laura Gomes Castanheira (ANVISA, Brazil) stated that the WHO and Canadian guidelines [15] were being used as the basis for developing regulations which were being implemented in Brazil in the following month. An RBP licensed and marketed in Brazil was preferred but if not available, an RBP from the same manufacturing site using the same production method (as the marketed product in Brazil) was allowed. Two pathways are defined in the regulatory framework – the biosimilar and alternative (abbreviated) pathway since manufacturers are reluctant to perform comparative clinical trials because of the high costs involved. She presented a case study which reviewed non-clinical data of a similar G-CSF product and included both non-comparative and comparative studies. However, the limited comparative studies presented demonstrated that there were no detectable and significant differences between the SBP and the RBP and were adequate for progressing with clinical development.

Dr Agnes Klein (Health Canada, Canada) gave an overview of the challenges and experiences of the Canadian regulators during approval of their first biosimilar, Omnitrope (GH). The terminology adopted for SBPs which are considered as 'New Drugs' in Canada is Subsequent Entry Biologics (SEB). The regulatory framework and guidance issued for SEBs/SBPs by Health Canada [15] is based on a balanced, science-based and rational approach to ensure that the products approved are of high quality, safe and are effective. For comparability, the use of an RBP from a well-regulated jurisdiction is allowed. The principles outlined in the guidance were evaluated during the approval of Omnitrope using Genotropin as the comparator which although approved is not marketed in Canada. Despite initial rejection/deficiencies (reasons included non-marketing of Genotropin, requests for indications not approved for Genotropin and the different standards used for growth assessment in clinical studies), Omnitrope was finally approved with post-marketing commitments being required. The process allowed flexibility and thorough evaluation of the product from the comparability perspective that was critical to the final outcome.

5. Better understanding of the principles of clinical evaluation

Dr Catherine Njue (Health Canada, Canada) explained the statistical issues related to equivalence and non-inferiority trials. As per the WHO SBP guidelines, equivalence or non-inferiority studies may be acceptable for comparing the efficacy and safety of the SBP with the RBP [1]. While equivalence trials are preferred, non-

inferiority trials may be considered if appropriately justified. The critical need for a thorough evaluation of all comparative data generated to ensure similarity between the SBP and the RBP prior to initiating a clinical study was emphasized. The protocol of the trial should explicitly define the purpose of the trial, e.g. demonstration of equivalence or non-inferiority of the SBP to the RBP. The choice of the equivalence or non-inferiority margin must be clearly justified. Importantly, equivalence and non-inferiority trials require different formulae for power and sample size calculations, and so the appropriate set of formulae should be used in each setting. Inadequately powered studies are unethical and should not be conducted. Only data obtained from robust equivalence or non-inferiority trials is capable of determining clinical similarity between the SBP and the RBP.

Dr. Alexander Berghout (Sandoz, EGA) provided an overview of the clinical data (PK and PD studies; efficacy and safety studies) that were submitted to the EMA for licensing of the three Sandoz biosimilar products currently marketed; these include Omnitrope® (Growth hormone, RBP - Genotropin®), Binocrit® (Erythropoietin α , RBP - Eprex®) and Zarzio® (G-CSF, RBP - Neupogen®). The clinical studies confirmed similarity of the SBPs with their respective RBPs. He pointed out that clinical comparability studies should preferably use the most sensitive model to detect differences, if any exist. As an example he presented the effects seen in the comparison of Zarzio® with Neupogen® in healthy volunteers which represents a very sensitive model especially at low doses due to the complex receptor-mediated drug disposition of filgrastim and the higher number of G-CSF receptors and a more responsive bone marrow than in neutropenia patients undergoing cytotoxic chemotherapy. Small differences in PK were detected due to unintentional small differences in the administered dose without any detectable differences in PD response. He concluded that SBPs have been extensively characterized at the physicochemical and biological level to demonstrate similarity. If in addition PK/PD comparability has been proven, it may be appropriate to use non-inferiority designs to demonstrate clinically relevant comparability, as it can be expected that the SBP will be neither inferior nor superior to the RBP.

