Meeting Report

First WHO implementation workshop on regulatory evaluation of biotherapeutics including biosimilars in the African region

Accra, Ghana
8-10 September 2015

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Abstract

The first implementation workshop in the African region on WHO guidelines for biotherapeutics (BTPs) and similar biotherapeutic products (SBPs) was organized by WHO HQ in collaboration with the Ghana Food and Drugs Authority in Accra, Ghana in September 2015. The workshop was a step towards the implementation of the two guidelines into the regulatory practices of African regulatory agencies, and towards developing African national regulatory frameworks to meet current international regulatory expectations. By reviewing and practicing a case study on SBPs exemplified by erythropoietin, better understanding on the importance of head to head comparability studies was achieved. Pre-workshop preparation was achieved using an online platform. This interactive forum was seen as a stage that could be developed for future collaboration and possible work sharing in the region. Various approaches for immediate and long term regulatory capacity building were discussed as an issue of critical importance for the future.

1. Introduction

Dr Prosper Tumusiieme (WHO African Region Office) opened the workshop with a welcome address which highlighted the importance of the workshop as a step towards implementation of two WHO guidelines [1, 2], adding that the workshop presented a good learning opportunity for what is expected according to global standards. In line with the resolution from World Health Assembly (WHA) in 2014 [3], the workshop forms part of the response of WHO to the needs of the African regulatory authorities in the implementation of the principles of the WHO BTPs (including SBPs) guidelines. Dr Tumusiieme commended Ghana FDA for their regulatory efforts especially in the area of vaccines, and advised the participants to make use of this opportunity to network after the workshop in the interest of improving regulatory capacity. He emphasized that the momentum being built should be maintained, and areas of common interest should be identified to keep the effort going.

Mr Hudu Moghtari (Chief Executive Officer of FDA, Ghana) made a remark in his welcoming address to emphasize the importance of the workshop. He stressed the need to apply science based rationale to the regulation and manufacture of BTPs adding that all participants had experience in challenges with regards to the manufacture or regulation of BTPs. Agreeing with Dr Tumusiieme, he added that the WHA, in 2014, adopted a resolution on the critical need in the area of BTPs in order to promote access to these products while ensuring their quality, safety and efficacy [3]. WHA 67.21 resolution, additionally requires WHO to support national regulatory authorities (NRAs) in the development of national regulatory frameworks to meet current international regulatory expectations. This workshop comes at a time that many innovator
BTPs are going off patent and the implication of this on SBPs’ manufacture and regulation is clear. He concluded by urging the participants to involve themselves in the workshop.

About forty experts participated in the workshop including: a) twenty-seven regulators from sixteen countries in Africa Regions, i.e. Algeria, Botswana, Burkina Faso, Burundi, Ethiopia, Gambia, Ghana, Kenya, Mozambique, Nigeria, Sierra Leone, South Africa, Tanzania, Uganda, Zambia, Zimbabwe; and b) six manufacturers from two manufacturers’ associations (i.e. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), The International Generic Pharmaceutical Alliance (IGPA)). For French speaking participants, translation was organized during the entire workshop.

Dr Elwyn Griffiths (WHO consultant, UK) was appointed the chairperson and Ms Jacqueline Rodgers (FDA, Ghana) served as rapporteur.

Dr Ivana Knezevic (WHO HQ, Switzerland) briefed the participants on the activities of WHO in the area of BTPs and the WHA 67.21 resolution recommendations for WHO and the member states [3].

She explained that WHO is the directing and coordinating authority for health on behalf of the 194 member countries in the United Nations system. In order to fulfil WHO objectives, a core WHO function for the period 2014-2019 is to set norms and standards, and promote and monitor their implementation through initiatives including assisting NRAs in the utilization of WHO Biological Reference Materials and application of the principles in WHO guidelines and recommendations, to ensure quality and safety of BTPs.

In the area of biological standards, WHO has eight collaborating centers. More than 90% of the WHO reference preparations are developed by the National Institute for Biological Standards and Control (NIBSC, UK). Recent developments in standards for BTPs include Etanercept and human antibodies to EPO which were submitted to the WHO Expert Committed on Biological Standardization for adoption.

