

# Revision of the World Health Organization's Guidelines on Similar Biotherapeutic Products: A Scientific Memo to WHO

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## Summary

A revision of the WHO's Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), in place of a Q&A, is urgently needed to enhance the knowledge and effectiveness of regulatory agencies based on scientific evidence. This should be based on the following scientific principles:

1. Demonstration of biosimilarity in quality is sufficient to assure safety and efficacy of most products
  2. Emphasis on quality testing should focus on impurity profiles and potency
  3. Well-designed pharmacokinetic/pharmacodynamic (PK/PD) studies will be sufficient, if clinical studies are needed
  4. Immunogenicity studies are only needed if SBP does not match the critical quality attributes related to manufacturing
  5. Interchangeability and extrapolation to all indications should be the default, unless there are scientific reasons to deny extrapolation.
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## Background

The World Health Assembly adopted a resolution (WHA 67.21) in 2014 asking the Secretary-General to convene the WHO Expert Committee on Biological Standardization to update the 2009 Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) in the context of technological advances in characterization of biotherapeutic products and fast-expanding national regulatory needs and capacities. The goal of this update was to increase access and affordability of biosimilar products across the globe. After consultation with several stakeholders, the WHO secretariat concluded that instead of a formal update, a better approach was a comprehensive Q&A document about the current guidelines. Although the draft Q&A has been published, a serious concern remains among the scientific community that presenting guidelines as a Q&A document alone does not serve the intended purpose. A revision of the current guidelines is still needed, as mandated by the WHA 67.21, to expand availability of safe and effective biosimilars.

## Rationale for Urgent Revision of the WHO Guidelines

The leading principles on which the WHO guidelines are based are *“the guidelines will serve as living document that will be developed further in the line with the progress in scientific knowledge and experience”* and also that *“it is expected that a guideline on the scientific principles for evaluation of SBPs will help harmonize the requirements worldwide and will lead to greater ease and speed of approval and assurance of the quality, safety and efficacy of these products.”*

These principles argue for a revision of the WHO guidelines rather than providing a Q&A document to better educate the national regulatory agencies about how to interpret the current guidelines. The current draft Q&A is far from perfect and will need major revisions. It is more than an explanation of the current guidelines, as it corrects and updates the guidelines; for instance, when discussing the need for animal data. Moreover, the European Medicines Agency (EMA) experience shows that it is possible to adapt the guidelines according to the progress of scientific knowledge and accumulation of experience by publishing new versions.

Another drawback of not issuing a revision is the gross misuse of the WHO guidelines by pharmaceutical companies. Using own interpretation of the sometimes unclear and outdated WHO guidelines as arguments, pharmaceutical companies are protecting their market power in Lower Middle Income Countries (LMICs) by putting pressure on governments to refuse marketing authorization of biosimilars. They have also sued regulatory agencies that have already approved biogenerics in order to invalidate marketing authorizations. Another form of litigation in LMICs is suing the government for issuing pro-competitive drug regulations that fulfil the mandate of WHA 67.21 to Member States “*to work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to quality, safe, efficacious and affordable biotherapeutic products, including similar biotherapeutic products*”. These three identified forms of legal actions to block competition always use, as an underlying argument, the fact that the country or the sanitary agency in a particular case has not followed WHO guidelines.<sup>1</sup>

As affordability is one of the pillars of the WHO regulatory approach next to quality, safety and efficacy, the revision of the guidelines should especially concentrate on the safety of SBPs, the need, if any, for clinical trials, extrapolation, interchangeability, and immunogenicity.

### **General Arguments of the WHO for a Specific Regulatory Pathway**

The arguments, formulated in 2010, for a specific regulatory approach as stated in the WHO guideline are as follows:

1. The approach established for generic medicines is not suitable for development, evaluation and licensing of SBPs since biotherapeutics consist of relatively large and complex proteins that are difficult to characterize.
2. Some clinical studies will be required to support safety and efficacy as clinical performance of biotherapeutics can also be much influenced by the manufacturing process. SBPs are manufactured and controlled according to their own development since the manufacturer of an SBP normally does not have access to all the necessary manufacturing information on the originator product.
3. Even minor differences in the manufacturing process may affect the pharmacokinetics, pharmacodynamics, efficacy and/or safety of biotherapeutic products.

