Access to Biotherapeutics undermined by WHO Expert Committee

By K M Gopakumar[1] and Chetali Rao[2]

The WHO's Expert Committee on Biological Standardisation (ECBS) has declined a request to revise its 2009 Guidelines for the Evaluation of Similar Biotherapeutic Products (WHO Guidelines), which set the requirements for the generic version of biotherapeutics known as "biosimilars".

The WHO Secretariat then decided to evaluate the scientific evidence to support the revision of WHO Guidelines. The procedural holes in the ECBS decision might be the reason behind WHO's decision to review the scientific evidence.

During its 70th meeting on 21-25 October 2019 the ECBS – which includes a panel of experts with proficiency in developing norms and standards related to vaccines, blood products, and biotherapeutics – considered a request initiated by a group of scientists and civil society organisations (CSO) to revise the WHO Guidelines on biosimilars.

[Therapeutic proteins from recombinant DNA technology are popularly known as biotherapeutics, which are larger in molecular size compared to the traditional chemical molecules.]

The executive summary of the 70th ECBS meeting states: "Chair of the Committee communicated the conclusions of the Committee to the WHO Assistant Director-General MVP (Access to Medicines, Vaccines and Pharmaceuticals) who said that WHO will evaluate current scientific evidence to support the updating of the 2009 Guidelines".

The request was made for the WHO Guidelines to keep up with the latest scientific evidence in order to simplify the marketing authorisation of biosimilars as mandated under Resolution WHA 67.21 adopted by the 67th meeting of the World Health Assembly in 2014. The Resolution called for consideration of the access challenges emanating from the existing regulatory pathway for similar biotherapeutic products (SBP) and requested the Director-General of WHO "*to convene the WHO Expert Committee on Biological Standardization to update the 2009 guidelines, taking into account the technological advances for the characterization of biotherapeutic products and considering national regulatory needs and capacities and to report on the update to the Executive Board*".

Since the adoption of the WHA resolution, efforts to revise the 2009 SBP Guidelines were dismissed by the ECBS without citing any scientific reasons. Following open letters from scientists and CSOs calling for a revision, the ECBS considered this issue in its October meeting.

As in the past, the ECBS rejected the request without citing any reasons for its decision. The Executive Summary of the ECBS meeting states: "*Following discussion, a second letter was addressed to the ECBS Chair proposing that the current section 10 of these WHO Guidelines,*

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on the clinical evaluation of SBPs, be reviewed and an independent expert consultation organized to discuss in depth the major issues raised, particularly the requirement for clinical trials. The Committee considered that the hypothesis that quality data alone would be sufficient to ensure the safety and efficacy of these products was not supported by the information provided".

The past two decades have seen major advancements in the development of therapeutic proteins popularly known as biotherapeutics – both in the market as well as in the development pipeline. Biotherapeutics are an important class of medicines since they serve patients suffering not only from diseases like cancer but also for those in need of novel therapies. The latest edition of the WHO Essential Medicines List (EML) contains 6 biotherapeutics. In 2018, biotherapeutics accounted for 5 of the 10 top selling branded drugs in terms of revenue.

However, not many patients have been able to access this class of drugs. In comparison to the small molecule segment, which witnessed very steep price erosion after the entry of generic versions, the price erosion for biotherapeutics after the entry of their generic versions popularly has not been steep. This is due to low generic competition in this segment due to rigid entry barriers relating to their manufacturing and marketing approvals.

One of the most important documents that is believed to be a harbinger for the introduction of biosimilars in the market is the WHO's 2009 Guidelines. This instrument was supposed to aid the entry of biosimilars in the market; however, contrary to expectations, the Guidelines' onerous requirements in fact stymied their entry. The Guidelines have been adopted by many developing countries to formulate their own regulatory pathways for biosimilars. In compliance with the Guidelines, many developing countries, including India, have made it mandatory to conduct clinical trials for obtaining the relevant marketing approval.

As a consequence, a non-originator seeking marketing approval has to carry out a Comparative Clinical Trial (CCT) consisting of 200 to 400 people to establish the efficacy and safety of the product. Since these trials are comparative in nature, it means that to seek marketing approval, 50% of the clinical trial subjects are administered the originator's product and the remaining 50% are administered with the non-originator product. The sourcing of the originator product, which is extremely challenging, constitutes almost 50% of the biosimilar developmental cost, thus making it unaffordable for most of the needy patients, especially in the developing countries.