Expanding on the key principles of WHO guidelines for evaluation of biological products, she stated that the guidelines should be used as a bases upon which national guidelines can be developed. The documents are living documents which are intended to assist with implementation of the principles, at national, regional and global levels. She concluded by saying that if all NRAs use the guidelines there should be no differences inter-NRA in regulation of BTPs. She stressed on the importance of working in line with the guidelines especially from the patient’s perspective, and the importance for regulators to be transparent in their activities to increase transparency and trust of clinicians and patients in SBPs. Referring to WHA 67.21 [3], she explained that the resolution requests WHO to support member states in strengthening their capacity in health regulation of BTPs including SBPs and support the development
of regulatory frameworks that promote access to quality, safe, efficacious and affordable BTPs as well as to update the 2009 guidelines to reflect technological advances in characterization of BTPs, considering NRA needs and capacities and to report to the Sixty-ninth WHA on progress in the implementation of the resolution. Since 2010, six implementation workshops on BTPs including SBPs have been organized at global level, and the outcomes of workshops have been published [6-9]. The outcome of various consultations and implementation workshops was the agreement that SBPs should not be regulated like small molecule generics and a head to head comparability exercise of quality, safety and efficacy is essential for a product to be considered to be a SBP. However, once licensed, a SBP has its own lifecycle. If major differences are found in quality, nonclinical or clinical studies the latter cannot be called ‘similar’. In these situations further development and licensing options should be considered. In more recent implementation workshops, it was realized that there is increasing alignment between jurisdictions in recognition of the role of WHO in promoting regulatory convergence. Most BTPs in developing countries are not licensed by a strict comparability exercise which is a concept not well understood. There was also a lack of expertise and capacity for evaluation of BTPs/SBPs.

At an informal consultation on SBPs in April 2015 it was agreed that it was not necessary to revise the current WHO SBPs guidelines, as all guiding principles are up to date, and an addendum to the SBP guidelines specific for SBP monoclonal antibodies is preferable to a separate document. The key WHO events in 2015 constitute a lot of progress in context of training materials and the usefulness of eLearning platforms in providing relevant information and much quicker access for information sharing. They include collaboration with the International Pharmaceutical Regulators Forum (IPRF) of the International conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to harmonize issues and challenges in regulation of BTPs amongst IPRF member countries. In a face to face meeting in Korea in July 2015, three specific deliverables were decided on: a) a public assessment summary information for BTPs (PASIB) to assure consistency and transparency of the review process; b) the development of a reflection paper on extrapolation of biosimilar indications; and c) specific training material for analytical comparability for SBP monoclonal antibodies.

Dr Hye-Na Kang (WHO HQ, Switzerland) specified that the purpose of the workshop was to facilitate implementation of WHO guidelines for BTPs and SBPs into regulatory and manufacturing practices in the African region (as requested by 16th International Conference of Drug Regulatory Authorities (ICDRA) meeting in 2014 [4]); additionally, to gain understanding of key regulatory issues relevant to assurance of quality, safety and efficacy in the region (as requested by WHA in 2014); and to test the effectiveness of using pre-workshop self-study components of developed e-learning portal (as requested by 16th ICDRA meeting in 2014) and of blended learning that combines e-learning and a face-to-face
meeting. She also presented the background of development of the case study on the role and influence of the quality assessment of biosimilar erythropoietin (EPO). The objective of group work practice with this case study at the workshop is to gain experience of the evaluation of quality attributes and the importance of structure-function relationships, since they inform the stepwise evaluation of biosimilarity. Participants are expected to have better understanding of: a) how to read and interpret data from quality comparability study; b) the influence of quality assessment results on clinical performance; and c) the importance of evaluation of an entire data package for quality, nonclinical and clinical parameters as a basis for making the decision to license a product.

