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The Opportunities and Challenges Involved in Registration of Similar Biotherapeutic Products in Emerging Countries

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ABSTRACT

Although global biosimilars market looks attractive and continue to grow, the regulatory and operational hurdles remain in emerging regions. Many emerging nations are establishing biosimilars regulatory pathways, giving sponsors opportunities to select research sites strategically to optimize overall development timelines and achieve registration goals. Implementing studies across countries with varying regulations involves layers of complexity, but these challenges can be overcome with in-depth knowledge of each local environment and early strategic planning.Due to the influence of EMA and U.S. FDA regulatory precedents, such a move would likely lead to harmonization globally in the long term. In fact, guidelines from several countries in emerging regions, notably Singapore, Malaysia, India, Saudi Arabia and Egypt (as well as in Canada and Australia, as they largely follow EMA guidance), already provide a certain degree of comparable harmonization in requirements and even include flexibility regarding data generated with reference products registered outside their jurisdiction if such products are marketed in key reference markets and/or meet certain requirements.WHO's role in building the technical expertise in NRAs worldwide is recognized as an important contribution towards better regulation of biotherapeutics as a whole. One of the specific tasks in coming years will be the provision of appropriate scientific principles for the evaluation of biotherapeutics as standalone products.

KEY WORDS*:* Biosimilar, Similar biotherapeutic product, Registration

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1. INTRODUCTION:

As per World Health Organization's definition, Biosimilar means "a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product"[1]. Biosimilars can be less expensive than the originator biologics and can potentially provide increased access to biologic therapies including monoclonal antibodies and therapeutic proteins that treat life threatening cancers, anemia and immunological diseases. Global biologics sales have grown to more than $100 billion. As an increasing number of biologics face patent expiration, biosimilars offer a major opportunity for drug developers. By 2020, patents will expire on twelve biologics with global sales of more than $67 billion[2].

By 2015, sales of biosimilars are expected to reach between US$1.9-2.6 billion, up from US$378 million for the year to the first half of 2011. Potentially, this market could be the single fastest-growing biologics sector in the next five years – albeit from a small base – spurred by the convergence of major

dynamics that will see new biosimilars enter the US market by 2014, bring additional molecules to Europe through 2015, and open up oncology kand autoimmune disease areas to biosimilars for the first time ever[3].

The changing outlook for biosimilars comes at a time when the global pharmaceutical market is feeling the combined impact of two key events: a period of unprecedented patent expirations on many of the world's largest pharmaceutical brands, and a financial crisis that has required healthcare systems to make significant and sustained cost reductions.

Because of the large and complex nature of biological molecules, biosimilars cannot be guaranteed to be identical to innovator biologics. Therefore, regulators have been concerned that undetected differences in biosimilars may result in reduced efficacy or different adverse reactions. Regulators have been working towards abbreviated licensing pathways to speed up the availability of biosimilars, but efforts have been slowed by complex issues related to demonstrate comparability of biosimilar with the safety and effectiveness of innovator biologics. European Medicines Agency (EMA) has issued guidelines in 2006 have helped Europe to become the most robust market, with 14 biosimilar products approved to date and several applications are now undergoing review. FDA draft guidances issued in 2012 are expected to encourage more biosimilars development in the U.S. where development has been lagging. Many emerging nations are developing biosimilars regulations, advancing opportunities to develop biosimilar products in these attractive but challenging markets.

2. OPPORTUNITIES:

More than 80 biosimilars are now in development, and the global biosimilars market is expected to reach $3.7 billion by 2015[4].The emerging pharmaceutical markets of Asia, Latin America and Eastern Europe offer especially attractive locations for biosimilars research and commercialization. Not only are these emerging nations characterized by growing middle classes and increasing healthcare expenditures, they are typically generics-driven pharmaceutical markets; this provides a positive medical and commercial environment for biosimilars.

Multinational biosimilar development programs include emerging nations to balance efficient patient enrollment, various levels of regulatory requirements and potential market opportunities. Variations in enrollment efficiencies and regulatory requirements can support biosimilar market registration sooner in some emerging countries, allowing developers to pursue strategies to earn registration first in emerging markets, then introduce biosimilar products in Europe and the U.S.