The current WHO Guidelines are based on a high degree of precautionary assumptions that do not hold true after 10 years of experience in the biosimilar area. For instance, at one place the Guidelines state: "*Even minor differences in the manufacturing process may affect the pharmacokinetics, pharmacodynamics, efficacy and/or safety of biotherapeutics product".* Such assumptions hold little value in 2019 in light of substantive and verifiable scientific evidence that is available to refute the assumption.

The WHO Guidelines prescribe stepwise development of biosimilars starting with a comparative characterisation of the molecule to prove the structural similarity with the originator molecule. This is followed by pre-clinical and clinical studies. According to some scientists working on biosimilar development, scientifically speaking structural similarity translates into functional similarity. Using the latest analytical techniques, the

characterisation exercise can establish a very close similarity with the originator's molecule structure.

Unlike small molecules, because of their inherent nature, protein-based molecules cannot exhibit a 100% structural similarity. This applies equally to both originator and biosimilar molecules. The variations are such that even different batches of the originator may not be 100% similar to each other. Surprisingly, the WHO Guidelines do not accept this scientific fact and insist on the clinical evaluation through CCTs. They further state that though "clinical trials are required to demonstrate similar efficacy between the SBP and the RBP, yet in certain cases, comparative PK/PD studies may be appropriate, provided that 1) the PK (pharmacokinetics) and PD (pharmacodynamics) properties of the RBP are well characterized, 2) at least one PD marker is a marker linked to efficacy (e.g. an accepted surrogate marker for efficacy), and 3) the relationship between dose/exposure, the relevant PD marker(s) and response/efficacy of the RBP is established." In many cases, PD markers for efficacy do not exist and hence biosimilar manufacturers are forced to carry out CCTs.

Since the adoption of the WHA 67.21 the Secretariat has shown a great degree of resistance to amend the WHO Guidelines. Instead of updating the guidelines, WHO reinforced its 2009 Guidelines framework through three more guidelines viz. Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Regulatory Assessment of Approved rDNA-derived biotherapeutics and the WHO Questions and Answers on Biosimilar products.

The document "Regulatory assessment of approved rDNA-derived biotherapeutics" is a clear example of the resistance to revise the 2009 SBP Guidelines as it states: "Products already approved under the pre-existing regulations will need to be reassessed to ensure that they meet the new requirements". This means that all the products that were in the market before the adoption of the 2009 SBP Guidelines should be reassessed.

The Secretariat further defended its stand by stating that the term "update" does not mean a revision of the 2009 Guideline, arguing that the adoption of the three documents fulfilled the obligation under the WHA resolution. The Secretariat's explanation compels us to state the dictionary meaning of the term update i.e. "to change (something) by including the most recent information".

Following the Scientists' Memorandum and CSO letter, the WHO Director-General agreed to set up a process to revise the WHO Guidelines in a letter dated 29th July 2019. First, the ECBS would review scientific evidence related to the set of WHO recommendations for the evaluation of SBPs regarding pharmacodynamic and pharmacokinetic studies. Second, the Expert Committee on Selection and use of Essential Medicines (EML) would review the evidence. Third, there would be a systematic review of all the scientific evidence on biosimilars.

Scientists and CSOs make formal request and presentation

Upon request of the ECBS secretariat a formal request along with supporting evidence was submitted to the ECBS requesting the review of the Guidelines as mandated under WHA 67.21. This formal submission was followed by a teleconference on 10th October 2019. From the WHO side experts who were part of the development of the WHO Guidelines participated in the teleconference. However, nobody raised any question on the evidence. One of the

proposals agreed during the teleconference was to highlight the part of the Guidelines which hampers access.

The presentation of Prof. Hubb Schellekens before the ECBS on 21st October focused on Section 10 of the Guidelines which requires CCT for the marketing approval of a biosimilar. The presentation was accompanied by a written submission, which made the following proposals complementing the Scientists' Memorandum:

- Biomolecular structure analyses have now, both technically and empirically, established rigorously that the structural comparability information is sufficient for regulatory purposes. Therefore, all efficacy examination requirements should be removed from regulatory guidelines. Detailed structural characterization requirements should be a part of the guidelines. The demonstration of similarity in quality is sufficient to assure the safety and efficacy of most products. The emphasis on quality testing should focus on impurity profiles and potency.