2. Development and practical uses of e-learning materials

Introducing the concept of e-learning, Dr Jean-Pierre Kraehenbuhl (HScT), expanded on the benefits and advantages of training and content management systems, including the copyright waiver benefit, where only credit has to be given as opposed to mandatory permission for use of published material. E-learning is a medium that facilitates multiple teaching sessions, consistency of information and rapid update compared to traditional learning methods. An advantage of the platform he described is that it does not work with an open access resource-like Moodle but with Microsoft technology, it is financed by the University of Geneva and free for users. The main advantage of Microsoft technology is that it permits access of all site information in spite of updates. Participants were encouraged to share their requirements in terms of networking, for improving the e-learning platform.

Dr Kraehenbuhl led the participants through a demonstration of the functions and animations of the e-learning platform for the pre workshop activities. He added that the e-learning platform can be accessed from tablets and cellular phones. The entire module can also be downloaded, worked on offline and reports comments / questions submitted online. An important limitation to on-line learning is that reliable broadband access is necessary. Course content access is renewable and indefinite, however participants are rejected after a year of no activity. Specialist are made available to answer questions posted in the forum, though what commonly happens is that in the discussions generated by forum questions, they are answered by other participants and the experts intervene as and when necessary.

2.1 Panel discussion: Experience sharing & Proposal for improvement

Prior to the workshops, pre-workshop self-study components were shared with participants through the e-learning platform mentioned above. During the panel discussion, regulators from four countries (Ghana, Burundi, Uganda, and Kenya) shared their experience and what they learned from the components to
facilitate a discussion with all participants. There was a general agreement amongst the participants that the pre-workshop activity was informative and useful for preparation for the workshop and improved the value of the workshop experience. It was suggested to improve the audio quality of some of the preparation materials and that there should be more easy access to the reading materials. Particularly, for improvement of the e-learning experience, inclusion of more case studies on the evaluation of BTPs and SBPs and development of a more interactive forum were suggested.

Dr Knezevic pointed out that the intention of the portal is to direct participants on where to access relevant information. There are two separate issues regarding the use of the portal as a platform for the:

1) workshop preparation

For that purpose, WHO Guidelines on BTPs and SBPs as well as published case studies and other relevant articles were posted as a source of information that the workshop participants should have reviewed before the workshop.

2) e-learning programmes

The intention is to prepare these programmes to help regulators to understand key principles for evaluation of BTPs including SBPs. The question whether they should be self-paced and/ or actively managed programmes is still being discussed. It is clear that both options have some advantages and disadvantages that would be considered in the preparation of these important tools. In terms of the expectations, e-learning should be considered as an additional tool rather than a replacement of appropriate professional training for evaluation of BTPs including SBPs.

She also stated the importance of having a forum for discussion among participants. However, there is no intention to use that platform for sharing product related confidential information. The purpose of the forum is to enable participants to ask questions and to clarify issues through the discussion with other colleagues and/or mentors.

3. Regulatory expectations in WHO similar biotherapeutic products guidelines

3.1 Quality aspect

Introducing the guidelines on evaluation of similar biotherapeutic products (SBPs) [2], Dr Hye-Na Kang (WHO HQ) explained that the guidelines were to provide globally acceptable science based principles for the regulation of SBPs. The scope of the guidelines is restricted to well established and well characterized BTPs, subject to a head to head comparison with a suitable innovator reference product. If a significant difference is determined in nonclinical or clinical studies, such a product cannot be referred to as a SBP
and so will have to be registered based on a full dossier. She specified that a case by case approach is necessary for each class of products. For the quality evaluation of a biosimilar, head-to-head comparison of SBP with the RBP represents an additional element to the “traditional” full characterization dossier (please see appendix 2 of [1]). The basis for reduced clinical and non-clinical data is the submission of a full quality comparability study which is also the basis for the claim of SBP. Regarding the quality similarity assessment, some differences are to be found, and such differences should be assessed for their potential impact on clinical safety and efficacy of biosimilars and justified. She listed three categories of differences: a) differences of unknown clinical relevance; b) differences in quality attributes known to have potential impact on clinical activity; or c) differences without triggering the need for extra nonclinical and/or clinical evaluation.