A number of top-selling biologic brands, including Herceptin, Enbrel, Humalog, MabThera, Remicade and Aranesp, are due to lose product patent protection over the next five years, opening up a wealth of new possibilities for biosimilars players. Key therapy areas such as cancer, diabetes and rheumatoid arthritis (RA) will spearhead this new wave of biosimilars, with attention focused on the real prizes of anti-TNF MAbs, MAbs for oncology, and insulins.

Table 1: Patent expiring drugs[5]

Brand Name	Paten Expiry	INN	Company Name
Remicade	2014	Infliximab	J&J
Humira	2016	Adalimumab	Abbott
Avastin	2018	Bevacizumab	Roche
Mab/reditux	2015	Rituximab	Roche/biogenidec
Hereceptin	2015	Trastuzumab	Roche
Enbrel	2012	Etanercept	Amgen/Pfizer
Orencia	2019	Abatacept	Bms
Aranesep	2016	Darbepoetinalfa	Amgen
Neulasta	2017	Pegpelgrastrim	Amgen
Rituxan	2013	Rituximab	Genentec

Regulators have been working to establish abbreviated licensing pathways to hasten the availability of biosimilars, but efforts have been slowed by issues surrounding requirements necessary for biosimilars to demonstrate comparability to the safety and effectiveness of innovator (reference) biologics. Guidelines issued by the European Medicines Agency (EMA) beginning in 2006 have helped Europe to become the most robust market, with 16 biosimilar products approved to date and two biosimilar approvals have been withdrawn; total 14 biosimilars are approved for use in Europe. FDA draft guidances issued in 2012 are expected to encourage more biosimilars development in the U.S. where development has been lagging. Many emerging nations are developing biosimilars regulations, advancing opportunities to develop biosimilar products in these attractive but challenging markets.

Table.2: Approved Biosimilars in Europe

Biosimilar	INN	Company	Approval Year
Omnitrope	Somatropin	Sandoz	2006
Valtropin		Biopartners	Approved in 2006 and Withdrawn on 10 May 2012
Binocrit	Epoetin Alfa	Sandoz	2007
Epotin Alfa		Hexal	
Abseamed		Medice	
Silapo	Epoetin Zeta	Stada	
Retecrit		Hospira	
FilgrastimRatiopharm	Filgrastim	Ratiopharm	Approved in 2008 and Withdrawn on 20 Apr 2011
Ratiograstim		Ratiopharm	2008
Biograstim		CT Arzneimittel	
Tevagrastim		Teva	
FilgrastimHexal		Hexal	2009
Zarzio		Sandoz	
Nivestim		Hospira	2010
Remsima	Infliximab	Celltrion	2013
Inflectra		Hospira	

Biosimilars also bring clear potential for payers in the emerging pharmaceutical or “pharmerging” markets, such as Brazil, India and China. Here, the need to broaden healthcare coverage to large populations increasingly must be balanced against limited budgets and growing demand for innovative drugs. Biosimilars offer one way of widening access and enabling better value to be obtained from the money spent on healthcare. In some cases (such as South Korea, India and Brazil) they are seen as a key macroeconomic driver of growth, attracting foreign capital by creating manufacturing and R&D centers of excellence.

3. CHALLENGES INVOLVED IN BIOSIMILARS:

While on the surface the market for biosimilars may seem very attractive, several significant obstacles will prevent its smooth growth. For new participants, biosimilars pose very different challenges to those presented by small molecule generics, with more demanding requirements in terms of clinical development, market access, manufacturing and sales and marketing capabilities:

3.1 High Development Cost:

Developing a biosimilar is not a simple process but one that requires significant investment, technical capability and clinical trial expertise. Average cost estimates range from US$100-250 million (various industry sources) if plant development is included (or US$20-100 million for non-plant cost). Whilst lower than the costs of developing a small molecule NCE, they are nevertheless orders of magnitude higher than the costs associated with developing traditional generics, which are typically around US$1-4 million.

3.2.Extensive Comparability Data:

Unlike generics, biologics products are complex large molecules and high molecular weight proteins/peptides; and there is a need to prove the similarity of molecule by generating extensive characterization data. The stringent regulations, as promulgated by EMA and the USFDA, require comprehensive structural and functional analytic comparative data to demonstrate comparability before initiating animal testing and clinical PK/PD studies. Biochemical analytical data and results of in vitro pharmacology assays are used to determine whether in vivo studies are necessary and how they should be designed. PK data are the foundation of the clinical program; trials at a specific dose level or at two different dose levels may be required, depending on the strength of preclinical data. When adequate data are available, sponsors may have an opportunity to progress directly into clinical evaluation. Regulators generally ask to review PK data prior to allowing clinical trials in order to ensure that patients will receive adequate exposure to the biosimilar. The amount of clinical comparability data required is determined case by case and is heavily dependent upon the molecule being developed.