Dr Teruyo Arato (Pharmaceuticals and Medical Devices Agency, Japan) mentioned that after the Japanese guideline became available [16], two follow-on biologics (Japanese terminology), Somatropin and Epoietin alpha, have been approved and more are in development. While the principles are similar between the EMA, Canada, WHO and Japanese guidelines, there are some differences in the scope (Low-molecular weight heparin is excluded from Japanese guideline) and also in terms of regulatory requirements pertaining to the RBP, stability testing, safety of process-related impurities and other criteria. She mentioned that for Epoietin Alfa BS "JCR" (JCR is a company name which should be positioned at the end of brand name of biosimilars according to Japanese notification), the non-clinical and clinical data required was different from those of erythropoietin biosimilar products approved in EU. In Japan, a system for naming of follow-on biologics has also been adopted such that for the INN of the follow-on biologic, 'BS' (bio-similar) is suffixed to the INN of the original biologic at approval along with the unique brand name (which includes dosage form, strengths and company name e.g. Epoietin Alfa BS Inj 750 "JCR") for product identification.

6. Case study on clinical efficacy

Dr Mark P. Fletcher (IFPMA) led an interactive discussion among participants on key issues in clinical trial designs for showing similarity of an SBP with an RBP as discussed in the WHO SBP guidelines. A case study based on a hypothetical product was

presented as a model to facilitate discussion on sample sizes and comparability margins for both an equivalence and a non-inferiority study design approach. In this context, the interpretation of possible clinical outcomes (e.g. data supporting approval or non-approval or being inconclusive) using these two clinical trial designs was explained. Ensuring choice of sensitive markers/end-points for safety and efficacy is a key consideration, particularly if a reduced clinical data package is intended for approval. Equivalence is the most suitable design for confirming that the SBP is similar to the RBP although non-inferiority designs may also be considered if appropriately justified. The need for a case-by-case approach was highlighted. More importantly, demonstration of a similar safety profile of the SBP and RBP requires significantly more data (more subjects, long duration) on the safety aspects than that required for showing similar efficacy.

7. Regulators and manufacturer's perspectives on implementation of WHO guidelines

Dr Hye-Na Kang (WHO) presented an update on the regulations governing biologicals including SBPs and the current situation regarding implementation of the WHO SBP guidelines. As expected, the regulations and terminologies used for biotherapeutic products including SBPs are diverse. Some countries have the same regulations for both drugs and biologicals while others have additional regulations for biologicals. Progress with development and implementation of SBP guidelines differs at the regional and country level. While some countries have developed SBP guidelines and the principles for acceptance of RBPs from different jurisdictions, others are clearly lagging behind. This is because some countries lack the expertise needed for assessment of biotherapeutics (from quality to clinical data evaluation). Based on the different level of expertise in the regulatory authorities, the need for training was highlighted as a major issue for many countries.

Dr Martin Schiestl (Sandoz, IGPA) emphasized the WHO SBP principles underlying the manufacture of SBPs which are systematically engineered using optimized processes to match the RBP and then evaluated in a comparative manner using a step-wise approach. He cautioned on the use of 'biosimilar' terminology (if products are not comparable in quality aspects) and route for products which do not comply with the biosimilarity concept. Using the example of Reditux (Shantha Biotech, India) which has the same amino acid sequence as the originator, Rituxan (anti-CD20 monoclonal antibody, Hoffman La Roche, Switzerland), he highlighted many differences at the quality level between the two products which clearly demonstrated that Reditux is not a biosimilar of Rituxan and may therefore have a very different safety and efficacy profile. Currently, SBP manufacturers are developing monoclonal antibodies (Mab) since patents for many of these are likely to expire soon. Setting criteria for biosimilarity for these potential SBPs is based on the variability observed with the original reference Mab product. This may be in part due to changes in the product over time. The experience gained by the regulatory agencies over time with regard to the assessment of those process changes of the originator molecule may thus be utilized for the evaluation of biosimilarity.