3.2 Clinical aspect

Dr Ivana Knezevic started by saying that since the WHO guidelines are to apply to 194 countries, they are a bit more general, and where NRAs alter the WHO guidelines feedback is appreciated as to the differences made. SBPs are not generic products and many aspect of evaluation of generic dossiers do not apply. In the evaluation of quality, non-clinical or clinical data, if differences are seen, then the product cannot be registered as an SBP. However, in reality there are sometimes grey areas which make it difficult to be definite about whether the similarity is enough to warrant SBP status or not.

Where an innovator product is licensed but there is not extensive use, it becomes difficult to use it as a RBP for a SBP. She added that the SBP and RBP must have the same drug substance. She compared different regulatory scenarios, where in the EU, there used to be strict requirement for a RBP to be licensed in the EU, while in Canada, the RBP does not necessarily have to be registered in that country, but it should have been licensed by an experienced NRA. Recently, the EU requirement became more flexible. In other cases, the registration of the RBP by a well experienced NRA may be acceptable providing that the acceptance criteria are met. The submission of a reduced package for non-clinical and clinical data depends on the quality package. The clinical study should be a parallel one and both non-inferiority or equivalence studies may be acceptable. As stated in WHO Guidelines on SBPs, in most cases, equivalence study design would be a preferred option but it’s important to understand that non-inferiority could also be a workable solution in some cases.

An important issue is the extrapolation of indications, which must be justified for the SBP. The biosimilar can have less but not more indications than the RBP. The debate on this is on-going, and extrapolation of
SBP indications to the range of that of the RBP is possible if the mechanism of action is understood, the target is the same, and this is demonstrated in a sensitive test model.

She noted that if a trial cannot show differences between the SBP and RBP it may be due to poor assay sensitivity, adding that even in well-designed trials, the views of statisticians and investigator may differ, so it is important that the interpretation of the analysis be done within the context of clinical relevance. Validation of the clinical data is an aspect of the trial that is often overlooked, and this was described as an important step in determining the validity of the trial conclusions.

The pharmacovigilance plan should be submitted at the time of submission of the application and should be functioning at the time of approval; however, in practical terms this does not always work well. The clinical implication of antibodies detected is also important.

4. **Stepwise approach and quality assessment for licensing of SBPs**

4.1 **Overview of characteristics and quality attributes to be considered in development of SBPs**

Dr Karin Heidenreich (IFPMA) differentiated between: a) innovator/originator biotherapeutics, which are registered based on a full analysis of a full quality, non-clinical and clinical dossier; b) SBPs which are highly similar to RBPs; and c) non-comparable BTPs. Non-comparable BTP is a term used by IFPMA and relates to products that claim a SBP status and refer to data of originator products, but have not been approved in accordance with the WHO SBP guidelines. That means these products are usually registered based on an abbreviated quality, non-clinical and clinical data package, and have not been sufficiently compared with the RBP. Thus, quality, efficacy and safety of this group of products are unclear. The development of SBPs in line with WHO guidelines follows a stepwise approach. The key steps are the selection of the target (the RBP), target directed development including analytical assessment of similarity and nonclinical as well as clinical assessment of similarity. The definition of the SBP specification is guided by the inter-batch variability of the RBP. Structural and functional characterization of the SBP against several batches of the RBP is necessary for the development of the SBP.

She noted that in the analysis of similarity it is necessary to match the SBP and RBP across multiple quality attributes, including primary and higher order structure. In the selection of the analytical methods, a number of different considerations have to be made, for instance the optical resolution of the chromatographs which should be precise enough to permit clear differentiation of peaks where such difference exists. In determination of similarity of the higher order structure of the two proteins, different techniques offer different advantages, for example CD spectroscopy is not as exact as X-ray crystallography however it is easier to run, and so has a practical advantage.
She concluded by saying that the development of SBPs is a time consuming and very complex step wise process. It involves a battery of analytical tests, needed to get adequate information on both the RBP and SBP via the comparability exercise to demonstrate the “totality of evidence” for the similarity of the SBP.

4.2 Evaluation and interpretation of quality results; Acceptable vs. relevant differences

Ms Ishwari Kavdikar (IFPMA) used the example of Eprex (epoetin alfa), which is approved for management of anaemia, to illustrate acceptable versus relevant quality differences, where the observed clinical signals in the post marketing setting led to a root cause investigation of manufacturing and supply chain management.