3.3.Clinical study

Biosimilar product development involves Phase-1 and Phase-3 clinical studies to prove its efficacy and safety. For global development programs, selection of reference product and clinical study population, ethnicity, etc become key hurdles. Some emerging markets require that biosimilars be developed locally, including the conduct of clinical trials in local populations. Some, for example South Korea and Taiwan, only require that a certain percentage of local patients be included in multinational studies. When choosing study sites and selecting appropriate reference products, sponsors must give careful consideration to the availability of patient populations appropriate for trials in the target indications. Additionally, prevalence of a targeted disease will vary between countries, making some locations

more attractive than others. However, there may also be more competition for study sites in countries where multiple sponsors are seeking large patient populations for a target indication.

3.4.Drug delivery devices:

Improved delivery devices can add significant value and enhance product differentiation. There are, however, a limited number of drug delivery companies, many of which are already working exclusively with the branded incumbents.

3.5.Supply chain management:

The supply chain for biosimilars will be very different to the current range of generic drugs. Biopharmaceuticals are less stable than chemical based pharmaceuticals and thus require cold chain distribution and have a shorter shelf life. This increases the cost and complexity of distribution.The required capital investment and operating costs of manufacturing will be much higher for biosimilars than for generic drugs.

4. REGULATORY FRAME WORK:

In the 1980s novel biological medicines produced by recombinant DNA technology appeared on the horizon. The biopharmaceutical industry has expanded dramatically over the last 30 years since the first successes of recombinant DNA technology.

Over the last five years, there has been a considerable increase in the range of biotech products with a corresponding increase in their use in multiple therapy areas. At a very early stage, the EMA and the US FDA developed guidelines and points to consider respectively for the development and evaluation of these new products. Such guidance set the scene for regulatory expectations both for clinical trials and marketing authorization. At the global level, WHO produced a series of guidance documents on the quality, safety and efficacy of products prepared by recombinant DNA technology, including specific guidance for certain types of products such as interferons and monoclonal antibodies.

4.1.India:

The government of India, Department of Biotechnology (DBT) and Central Drugs Standard Control Organization (CDSCO), published guidelines for an abbreviated pathway for biosimilars registration in June 2012. India’s guidelines are similar to EU and U.S. guidelines in many aspects, including the

recommendation of a stepwise approach to demonstrating biosimilarity, starting with extensive quality characterization comparing the "similar biologic" against the reference biologics.

The reference product should be an innovator product licensed in India or, if it is not yet registered in India, it should have been licensed and widely marketed for four years in the innovator's country of origin in a jurisdiction with a well-established regulatory framework.

Potential exists for reduced preclinical and clinical testing programs with proof of strong quality comparability and manufacturing process consistency. Nonetheless, there is a requirement to conduct both PD and toxicological studies before initiation of any clinical trial in India. Similar to guidelines in other markets, the requirement for *in vivo* PD studies may be waived if clinically relevant *in vitro* assays are available. Unlike most other markets, however, India's guidelines prescribe detailed requirements for animal toxicological evaluation of the proposed biosimilar, which, depending on the administration route, should include local tolerance testing.

Indian bio-pharma companies carry the advantages of low cost manufacturing and a highly skilled workforce with global expertise. India is also a semi-regulated market with regards to biosimilars, and these factors combined give a definite competitive edge to Indian marketplayers. Firstly, biosimilars developed in-house give a substantial cost advantage as compared to imported biosimilars, therefore being more commercially viable. Secondly, less stringent regulatory framework for biosimilar approvals also helps to maintain low clinical evaluation costs and unhindered product launches. Companies of regulated markets also have an opportunity to develop post-marketing safety and efficacy data by launching its biosimilars in India.