Dr Hyi-Jeong Ji (LG Life Sciences, Ltd., Republic of Korea) presented the practical points to consider from the Korean industry's perspective in implementing the development of SBPs according to the WHO guidelines. She emphasized WHO's role in harmonizing regulatory oversight and facilitating development of the experience and expertise of NRAs in evaluating SBPs. The establishment of the criteria for regulatory evaluation of SBPs among NRAs in line with the current WHO guidelines is critical. It is important to achieve the goal of the guideline established by WHO with an aim of promoting global consensus on the regulation of SBPs to enhance the

availability of safe and effective SBP worldwide. From the practical point of view, the speaker proposed two key needs for facilitating the development of SBPs. The first key need is the availability of a reference standard for validating methods in quality assessment of the SBPs. The second need is to establish product-class specific guidance which define at least minimum requirements for planning the studies required for product development (e.g. EMA guidelines for products such as insulin, growth hormone etc).

Dr Xu Chen (Beijing Tri-Prime Genetic Engineering Co., China) presented an example of developing interferon eye drops for use in treatment of herpes simplex keratitis. According to Provisions for Drug Registration in China, this product belongs to biological products in category 14 and 15 which are the products with a change in route of administration (not including category 12) and admitted with national standards. Preparation process (e.g. inoculation, fermentation and purification) and quality standard (e.g. the biological activity, purity, molecular weight, mouse IgG residue) were compared to evaluate the consistency between the product under development and the marketed one (interferon for injection). Head-to-head comparison of these two products in clinical trial was performed, but not required for quality part. In the context of good consistency, clinical safety and effectiveness of the product, toxicological study with only one animal species is generally required and long-term toxicity testing may be shortened. If the applicant provides evidence to confirm a product's consistency with the reference product, they can also apply for exemption from conducting pharmacology and toxicology studies.

7.1. Panel discussion

During the panel discussion, it became clear that the situation in terms of SBPs and implementation of the WHO guidelines is very diverse in different countries. Consequently, a harmonized approach for SBPs worldwide is unlikely to occur rapidly. While some countries have developed guidelines or are developing guidelines, some countries are taking a relaxed view and are not committed on the approach to adopt for approval for SBPs.

In some countries, guidelines have been developed which use two approval pathways; the biosimilar route (same as WHO SBP) and a highly divergent pathway. For example, Brazil explained the basis of the alternative pathway for SBPs, a route that is being followed by the country (simultaneously to the biosimilar pathway). This avoids the comparison with the innovator product and allows licensing with abbreviated non-clinical and clinical data. Concern was raised among the participants as this route is not recommended in the WHO SBP and was specifically not included in the approved guideline following considerable discussions. Moreover, approval by this process does not provide assurance that the product has a similar benefit to risk ratio as the reference product although in some instances post-marketing commitment is requested in an attempt to address this. The terminology for defining these products is also a matter of concern.

Some countries such as Thailand plan to develop guidelines based on the WHO guidance within 1–2 years. Malaysia has developed guidelines using the EMA concept but will harmonize with WHO regarding acceptability of the RBP; no biosimilars have been approved so far. Similarly, the Cuban approval procedure is based on WHO guidance. Canada and Japan have adopted biosimilar guidelines that are based on the same principles as EMA and WHO Guidelines [15,16]. However, there are several requirements that are more specific than the principles in WHO Guidelines. For instance, labelling in the case of Japan, and intellectual property issues in the case of Canada.

While it is clear that the main goal of India and China, which are growing economies with large populations, is to increase patient

access to these biomedicines, these countries have several manufacturers of these products who are targeting not only local but also other territories. These countries are currently lagging behind in terms of their regulations and need to act rapidly in developing appropriate regulations/guidelines for product approval so the locally manufactured products are comparable to the innovator products in terms of their efficacy and safety profile.