In the product life cycle, the replacement of human albumin with polysorbate 80 as a regulatory requirement caused leaching from the syringe stopper into the product. Characterization and stability studies were undertaken to support this change as well as clinical studies using the new formulation in vials. Following the change to prefilled syringes, there was an increase in immunogenic response to the product when administered by the sub cutaneous route, resulting in a raised incidence of pure red cell aplasia (PRCA). This illustrates how a seemingly straightforward change can have drastic clinical consequences. Thorough understanding of the manufacturing and handling process is therefore essential to defining the product characteristics and ultimately its safety and efficacy.

The Eprex example also shows that some (rare) safety issues become apparent only in the post-marketing setting when larger numbers of patients are being treated. In the Eprex example, an enhanced pharmacovigilance program was used to understand wider clinical safety implications of the stopper change. This highlights the importance of having a functional pharmacovigilance system and a RMP in place.

5. Case study on quality assessment of biosimilar EPO

Dr Lorenz Scheppler (IFPMA) led an interactive discussion among participants on a case study which was based on a fictional situation to facilitate discussion on quality assessment of a recombinant biosimilar EPO product. Participants were informed that preliminary non-clinical studies have demonstrated equivalent in vitro and in vivo potency between the SBP candidate and the RBP and were asked to determine what additional non-clinical and clinical studies will be required in the stepwise biosimilar development exercise. The tasks of the work groups were to determine: a) if the quality data of the SBP candidate EPO demonstrated adequate biosimilarity with the RBP to qualify as a SBP; and b)
how ‘residual uncertainty’ could be addressed in non-clinical and/or clinical studies. The lower sialylation and higher polylactosamine content in the candidate SBP could each independently impact in vivo potency, albeit in opposite directions and the similar rates in haemoglobin increase in rodent studies is not conclusive due to the confounding effects of anti-drug antibody formation. Therefore, a head-to-head clinical study in patients with chronic renal insufficiency is probably necessary to establish similar efficacy. The applied techniques to determine subvisible particles and aggregates are relatively insensitive to the particle composition and to higher order species. As higher order soluble and insoluble aggregates may be potentially immunogenic and as animal studies are not informative of a similar risk for human immunogenicity, further data would be needed, e.g. head-to-head clinical immunogenicity studies. A pre-approval comparative immunogenicity study should assess the incidence and characteristics (antibody titer, antibody class and subtype, neutralization potential, etc.) of any anti-drug antibodies in the SBP and comparator arms. Such a study should be powered to detect adverse events with a 1% or greater incidence (approximately 300 patients) which should be able to detect a significant increase in the incidence of binding antibodies. Given that neutralizing antibodies develop over time, it may be necessary to study immunogenicity in patients treated for 6 to 12 months. As PRCA is an extremely rare event (less than 1 per 10,000 patient years) it is unlikely that such a study could detect a small difference in PRCA risk and consequently it is necessary to evaluate the risk for PRCA via post-marketing pharmacovigilance.

6. Guiding principles for regulatory assessment of approved biotherapeutics

Dr Elwyn Griffiths (WHO consultant), commented that regulatory assessment of BTPs is a rapidly growing area, and there has been a lot of progress in the last 30 years. He noted that nomenclature has caused some problems and proceeded to explain the principles of biotechnology, explaining that great progress has been made in the purification of biological macromolecules which are literally produced by cutting their gene sequence out of one organism and producing the related protein in another organism. He explained that these are highly complex molecules some with multiple functionality and therefore their clinical performance cannot be fully predicted from physicochemical characteristics alone. He noted that during translation of ribonucleic acid to protein, minor variances can occur and these could cause problems; in certain cases the potency of the resulting protein could actually increase. He listed some critical manufacturing points, stressing that slight changes in the process could lead to slight changes in the product but with a major impact on safety and efficacy, adding that an issue that is often forgotten is viral safety. New challenges include new production processes and new product types raising new scientific, technical and regulatory issues. It is important that international regulation is positioned to
reflect the scientific advances in this area. Outcomes of previous implementation meetings identified
difficulties with licensing of BTPs due to a lack of adequate understanding of BTP regulatory issues.
Some countries in the past have registered biotechnologically derived products applying guidelines for
generic products, hence ‘copy’ products have been registered as ‘biogenerics’. There is also a lack of
harmonization of regulatory oversight for BTPs in general. For products already licensed without
application of the principles in the two guidelines, it is essential to develop approaches for their re-
evaluation or to phase them out.