There are several reasons to revisit the above-mentioned arguments on the need for a specific regulatory pathway for SBPs, besides the classical regulatory approach for small-molecule generic products. Some of them are given below:

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<sup>1</sup> See for example the lawsuit by big pharma (AFIDRO) against the Ministry of Health of Colombia in order to get the Supreme Court to invalidate the presidential decree that contains the requirements for marketing authorization for biologics, including biogenerics. Another example is the preliminary injunction issued by a judge against the regulatory authority of Ecuador after it approved a generic version of bevacizumab. The legal documents for both cases are available, if needed.

1. The methods to analyze proteins have improved dramatically in the last decade reducing the possibility that a difference between SBP and Reference Biotherapeutic Product (RBP) is missed, which has possible clinical consequences. These methods allow full characterization of proteins, in detail, regardless of their size and complexity. For instance, we have seen a ten-fold increase in sensitivity to identify different glycoforms of glycoproteins such as shown for epoetins and monoclonal antibodies.
2. The technology and also the experience of scientists involved in the production of biotherapeutics have matured in the last 20 years. The overall quality of these products has improved, and the number of safety issues associated incidents has been extremely low. These evolutions have greatly reduced the likelihood of a difference between SBP and RBP with a clinical impact.
3. With advancement in technology, the best practices for the production of different biotherapeutics have become highly comparable. Also, the hardware and ingredients used in the production are similar and sourced from the same limited number of suppliers. The downstream processing is always a combination of affinity, ion-exchange, size exclusion chromatography and filtering steps that is equally adopted in the production of SBPs.
4. The statement that even minor differences may affect safety and/or efficacy of biotherapeutic products needs more clarity in 2019. Earlier, there were few examples of safety and efficacy concerns caused by manufacturing changes in the marketed biotherapeutics, though a manufacturer of a biopharmaceutical on average introduces one major manufacturing change a year in their production process. There are no reported safety issues with the current SBP in the European market. More than 35 SBPs have been registered in the EU, and there is experience now in more than 700 million patient days of treatment, all without a single SBP-related side effect reported.

What has been missing in these general considerations is the discussion on the specific properties of biotherapeutics in determining the safety of SBP.

The most frequent side effects of biotherapeutics are local reactions at the injection site. These side effects are in most cases caused by the formulation and not by the active molecules. Biotherapeutics have lower toxicity because they act by binding ligands either on the surface of cells or ligands that are free-floating in extracellular fluids, including the blood and lymph. Unlike small molecules, biotherapeutic proteins are degraded into amino acids (and sometimes sugars) that are normal constituents of body metabolism. The side effects of biotherapeutics are often the result of the pharmacodynamic effect. Hence, if the SBP has the same potency as the RBP, their side effect profiles will be the same.

The major problem with biotherapeutics is immunogenicity. Every biotherapeutic is potentially immunogenic to some degree in a small number of patients, even if thoroughly “humanized.” In the majority of cases, however, antibody response against a biotherapeutic leads to no other biological or clinical consequences apart from the loss of efficacy and immune complex formation resulting in infusion reactions and serum sickness. In rare cases in which the biopharmaceutical is a homolog of an important regulating factor, like erythropoietin, the antibodies may lead to inactivation of the endogenous factor leading to major problems like Pure Red Cell Aplasia (PRCA). This was first reported in 2002 after a formulation change in an epoetin product-induced immunogenicity. The new formulation made the product more sensitive to mishandling and aggregate formation leading to an

immunogenic response. Comparative data, including stability studies, are a standard requirement of SBP marketing authorization request, which would avoid such a problem occurring with a biosimilar product. The knowledge about the product factors responsible for immunogenicity has expanded widely making it highly unlikely for a biosimilar biotherapeutic product with the same impurity profile as the RBP to differ in immunogenicity.

### **Extent of Clinical Trials for SBP**

The development of SBP is considered a step-wise process. The basis of its development involves an extensive analysis of different batches of the RBP. On the basis of the physical, chemical and biological characteristics of the RBP, a manufacturer designs own process aiming to have a product which is similar to the RBP. Applying the current WHO guidelines, this similarity should be confirmed by preclinical and clinical studies. However, the logic should be the opposite; preclinical and clinical phases should not be used to confirm findings made during the analytical phase, but to discard any major residual uncertainties remaining from comparative characterization about safety and efficacy. The approach by the regulatory authorities should be that the comprehensive characterization and comparison at the quality level are the basis for possible data reduction in the non-clinical and clinical development. In other words, the more similar the product in physical-chemical and in vitro biological characterization is, the less is the need for a clinical trial.