There was general consensus that the terminology of 'biosimilar' products should reflect that the products are biosimilars based on a comprehensive comparability exercise at the quality, non-clinical and clinical level. Products not authorized by this comparability regulatory pathway should not be called biosimilars. Labelling of the product was also discussed. Japan has BS in the product name to reflect that the product is a biosimilar but in other countries e.g. EU, there is no identifier in the name to indicate whether the product is a biosimilar. If a product has no trade name, the INN followed by the manufacturer name is used in the EU. For products that are not SBPs however, the terminology and labelling is a challenge which needs to be addressed.

During the closed session, the question of 'SBPs prequalification' was raised. It is clear that the example of vaccine prequalification does not apply to SBPs due to a number of differences in the use of these products and public health interest. Moreover, none of the international agencies expressed an intention to procure SBPs contrary to the situation with United Nations Children's Fund (UNICEF) and vaccines. Therefore, different mechanisms need to be explored.

Another issue discussed in the closed session is related to the applicability of clinical data generated in one ethnic group to another. One problem with this is that certain ethnic groups will have certain gene mutations and may be highly responsive to therapy compared with other populations. For example in an oncology setting, Iressa treatment induced a 6% response rate in most populations, but a 34% response in Asian populations. The genetic susceptibility and genomic profile of patients are very important in this respect. It was proposed to consult ICH Guidelines E5 where this situation was specifically addressed (question 11) in response to the request from Japan [17].

7.2. Main conclusions and way forward

1. WHO Guidelines on the evaluation of SBPs were recognized by the workshop participants as a tool for harmonizing regulatory requirements worldwide.
2. Representatives from National Regulatory Authorities from 10 countries reported that their national requirements are being defined on the basis of the principles outlined in WHO Guidelines. However, variations in terms of the national requirements for quality, safety and efficacy of these products revealed diversity in the regulatory expectations in different countries and regions. It is important to monitor progress at the global level and WHO secretariat accepted to take a lead in collecting and sharing the information on a regular basis.
3. Link between terminology and the regulatory evaluation is critical. It was agreed that the products for which similarity to an RBP, in terms of quality, non-clinical and clinical performance, demonstrated through the full comparability study should be named SBPs. However, lack of terminology for the products developed as copy products (so called "me too" products) with a partial comparability to an RBP, led to a great diversity in evaluating as well as naming these products. Revision of WHO Guidelines for assuring the quality of products prepared by recombinant DNA technology (WHO TRS 814) is seen as an opportunity for elaborating on this point [18].
4. Concept of comparability studies is not used in developing countries as it is the case in EU. In some countries in PAHO/

AMRO region, the comparability concept as described in WHO Guidelines and EMA Guidelines is not supported. Therefore, the application of the principle for comparability to the RBP was recognized as an issue that needs to be addressed in one of the future implementation workshops.