He introduced a new WHO document ‘Regulatory assessment of approved r-DNA derived
biotherapeutics’ [5], which is undergoing final stages of public consultation and invited comments from
the participants. He explained the step wise regulatory approach in the document which sets out four
options for dealing with BTPs and SBPs registered prior to implementation of the current guidelines. He
concluded by saying that the length of the interim transition period will be country and product specific
and will depend on a number of aspects, including whether there are already recognised safety issues.

6.1 Panel Discussion: Concept of regulatory assessment and the role of WHO

Two questions were raised for the discussion: a) value of the new document on regulatory assessment of
approved BTPs; and b) the best way for WHO to implement the principles set out in the document. It was
concluded that the document has the various value mentioned below:

- raising awareness of the products currently available (limited data)
- strengthening available guidance
- screening check-list for dialogue between regulator and manufacturer
- changing practices for improving quality of biological medicines such that patients receive
efficacious and safe products
- updating regulatory information and systems on a regular basis
- emphasizing regulatory oversight throughout the life-cycle of a product

The issue of inadequate regulatory assessment for BTPs registered in the past had been recognised by
many other countries; however a decision on how to go about the re-evaluation of the products had not
been taken partly due to lack of capacity and lack of guidance. To this end, the document was seen as a
welcome development by the participants, for example Tanzania intends to apply the fourth option at the
time of registration renewal of affected products’ five-year registration. In countries like Sierra Leone where the concept of specific regulatory requirements for BTPs and SBPs is relatively new, national policies do not as yet exist, and the document is seen as serving a dual function providing immediate guidance for registration procedures and serving as the basis for appropriate policy development. In addition to providing guidance on the issue of regularization of registration to bring these products into conformance with current scientific understanding, the document gives the NRAs a credible reference for requests for additional data, quality information and risk management plans from manufacturers. Several countries called for a harmonization effort in BTP evaluation in their sub-region for shared/joint evaluation of these products. It was further suggested that a training programme for better understanding of the application of the principles in the document would be useful. Actual evaluation of additional data packages alongside experienced assessors was seen as a way to help in understanding the application of the document. It was noted that because most of the applicants for licenses are from India and China, a guidance document and training of the manufacturers on preparation of the relevant additional data packages will be an important addition. Several countries suggested setting up joint regulatory reviews for the joint evaluation of products of common interest, as this will reduce the burden and duration of the evaluation process. The education of policy makers and clinicians was determined to be relevant to the success of the process.

Dr Knezevic commented that where two or more NRAs realize there is a lot that they could achieve together without waiting for WHO to lead, memorandum of understanding is sometimes established on a bilateral basis, which define the way in which information is shared, and the scope of permission to share. Also from past experience, small blocks are better for work sharing. The objectives of the work groups can be updated where initial objectives have been achieved, while big blocks are better for information sharing only. Joint reviews have worked well in the past, with WHO just matching expertise with need.

She suggested that the forum will help but countries will have to collaborate for specific work needs. In previous experience this bilateral agreements have sometimes shown great usefulness.

The issue of site inspections as part of the registration or licensing process was discussed at length. Suggestions included inspections by NRAs at the country level, joint inspections and development of a pre-qualification system. Lack of capacity and expertise were recognized as challenges in the practical application of the document, and a hindrance to mutual recognition of registration amongst NRAs.

7. Discussion in closed session with regulators
During the closed session, regulators were asked to report their country situations on the regulatory framework in licensing BTPs including SBPs. Defined regulations for BTPs exist in Algeria, Ethiopia, Ghana, Nigeria, and South Africa, and the development of new regulations is in process in Gambia, Kenya, Tanzania, and Zambia.