As it is impossible to quantify the level of similarity established in the laboratory, the approach mentioned above is a difficult concept to put in practice. This is because the advancement in analytical tools makes them more sensitive and therefore more prone to detect differences. As sciences develop, we should expect finding more differences between an SBP and an RBP, rather than less. The issue is not finding differences (which will be found for certain), but their clinical relevance. In reality the regulators use quality data in a yes or no decision about the level of clinical data needed, as stated in the WHO guidelines that “demonstration of comparability of a SBP to its RBP in terms of quality is a prerequisite for the reduction of the nonclinical and clinical data set required for licensure”.

In WHO and EMA guidelines, factors other than comparability drive the option for waiving the confirmatory clinical trial in at least one indication. The WHO guidelines state that in certain cases, comparative PK/PD studies may be appropriate, provided that a) the PK and PD properties of the RBP are well characterized; b) at least one PD marker is a marker linked to efficacy (e.g., an accepted surrogate marker for efficacy); and c) the relationship between dose/exposure, the relevant PD marker(s) and response/efficacy of the RBP is established.

The EMA guidelines offer wider possibilities to waive the comparative trials with a clinical endpoint in at least one indication as they state that:

*“In certain cases, comparative PK/PD studies may be sufficient to demonstrate clinical comparability of the biosimilar and the reference medicinal product, provided that the following conditions are met:*

*The selected PD marker/biomarker is an accepted surrogate marker and can be related to the patient outcome to the extent that demonstration of a similar effect on the PD marker will ensure a similar effect on the clinical outcome. Relevant examples include an absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons, and euglycaemic clamp test to compare two insulins. Magnetic resonance imaging of disease lesions can be used to compare two*

*β-interferons in multiple sclerosis.*

*There may be PD-markers that are not established surrogates for efficacy but are relevant for the pharmacological action of the active substance and a clear dose-response, or a concentration-response relationship has been demonstrated. In this case, single or multiple dose-exposure-response studies at two or more dose levels may be sufficient to waive a clinical efficacy study. This design would ensure that the biosimilar and the reference can be compared within the steep part of the dose-response curve (assay sensitivity, see ICH topic E10).*

*In exceptional cases, the confirmatory clinical trial may be waived if physicochemical, structural and in vitro biological analyses and human PK studies together with a combination of PD markers that reflect the pharmacological action and concentration of the active substance can provide robust evidence for biosimilar comparability.”*

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.

### **Clinical-significant Differences**

Biotherapeutics are considered complex mainly due to their heterogeneity. This heterogeneity is partly the result of the production process, storage and handling, and also naturally occurring, like in the epoetins, growth hormones, monoclonal antibodies. Heterogeneity is often the result of evolution and expands the conditions under which the natural molecules will be active. Many factors in upstream and downstream processing, formulation and handling influence this heterogeneity and act as the main reason for differences between batches and between products.

For regulators, homogeneity and reproducibility are important issues, but these are impossible to achieve with biopharmaceuticals. This may explain why the regulations are confusing and even contradictory, as evident from the following statements and positions:

1. Even the smallest difference can have a clinical impact on safety and efficacy
2. There will always be differences between SBP and RBP
3. Comparability in quality between SBP and RBP is a prerequisite for reduction of need for clinical trial data
4. Clinical data cannot be used to justify significant differences between SBP and RBP.

The above statements do not add up. If there are always differences and these differences can have clinical effects, full clinical data will be needed in all cases. At the same time, there is also the statement that clinical data will not be helpful in justifying these differences.

There is now 12 years of experience with SBP in Europe, Canada, Australia and other regions with dedicated biosimilar regulations. No safety or efficacy issues have been found during the use of SBP, despite known differences between SBPs and RBPs.

In addition, data are available about differences between batches of RBPs collected by the companies developing SBPs. Many of these data are in the public domain and/or reported to

the regulatory authorities. They show that the differences between batches of RBPs are sometimes considerable and larger than what would be accepted between SBP and RBP. However, no clinical effects have ever been associated with these differences notwithstanding the differences in batches.