5. Reference Biotherapeutic Product (RBP) is an issue where regulatory requirements differ. Majority of the NRAs involved in the discussion will accept RBP which is not licensed in their country but is licensed and used in another country (so called "foreign RBP"). However, two countries in addition to EU will insist on the RBP licensed in their own country (Japan and Singapore) [6,16].
6. Clinical evaluation of SBPs and related statistical analysis are critical for regulatory decision. These two aspects are recognized as weak points in the overall assessment of biological products in general, and SBPs in particular. Lack of expertise in reviewing clinical data is an issue that majority of NRAs are struggling with. NRAs are encouraged to build capacity in clinical trials review and statistical analysis.
7. Non-clinical evaluation of SBPs is an area where the principles outlined in WHO Guidelines were well accepted by the regulators and SBP manufacturers. The experience in EU revealed an evolving concept of non-clinical studies and a discrepancy between the evaluation of products before EMA guidelines and after.
8. Quality assessment of SBPs is the issue that the workshop recognized as a key topic for the next implementation workshop. Comparability in terms of quality parameters is an issue of great diversity in the national requirements. In some countries such as China, comparability in the quality aspect means a comparison to the national standards (*i.e.* Pharmacopoeial). It was agreed that a review article on the intended use of the international reference preparations should be published as a tool for information sharing. Another aspect that requires further discussions is related to continuous and frequent changes of the originator products. How to relate this issue in demonstrating similarity to the reference product is perceived as one of the most complex issues.
9. Labelling is an important issue for the use of SBPs. Majority of countries reported that the indication of SBP in the label of the product is not required. The exception is Japan where SBPs should be distinguished from originators in the product label. In Malaysia, this distinction has to be made in the package insert but not in the product label. It is a common practice to use trade name, company name and INN. Workshop participants recognized that the labelling approach for SBPs differ from the generic products where the use of INN and a company name without trade name is a common practice.
10. Information sharing among NRAs is a good practice that should be promoted at the global level. One of the actions for NRAs is to publish assessment reports on their web sites following the example of EMA and Health Canada.
11. WHO should assist NRAs in building and improving technical expertise in the evaluation of SBPs by providing some learning tools as well as opportunities for information and knowledge sharing. In line with this, it was agreed to publish outcomes of this workshop in a peer-reviewed scientific journal and to prepare Questions and Answers for WHO biologicals web site.
12. Key messages for ICDRA meeting are: a) NRAs should take an active role in building capacity for regulatory evaluation of biotherapeutics; b) the workshop participants required revision of WHO Guidelines for assuring the quality of products prepared by recombinant DNA technology (WHO TRS 814); and c) WHO should continue monitoring progress with the implementation of the Guidelines on the evaluation of SBPs

into regulatory and manufacturers' practices and provide information on a regular basis.

Conflict of interest

The authors have disclosed no potential conflicts of interests.

Disclaimer

This report contains the collective views of an international group of experts, and does not necessarily represent the decisions, policy or views of the World Health Organization.

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Annex. Assessment of questionnaire responses to evaluate the workshop

The objectives of the questionnaire were:

1. To survey participant satisfaction in the workshop
2. To identify the areas proposed for planning future workshops
3. To identify current gaps and additional needs in implementing the WHO Guidelines
4. To identify further needs of WHO assistance to improve the system in countries

With the exception of WHO staff, a total of 38 experts from 13 different countries, *i.e.* Brazil, Canada, People's Republic of China (China), Cuba, India, Iran, Japan, Jordan, Republic of Korea (Korea), Malaysia, Singapore, Thailand, and United Kingdom of Great Britain and Northern Ireland (UK) attended the Workshop. 32/38 participants (84%) returned the questionnaire. Most participants (63%) were regulatory authorities, and some experts were from the industries (31%) and from academia (6%) (Fig. 1).

I. The summary of responses about the Workshop as follows:

1. 29/32 (91%) responders considered that the Workshop was the right length (Fig. 2).
2. 25/32 (78%) responders considered that the Workshop was timely balanced between presentations and discussion (Fig. 3).
3. Responders considered the following points for the most informative sections in the Workshop (included multiple responses) (Fig. 4).
 - a. Updating region/country situations (56%)

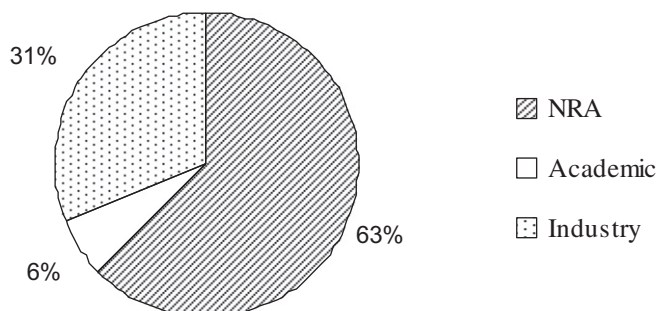


Fig. 1. Participant affiliations.