- While biomolecules are indeed structurally distinct from small molecules sufficient to cause regulatory uncertainties about structure, their pathways of efficacy are known with certainty at the molecular-cellular levels. Therefore, *in vitro* tests examining the triggering of molecular-cellular pathways involved in efficacy are more than sufficient as efficacy analyses for regulatory purposes. Efficacy for biomolecules should be evaluated *in vitro*, not *in vivo*, for biosimilar macromolecules. All efficacy-directed examinations *in vivo* should be removed from the guidelines and be replaced by in-vitro test requirements.

- Given the demonstration of structural similarity and in-vitro surrogate efficacy analyses, further comparability analyses for demonstration for non-inferiority should not ordinarily be required. However, if and where necessary, evaluation of comparative potency in cellular-molecular analyses *in vitro* would be deemed sufficient for regulatory guidelines.

- Immunogenicity studies are only needed if SBP does not match the critical quality attributes related to manufacturing.

- Interchangeability and extrapolation to all indications should be the default unless there are scientific reasons to deny extrapolation.

The submission also made the following proposals:

- To organize an expert consultation of experts free of conflict of interest to be coordinated or in coordination with the Committee on Essential Medicines and Science Division. The purpose of this expert consultation is to have an in-depth discussion on the major issues related to the 2009 SBP Guidelines, especially the requirement of comparative clinical trial, interchangeability and extrapolation etc.

- To make public the ECBS responses to the above-mentioned proposals as well as those in the Memorandum with supporting verifiable evidence.

During the discussions no one raised concerns on the proposal that evaluation of comparative potency in cellular-molecular analyses *in vitro* is enough to satisfy the efficacy requirements for the regulatory purposes. All the questions were focused on whether CCT is required to address the safety concerns.

[It was unfortunate that the ECBS Chair and the Secretariat denied permission to circulate the printed version of the submission and the supporting documents to ECBS Members at the 21st October meeting.]

Scientists from across the globe are questioning the rationale behind CCTs. According to them, CCTs do not provide any valuable information on efficacy, safety, and immunogenicity – the three most cited reasons for conducting CCTs. One of the scientists from among the growing scientific community, Francois-Xavier Frapaise, in his paper states that: "Clinical trials are not powered to detect meaningful differences in the safety profiles of biosimilars, and when numerical imbalances in adverse events are observed during clinical development of a biosimilar, the interpretation of limited differences is very difficult, only large cohort studies may detect differences, if there are any, in safety parameters." Questioning the utility of clinical trials for cancer treatment in which biotherapeutic drugs are often administered in combination with other drugs, another scientist Christopher J Webster explains that clinical trials are nothing more than a "ritual".

Regarding efficacy aspects, the Scientists' Memo states that the clinical trials are of little use. Instead of clinical trials they proposed: "*Regulators are of the opinion that if appropriately designed and performed such PK/PD studies are often more sensitive to detect potential differences in efficacy than trials using clinical endpoints. They also demand that the efficacy should be studied in conditions providing the highest sensitivity to detect differences. They argue for making well-designed PK/PD studies the norm rather than the exception*". Webster et all writes in a recent article that "*no biosimilar that has been found to be highly similar to the reference by both analytical and human PK studies has been failed to be approved because it was found not be clinically equivalent to its reference in a powered study".*

Though the CSO Letter and the submission to the ECBS requested for reasons with verifiable evidence for its decision, the executive summary does not provide any reason or evidence for its decision.

It fact the WHO staff who is Group Lead for Norms and Standards for Biologicals was one of authors of the 2009 WHO Guidelines. Therefore, the consideration of the request for review by ECBS also involves procedural lapses. Apart from the above mentioned WHO staff, at least two more persons involved in the drafting of the WHO Guidelines attended the 70th ECBS Meeting which considered the request for review. This could have resulted in the decision to maintain the status quo .

The refusal of the ECBS to provide any verifiable reason/evidence for its conclusion and the refusal to hold an open consultation of experts shows the non-transparent way in which it functions. The ECBS's defence of its indefensible position and the non-transparent way of working raises serious questions on the accountability of WHO and ECBS. The lack of accountability in the functioning of expert committees like ECBS gives way to a few people holding the health of millions of people at ransom without any verifiable evidence to support their views.+