Hence, most differences have no impact, and the critical differences are either impurities or especially aggregation because they may lead to differences in immunogenicity. The other important difference would be potency, as this may lead to differences in efficacy and safety, considering that the side effects of biotherapeutics are driven by the pharmacodynamic effect of the biopharmaceutical.

### **Interchangeability**

Interchangeability of the SBP for the RBP is currently the most important issue if SBP is to reduce the healthcare costs and increase access. Most expensive biotherapeutics are chronically administered, and the possibility of shifting to the more affordable product is especially important in LMICs. In the current WHO guidelines, each of the words “interchangeability” and “substitution” occur only once.

The discussion on the interchangeability of biosimilars has been initiated by the producers of RBP as a means to protect their markets. Alleging increased risk of immunogenicity, they argue that switching from RBP to SBP is unsafe. The incident with the increased immunogenicity of an epoetin biopharmaceutical resulting in PRCA reported in 2002 was most often used as evidence for this risk. However, the increased immunogenicity was the result of a formulation change and was not related to switching to a new product. Another often-quoted study involves the development of antibodies in factor VIII users after being switched between different originator products<sup>2</sup>. In this case, the loss of efficacy was attributed to neutralizing antibodies. This study, however, was in a small number of patients who differed in their factor VIII gene defect which influences the sensitivity for immunogenicity in hemophilia patients. However, later studies could not confirm this observation.<sup>3</sup>

There is no scientific argument against the interchangeability of an SBP. The immunogenicity of biotherapeutics has been extensively studied over the last 15 years, and there are no data reported in the more than 16,000 papers published that suggest an association between switching and immunogenicity. In the pre-biosimilar era, physicians had been switching RBPs like growth hormones, epoetins, interferons and factor VIII's without any concerns. Recent extensive reviews have found no evidence of negative effects of switching to SBPs. Moreover, in the 12 years of SBPs in the EU, not a single side effect associated with switching has been reported<sup>4</sup>.

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<sup>2</sup> Roussel-Robert V, Torchet MF, Legrand F, et al. Factor VIII inhibitors development following introduction of B-domain-deleted recombinant factor VIII in four hemophilia A previously treated patients. *J Thromb Haemost.* 2003;1(11):2450-2451

<sup>3</sup> Santagostino E, Auerswald G, Benson G, et al. Switching treatments in haemophilia: is there a risk of inhibitor development? *Eur J Haematol.* 2014;94(9):284–289.

<sup>4</sup> Trifiro G, Marciano I, Ingrassiotta Y. Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. *Expert Opin Biol Ther* 2018;18:309–15.

Like the EMA, the WHO does not include a statement on the interchangeability of SBP and leaves the decision to national authorities. Interchangeability is closely linked to reimbursement which in the EU is a national responsibility. However, regulatory agencies from Finland, Germany, Norway and the Netherlands have stated that “biosimilars” licensed in the EU are to be considered interchangeable.

The FDA had the position that the risk in terms of side effects or diminished efficacy of switching should be shown to be equal to the risk of using the reference product without such alternating or switching for a biosimilar to be considered interchangeable. It had issued draft guidance on the studies that needed to be done to get a designation of interchangeability for SBP. However, the FDA is currently reconsidering its position regarding biosimilars because of the slow pace by which SBPs are introduced in the US. The FDA “intends to issue future draft guidance” to “address potential challenges faced by biosimilar sponsors in designing studies that are intended to demonstrate that a proposed biosimilar product is highly similar to a reference product” and “providing appropriate flexibility for sponsors in order to help spur the efficient development of biosimilars without compromising the agency’s rigorous scientific standards for evaluating marketing applications for biosimilars.” It is noteworthy that to date the FDA has not approved any interchangeable biosimilar product.

In Australia, the Pharmaceutical Benefit Advisory Committee (PBAC), advising the government about reimbursements of drugs based on cost-benefit analysis, has issued a statement that biosimilar substitution at the pharmacy level is acceptable when there is “absence of data to suggest significant differences in clinical effectiveness or safety compared with the originator product” that argue against such action.

In order to avoid that the position of the WHO is used as an argument against substitution, which would substantially increase the access to SBP in LMICs, WHO should accept the position that SBP is in principle interchangeable unless there are scientific reasons for the National Regulatory Authority (NRA) to deny this designation. This should be stated clearly in the revised guidelines. The WHO may adopt a statement as the FDA states: “there is no clinically meaningful difference between the SBP and the RBP” and let the payers decide on accepting them as interchangeable.