Clinical evaluation parameters in India for biosimilars also contribute to its cost effectiveness. The total cost of developing a biosimilar in India is therefore far lower than elsewhere, ranging between $10 million-$20 million only, and this can lead to biosimilars being sold 25-40 per cent cheaper than the original biologic, therefore extending the economic benefits to patients[6]. The interchangeability of innovator biologics and biosimilars is high in the domestic market, and takes place almost as soon as the product is launched. Therapies in India are primarily chosen by the physician, in consultation with the patient. Companies therefore place high importance on marketing strategies, such as improving brand recall and maintaining competitive pricing. When Dr Reddy's Laboratories launched 'Reditux' in April 2007, the biosimilar version of Biogen Idec/ Genentech/ Roche's 'Rituxan' (rituximab), it was priced at roughly 50 per cent less than the price of the original drug, leading to rapid popularity.

4.2. China:

China has not established a regulatory pathway for biosimilars development, although the guideline for biosimilar is still under the draft stage, there is some indications that the regulatory authorities are considering biosimilars regulation. In general, a biosimilar product is currently considered a new biologic and must complete a full clinical development program, and submission documents and timelines for biosimilars are the same as for all clinical trial applications.

Abbreviated timelines may be possible depending on classification of the product. Early planning and communication with authorities in China is critical to determining whether a product meets the criteria for an abbreviated pathway. In China, biosimilars development generally requires the same amount of time and cost as new product development, but sponsors may be willing to make this investment in order to gain product registration in what is expected to become the world's largest pharmaceutical market by 2050.

Domestic biosimilars have been marketed in China for 20 years. The high number and increasingly wide range of local offerings have left little space for new entrants. Due to the relatively low entry barriers and waves of investments, there are now over 100 biologics (excluding blood-derived products, whole bacterial products and vaccines) in China. Most biologics manufactured by domestic players are first generation biosimilars including rhEPO, rhIFN, rhInsulin, rhIL-2, rhGCSF, rhGM-CSF, and rhGH suggesting innovative MNCs with a complex biosimilar portfolio might have a competitive advantage.

Local manufacturers also benefit from low development costs as well as government support. The average discount for the leading biosimilars in China is 60 per cent, while the average discount is 23% in Europe, 20% in the US and 30% in Japan[7]. Optimisation of clinical development and increasing manufacturing scale are projected to maintain the low-cost advantages of domestic players in the near to mid-term future.

On a global level, partnering with Chinese biosimilar players can provide synergies across multiple functions. Other less regulated emerging markets in Asia and Latin America are also expected to have a surge in demand for biosimilars in the next five to 10 years, of which both the Western and low-cost biosimilar manufacturers anticipate a share.

4.3. Brazil:

Up to 2002, there was no specific regulation for biological products in Brazil. In 2002 the first regulation related to biological products in Brazil (RDC 80/2002) was published. This regulation had

the same pathway for new biological products and copies. The applicant needed to present a full dossier with whole quality information and a complete clinical development (non-clinical data, Phase I, II and III studies data).

Three years later, ANVISA replaced the RDC 80/02 by RDC 315/05, with a new regulation regarding biological products. This regulation still had the same pathway for both new biological products and copies and the applicant was still required to present a full dossierwith the whole quality information and to complete the clinical development (non-clinical data, Phase I, II and III studies data).

In view of the considerable interest and questions both nationally and internationally regarding the regulatory oversight of similar biotherapeutic products, it was necessary to update the Brazilian Regulations related to biological products. Thus, at the beginning of 2010, ANVISA published a draft of a new set of regulations called, a Public Consultation 49/2010 (CP 49/10) and by the end of 2010, the new regulation (RDC 55/2010) was published[8].

This new regulation has different and specific regulatory pathways for new biological products and for copies. This regulation has been proposed for biological products in Brazil and has the classical pathway for new biotherapeutic products, based on a full dossier presentation by the applicant.

For the similar biotherapeutic products, there are two regulatory pathways: a comparative pathway and an individual development pathway. According to the new regulation in Brazil, the new Biotherapeutic products are called new biological products and the copies are called biological products that can be licensed by the comparative pathway or the individual development pathway. The information about the pathway used to license the copies are available in the approval letter, inserts and package of the product.