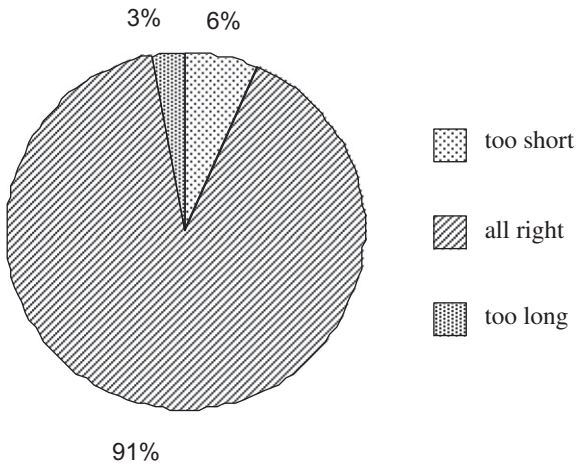


Fig. 2. Satisfaction of length of workshop (n = 32 responders).

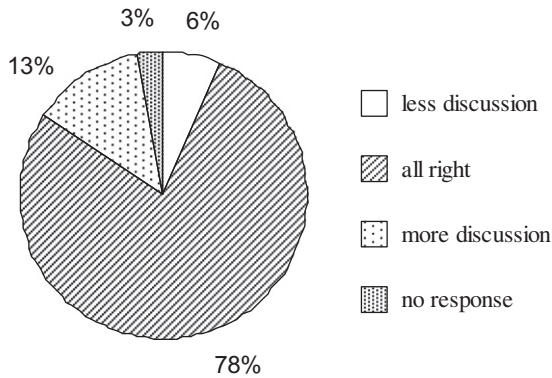


Fig. 3. Satisfaction of time balance between presentations and discussion (total 7 h discussion was stopped by chair at the end of each presentation) (n = 32 responders).

- b. Case study, i.e. practicing clinical evaluation through simulated case studies (53%)
 - c. Better understanding of principles of clinical evaluations, i.e. lecture and reviewing practical examples (34%)
 - d. Sharing experiences of comparability studies and RBPs (19%)
 - e. Manufacturers' perspectives on implementation of WHO Guidelines (13%)
 - f. Challenges raised by reviewers (9%)
 - g. Introduction (6%)
4. Additional written proposals (20 responders) for the future workshops were (included multiple responses) (Fig. 5):
- a. Include topics for quality issues, e.g. comparability study, international standards (45%)
 - b. Include more case studies (20%)
 - c. Invite more influential people, e.g. regulatory authorities from USA and India, and director of authorities (15%)
 - d. Include more information about clinical design and analysis (10%)
 - e. Include the topic for risk management plan (10%)
 - f. Others: include the topics for rDNA products in general, interchangeability, immunogenicity.

II. The summary of responses about implementing the WHO Guidelines as follows:

1. 9/13 (69%) countries indicated that the main principles of the WHO Guidelines could be applicable to their national regulations (Fig. 6).
2. 4/13 (31%) countries indicated that the following points of the WHO Guidelines could not be applicable to their national regulation:
 - a. China: head-to-head comparability exercise in clinical trial
 - b. Cuba: head-to-head comparative clinical study for application of monoclonal antibody products
 - c. India: equivalence study in clinical trial because of demand for great expense of RBPs
 - d. Iran: equivalence study in clinical trial because of requiring large number of sample size