Another issue discussed in the closed session was again related to work sharing in the region. For example, discussions are underway for creating an expert pool with Ghana, Sierra Leone, Nigeria, Liberia and Gambia for medicines regulation including BTPs. Mozambique proposed to arrange a work sharing with more experienced NRAs in Africa as a short term plan to fill the gaps of resources for reviewing products. Ghana suggested that WHO set up a monitoring system to see how the guidelines are used in country specific situations. Sierra Leone stressed the need to understand the scientific principles involved in development and manufacture of BTPs. Experience sharing amongst NRAs with WHO in the facilitator role is a possible way of developing expertise. There was a suggestion from Zambia in the development of a standard format for their registration in the region. All the participants agreed that the platform for e-learning as part of workshop preparation was useful, and expressed the desire to use the forum for further collaboration and regulatory work sharing.

8. Conclusions

8.1 Summary of discussion and key regulatory issues identified

1. Specific development of expertise in the area of BTP and SBP regulation within the African continent is an immediate need. Though some NRAs have dedicated assessors for BTPs and SBPs, and have developed appreciable levels of competency in BTP and SBP assessment, in other NRAs misunderstanding of terminologies still exists. This was exemplified by confusion about the difference: a) between reference standard and reference product; and b) of substitutability vs. interchangeability. There was also lack of clarity on the role of pharmacopoeia monographs in the evaluation of BTPs.

2. Lack of expertise requires capacity building which is a lengthy, resource intensive process. Work sharing should be explored as an intermediate or long term solution.

3. WHO should assist NRAs in developing capacity in understanding the impact of differences in comparative quality assessment of SBPs and RBPs, determining whether the differences are acceptable or relevant, and assessment of interchangeability of BTPs.
4. High rate of rejection of submissions of BTPs/SBPs from inexperienced manufacturers results in waste of a lot of time of regulators. It could be reduced by education of manufacturers in the implementation of the two guideline principles into their manufacturing practices. In addition, using a checklist was proposed as the first step in routine screening to see if all necessary data package is submitted.

5. Emphasis should be on stepwise evaluation of the quality, nonclinical and clinical aspects of the dossier. Understanding of impact of differences in comparative quality assessment of SBPs and RBPs (acceptable or relevant) is critical.

6. Health care professionals need to be sensitized to the nature of biosimilar principles and to build confidence in SBPs licensed on the basis of appropriate rational science based guiding principles.

7. The following should be understood well:
   a. The principles of extrapolation of indications of SBPs in respect to the RBP;
   b. The importance of traceability in pharmacovigilance.

8. An evaluation process requires input from reviewers who may be in different units (quality, clinical, pharmacovigilance), and it is important to make sure that they have productive discussions before making decisions.

9. Better understanding of pharmacovigilance plans and related activities (registries, surveillance, and traceability) is needed. This may be provided through the implementation workshops/e-learning programmes.

8.2 Main conclusions and way forward

1. The two WHO guidelines for the evaluation of BTPs and SBPs [1,2] were recognized by the participants as a standard to provide science based principles to set up the national requirements in Africa countries for these products.

2. The concept and role of RBPs are still unclear to some of African regulators. In addition, there is a misunderstanding of the role of pharmacopoeia monographs in the evaluation of SBPs. It is necessary to re-emphasize the differences between RBPs and reference standard materials [10].

3. Suggestions for future training include evaluation of clinical data, result interpretation of immunogenicity study, and good manufacturing practices inspections specific to BTPs and SBPs.
4. Because different NRAs in the continent are at different levels of competence in BTP and SBP regulation, a means of assessing existing competencies and a structured training plan could offer a high level guide for development of expertise.

5. Work sharing and information sharing were recognised as possible avenues for the development of expertise within the continent as a short term measure. In the long term this is expected to promote mutual recognition of registration in the area of BTPs. WHO was asked to facilitate this effort. Though regional harmonization blocks exist, some are inactive and none are currently addressing BTPs.

Reference


5. Regulatory assessment of approved rDNA-derived biotherapeutics, adopted by the Sixty-sixth meeting of the World Health Organization Expert Committee on Biological Standardization; 2015


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