### **Immunogenicity**

Since the release of the WHO guidelines, the immunogenicity of biotherapeutics has been extensively studied, and this has led to much more insight into its causes and consequences. Immunogenicity is a property of biotherapeutics in general. It is difficult to predict the level of immunogenicity of a protein, but the question in the case of an SBP evaluation is its immunogenicity compared to the RBP.

Biotherapeutics have intrinsic and extrinsic immunogenicity. The intrinsic immunogenicity is dependent on the amino acid sequence, which determines the two- and three-dimensional structure of the protein. Biotherapeutics can potentially be “processed” (i.e., digested in endosomes) by antigen-presenting cells (APC), and fragments of the polypeptide chain can be

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Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability of Biosimilars: A European Perspective. *BioDrugs* 2017;31:83–91

Inotai A, Prins CPJ, Csanadi M, Vitezic D, Codreanu C, Kalo Z. Is there a reason for concern or is it just hype? - A systematic literature review of the clinical consequences of switching from originator biologics to biosimilars. *Expert Opin Biol Ther* 2017;17:915–26.

presented to T-cells. Humanized biotherapeutics are typically made up of amino acid chains that are the same as found in humans, notwithstanding genetic diversity. Peptide fragments produced from these do not typically activate T-cells when “presented” for antigen recognition. Non-human sequences are the main drivers of the classical immune response. This type of immune response is typically seen with biopharmaceuticals of non-human origin like microbial asparaginase and streptokinase. No difference in the intrinsic immunogenicity can be expected if the quality of the two products is shown to be similar, because the regulations demand the SBP have the same amino acid sequence as the RBP.

There is a lot of speculation in both the SBP regulations as well as the scientific literature about the immunogenicity of glycan structures in glycoprotein and the possibility that the differences in glycosylation may lead to differences in immunogenicity. However, there is no evidence in the literature about the immunogenicity of glycan structures. Hypersensitivity reactions to non-human glycan structures on biotherapeutics produced in animal cells have been described, but these were based on pre-existing (“natural antibodies”). These hypersensitivity reactions seem to be geographically determined to suggest the pre-existing antibodies to be induced by infections endemic in specific regions.

In most cases, biotherapeutics are human proteins towards which most patients are immune tolerant. Their immunogenicity is driven by extrinsic factors of the product, product- and process-dependent impurities. In almost all cases, aggregation has been identified as the main immunogenic factor. Although there is a lot of speculation in the literature of the role of host cell derived impurities as immune stimulants such as C-G rich bacterial DNA or endotoxins, well-known activators of Toll-like receptors, evidence of their actual role in biotherapeutics is lacking. In any case, if the SBP and RBP have comparable purity and levels of impurity and especially aggregates, there is no reason to suspect differences in immunogenicity and to ask for immunogenicity studies. An exception could be for products which can induce neutralizing antibodies to important endogenous factors like the epoetins, or life-saving products for which there is no alternative and of which efficacy may be lost by neutralizing antibodies such as enzyme-replacement therapies.<sup>5</sup>

### **Extrapolation of Indications**

The regulatory principle for approval of any SBP is the use of an abridged procedure. Without providing a reduction of the data package compared to a full dossier that was required from the producer of the RBP, the purpose of introducing SBPs cannot be served. Reduction of the data package concerning clinical similarity has the highest impact on the cost and complexity of developing a SBP. This consideration makes the extrapolation of indication the most important aspect of the amendments to the WHO guidelines as it will have the biggest impact on affordability and access to these products in LMICs.

The WHO guidelines state that if similar efficacy and safety of the SBP and RBP have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the RBP (not studied in independent clinical studies with the SBP) may be possible. However, the guidelines have the following conditions:

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<sup>5</sup> Baldo BA. Enzymes approved for human therapy: indications, mechanisms and adverse effects. *BioDrugs*. 2015 Feb;29(1):31-55.



- Usage of a sensitive clinical test model
- Ensuring same clinically relevant mechanism of action and/or involved receptor(s)
- Sufficient characterization of safety and immunogenicity of the SBP.