In the individual development pathway, a reduced dossier can be presented. The applicant needs to present complete data regarding quality issues but it does not have to be comparative. Non-clinical and clinical studies can be reduced, depending on the amount of knowledge of pharmacological properties, safety and efficacy of the originator product. At least one comparative Phase III study (equivalence or non-inferiority) with the originator (new) biological product is mandatory. Extrapolation of indications will not be accepted in the individual development pathway. The comparative data are only provided to characterize the therapeutic effect, while a complete dossier is expected for the license application presenting details on the development, manufacturing, quality control, non-clinical and clinical data.

For the comparative pathway, a biologic product previously authorized in Brazil must be selected as reference product. The comparable biological product is then developed to demonstrate comparability to the reference product in terms of quality, safety and efficacy based on pre-clinical and clinical data.

The Brazilian regulatory authority, the National Health Surveillance Agency (ANVISA), published additional guidelines in 2011 regarding this pathway, especially for interferon-alpha, comparability studies and clinical reports.

Dialogue with ANVISA is strongly recommended to define the requirements for licensing. There is no difference in approval timelines of new biologic drugs compared to comparable biological drugs approved using individual or comparative pathways. In general, approval time for new biologics is about 24 months. ANVISA reviewers carefully consider immunogenicity studies and details on pharmacovigilance plans aimed at minimizing risks to patients.

In Brazil, the use of different biological products (vaccines,biotherapeutic products, monoclonal antibodies, blood derivativeproducts) for different types of treatment is covered by thegovernment through specific Health Programs of the Ministry ofHealth and it consumes a significant portion of the health budget.For example, the biotherapeutic products represent 2% of allmedicines distributed by the government through specificprograms, but represent 41% of total amount that the Ministry ofHealth spends on medicines in specific health programs annually[8].

Similarly, amongst the biological products themselves, monoclonalantibodies represent 1% of the total amount of Biotherapeutic products distributed but account for 32% of total amount spent onbiological products by Brazilian Ministry of Health.Thus, the Brazilian Government has a big interest in these kindsof products especially if they could be produced in large numbersby national and international producers so as to increase theiravailability, reduce costs and improve access. But it is clear thatpotential opportunities to reduce prices and increase access need tooccur with the assurance that the products themselves will be ofhigh quality, safety and efficacy.Updating the biological regulations to deal with this newscenario will have a key role in developing the biological industry inBrazil.

4.4. Mexico:

In Mexico, biosimilars are termed “biocomparable biotech drugs” to avoid issues with certain local trademarks that use the term biosimilar. In 2009, Mexico established general regulatory principles pertaining to biosimilars; specific requirements were further defined in 2011. An important provision is that the innovator product must serve as the reference product, although an approved biocomparable may also serve if the originator reference product is not approved in Mexico.

Further guidance was issued in June 2012, the latest version of the guidelines requires preclinical and clinical studies to demonstrate that the quality, safety, and efficacy of the biosimilar are equivalent to those of the original biologic. It also states that once the biosimilar has demonstrated physicochemical comparability, then the scope of clinical trials required for registration can be reduced depending on the

type of biosimilar. Our primary research suggests that phase III comparative trials may not be required for biosimilars and the main factor influencing the decision will be the product type. Extrapolation of indications is unlikely to be permitted in the Mexican market[9].

Applicants must demonstrate comparability in terms of safety, efficacy and quality profiles, including immunogenicity. It is important to discuss requirements with the Mexican regulatory authority, COFEPRIS, as early as possible. Regulators may require clinical trials to be conducted in Mexico and may have requirements pertaining to studies involving Mexico's participation in global development plans. These issues should be addressed at the time of interaction with the COFEPRIS New Molecule Committee. The scope and extent of comparability trials depend on the level of characterization and comparability available. It is also important to note that risk management plans are required for all biologics and thus biocomparables.

Although there was no regulatory pathway until recently, biosimilars have been available in Mexico for many years. Because of the increasing number of biosimilars coming into the market, the new biosimilar pathway was designed to increase access to biosimilars while maintaining quality, efficacy, and safety. As the regulatory pathway is still fluid, there are a few potential issues that could affect future regulation and subsequent utilization.

Thus far only relatively simple biosimilars have been approved for use in Mexico. As the regulatory pathway will most likely depend on the complexity of the biosimilar, more complex biosimilars may be subject to the same clinical trial requirements as the originator biologic, as described in other biosimilar regulatory guidance.