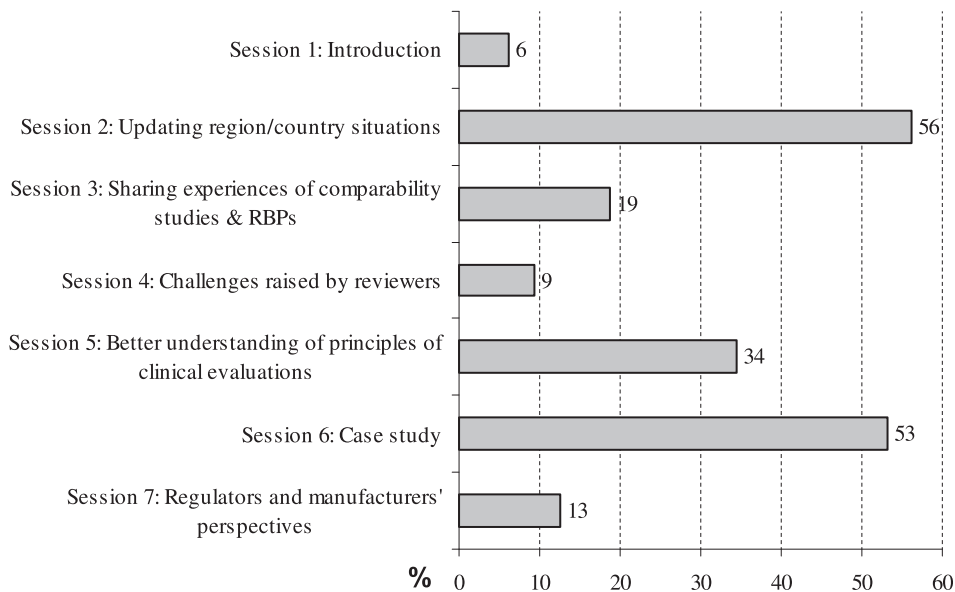


Fig. 4. Informative sessions of the Workshop (n = 32 responders; Feedback includes multiple responses).

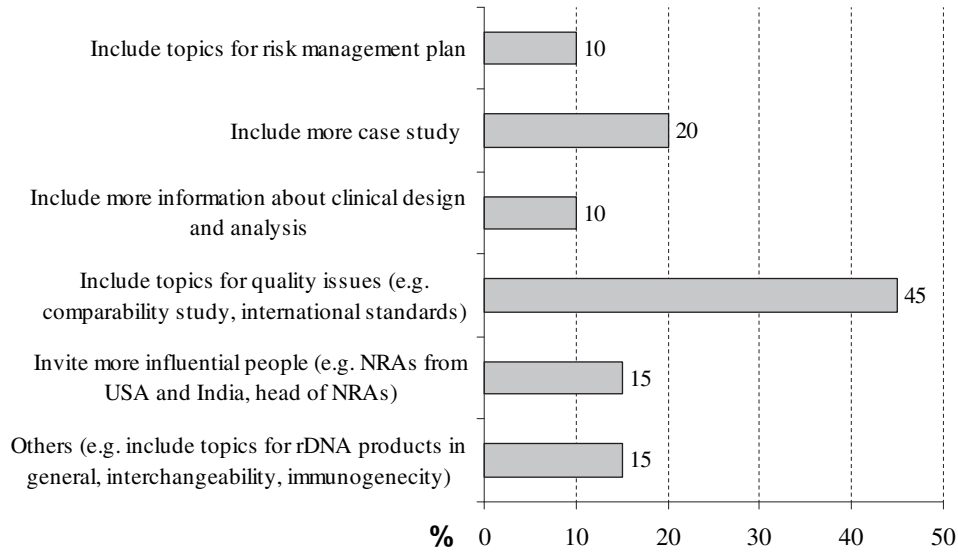


Fig. 5. Proposal for the topics of future workshops ($n = 20$ responders; Feedback includes multiple responses).

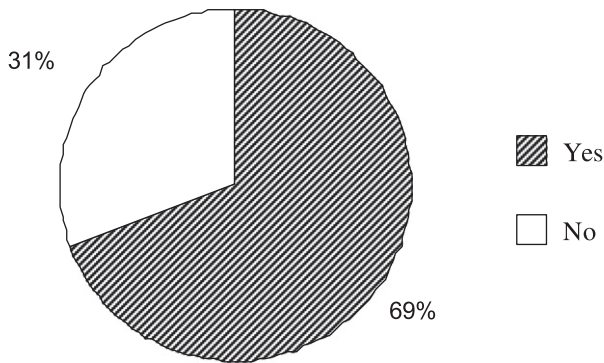


Fig. 6. Applicability of implementing WHO Guidelines into the national regulation ($n = 13$ countries).