If the efficacy trial used a non-inferiority study design and demonstrated acceptable safety and efficacy of the SBP compared to the RBP, the applicant should provide convincing arguments that this finding can be applied to the extrapolated indications. For instance, results from a non-inferiority trial in an indication where a low dose is used may be difficult to extrapolate to an indication where a higher dose is used, from both efficacy and safety point of view.

Two of the conditions for extrapolation in the WHO guidelines are not well founded in science. One of the major clinical-relevant characteristics of biotherapeutics is their high degree of specificity. Factors like epoetins, the interferons, growth hormone, etc. react with specific receptors. This receptor activation will be the same in all conditions. Monoclonal antibodies, which neutralize Tumor Necrosis Factor (TNF), will do that with the same specificity in Rheumatoid Arthritis (RA) as well as Psoriasis, Crohn disease or any other disease condition. Whether this activation or neutralization leads to an effect is dependent on the pathophysiology of the disease condition and is independent of the biopharmaceutical. Hence, if an SBP is shown to be comparable in quality including in vitro PD markers, it is hard to imagine differences in the clinical efficacy or safety in the different indications of the RBP.

The dose-effect relations of biotherapeutics in patients are not linear, but bell-shaped. In most cases, the dose-response of biotherapeutics is not known, but most labeled doses of these products are in the plateau phase of the curve. At that level, there is no sensitivity for showing differences in potency between products, neither to show bioequivalence or non-inferiority. At a low dose, in the ascending part of the dose-response, relevant differences in clinical activity will show up. Hence, a low dose will be more informative than a high dose in contrast with the suggestion in the WHO guideline.

Again it is difficult to justify the assertion that if SBP and RBP have the same potency, their safety and efficacy may differ in the different indications. The guidelines should make extrapolation the default position for a SBP, which NRA can always deny if there are convincing scientific arguments. The lack of clinical trials in all indications is now used by the manufacturers of RBP to create doubts about SBPs. A clear, science-based position of regulating bodies will improve the acceptance of the SBPs by prescribers and patients.

## **Conclusion**

The revision of the WHO SBP guidelines should be guided by the following principles:

1. Demonstration of biosimilarity in quality is sufficient to assure safety and efficacy of most products
2. Emphasis in the quality testing should focus on impurity profiles and potency
3. Well-designed PK/PD studies will be sufficient, if clinical studies are needed
4. Immunogenicity studies are only needed if SBP does not match the critical quality attributes related to manufacturing
5. Interchangeability and extrapolation to all indications should be the default, unless there are scientific reasons to deny extrapolation.

**Addendum: In vitro head-to-head comparison for full biowaiver of “comparator” efficacy trials.**

The efficacy of humanized biotherapeutics in any indication is primarily based on the affinity towards the biomolecule it is intended to bind with. Such affinity can be precisely quantified in cell-free experiments that measure the binding constants when different proportions of the ligand and receptor are present in solution. The dissociation constant ( $K_d$ ) of a pre-formed receptor-ligand; or the association constant ( $K_a$ ) of formation of a receptor-ligand complex can be accurately and precisely measured by a variety of techniques. If a manufacturer is able to demonstrate that the efficacy of an SBP for a given indication is predicated on the binding affinity of the SBP to a specified cognate ligand and that the binding constant of the RBP is statistically indistinguishable from that of the SBP in 3-10 experiments, this evidence may be considered both **necessary** and **sufficient** by the regulator to grant biowaiver of efficacy trials, especially head-to-head comparison with the RBP.

A cell culture assay may similarly be used to demonstrate "similar" efficacy with a RBP, if the efficacy of the RBP is predicated on its ability to transduce a signal to the living cell when it binds to a receptor on the cell's surface. An analogy may be drawn with the importance that toxicologists accord to assessing small molecule toxicity through evaluation of the signal transduction through G-Protein Coupled Receptors (GPCRs) and the *hERG* channel, etc. If a manufacturer can demonstrate “equivalence” in the strength of the signal transduced via a specified receptor in a specified cell line by a RBP and SBP in a cell culture assay, this evidence can be considered **sufficient** by the regulator to conclude that no efficacy trials are necessary.

Such biowaivers can potentially do away with un-needed clinical testing and dramatically reduce the time-to-market, as it is the case nowadays with small molecule generics. The mechanism is also favorable for patients in need of SBPs, who are currently denied access on account of the long duration of the regulatory diligence that the current guidelines insist upon.

This possibility of full biowaiver should be included in the updated WHO guidelines.

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