3. Proposals (26 responders) for additional information to be included in the Guidelines were (included multiple responses) (Fig. 7):
- a. Include product specific and more detail guidelines (46%)
 - b. Include INN issues (12%)

- c. Include topics for PMS and PhV plan for the specific of SBPs (8%)
- d. Others: include Q&A, alternative pathway, advanced methodology in clinical evaluation, labelling issues, interchangeability, etc (23%)
- e. No needs (31%)

III. The summary of responses about further needs of WHO assistance to improve the system in countries ($n = 13$ countries; Feedback includes multiple responses) (Fig. 8)

1. 8/13 (62%) countries indicated that training including workshops in their countries was necessary assistance from WHO
2. 3/13 (23%) countries indicated the needs of exchanging experience among NRAs
3. 2/13 (15%) countries suggested arranging a meeting with the heads of their national regulatory authorities to motivate them
4. 2/13 (15%) countries indicated the needs of revision of rDNA product guidelines in general
5. Others: help to get RBPs, prequalified SBPs by WHO

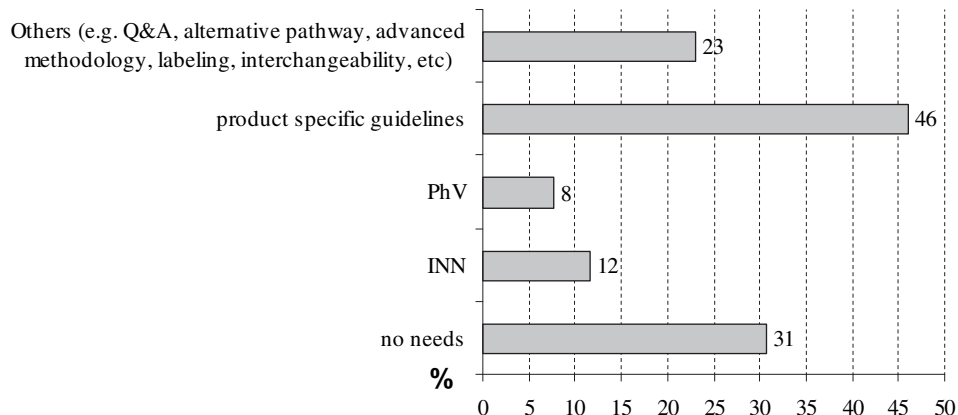


Fig. 7. Proposal for additional information to be included in the Guidelines ($n = 26$ responders; Feedback includes multiple responses).

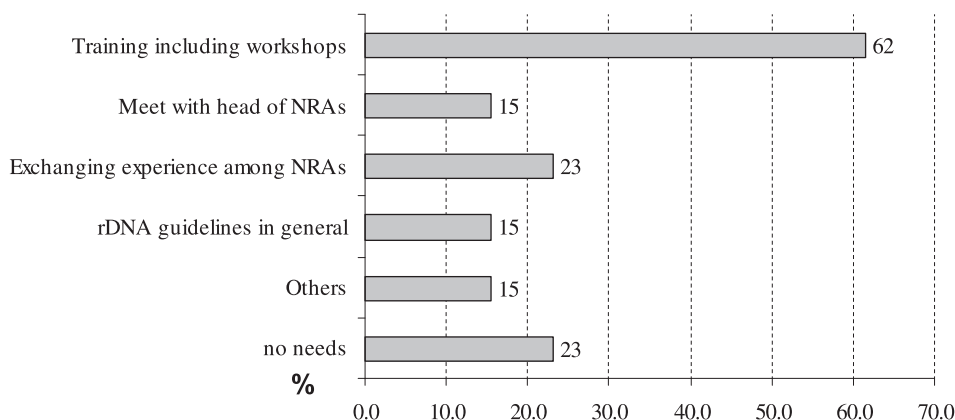


Fig. 8. Further need of WHO assistances to improve the system in countries.

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