The Mexican government realizes the potential savings associated with biosimilars and expects them to have large discounts relative to the originator biologic. The government is actively pursuing cost savings through favouring biosimilars over branded agents for government contracts. In addition, the Mexican government will most likely promote the active substitution of biosimilars over the originator biologic. The Mexican biosimilarmarket should continue to grow and develop in the foreseeable future.

4.5. South Korea:

South Korea is the most attractive development venue of the smaller Asia Pacific nations. South Korea's Ministry of Food and Drug Safety (formerly, the Korean Food and Drug Administration) issued guidelines on evaluation of biosimilars products in 2009, consistent with the EMA model. This was followed by guidelines on product specific biosimilars, on immunogenicity of biosimilars and on monoclonal antibody biosimilars. The definition of a biosimilar product is a biotechnological product that is proved to be comparable to an already approved reference product in terms of quality, non-

clinical and clinical evaluation. The scope of biosimilar products is applied to well-characterized recombinant protein products.

The key issue in quality study is 'how similar is similar' because a protein drug cannot be characterized completely by physiochemical methods, which has the potential to affect the efficacy. Full CMC dossier with comparability exercise data are required, including extensive side by side characterization, physicochemical properties, biological activity, immunochemical properties, impurities and purities, specification, and stability. Analytical techniques should utilize state of the art technologies capable of detecting slight differences in quality attributes. The impact of observed differences in the quality attributes should be assessed and then non-clinical and clinical studies should be designed and conducted on the basis of the results. Acceptance criteria in setting up the specification should be established and justified based on the data obtained from analyses using a number of representative lots of both reference and biosimilar products.

Approval of Remsima is a strong indicator of the potential strength of the biosimilars market in South Korea. Corporate and government initiatives offer further evidence. Samsung, for example, is investing $389 million in biosimilars development over the next five years. The South Korean government has announced its goal to control a 22% share of the global biosimilars market by 2020[10].

4.6. Russia:

Although requirements for the registration of biological products are available, Russia has no specific regulation pertaining to biosimilars. Russian legislation on the registration of medicinal products is expected to be overhauled, and requirements for the conduct of clinical studies for biosimilars are now a topic of much discussion. Under current regulations, biologic product registration requirements can be fulfilled either by including Russia as part of a global development program in a multicenter international study, or by conducting a local study. The local study can be conducted within the scope of the full registration process only – that is, with the provision of a full registration dossier.

It is advisable for developers to fulfil this obligation as part of their global product development and include Russia in the mix of countries where international studies will be performed. The pending legislation overhaul is expected to address the issue of requirements for local studies and may even establish data requirements for generic registration, but it is uncertain how fully it will address the data requirements for biosimilar legislation. Russia's market size makes it a key country for consideration for biosimilars development and even for marketing approval submission. Biosimilars projects can succeed in Russia through close interaction with regulatory agencies.

5. DISCUSSION AND CONCLUSION:

Although global biosimilars market looks attractive and continue to grow, the regulatory and operational hurdles remain in emerging regions. Many emerging nations are establishing biosimilars regulatory pathways, giving sponsors opportunities to select research sites strategically to optimize overall development timelines and achieve registration goals.Implementing studies across countries with varying regulations involves layers of complexity, but these challenges can be overcome with in-depth knowledge of each local environment and early strategic planning.

Looking towards the future, there is a trend towards harmonization of reference product requirements. This is seen particularly between the EU and U.S., with possibility that both EMA and the U.S. FDA will permit the use of clinical data with reference products registered in each other's jurisdiction in market applications. Thus, in the future it may not be necessary to conduct global studies that include comparators from each market as long as there is sufficient scientific and regulatory rationale. However, such criteria are yet to be determined.

Due to the influence of EMA and U.S. FDA regulatory precedents, such a move would likely lead to harmonization globally in the long term. In fact, guidelines from several countries in emerging regions, notably Singapore, Malaysia, India, Saudi Arabia and Egypt (as well as in Canada and Australia, as they largely follow EMA guidance), already provide a certain degree of comparable harmonization in requirements and even include flexibility regarding data generated with reference products registered outside their jurisdiction if such products are marketed in key reference markets and/or meet certain requirements.

WHO's role in building the technical expertise in NRAs worldwide is recognized as an important contribution towards better regulation of biotherapeutics as a whole. One of the specific tasks in coming years will be the provision of appropriate scientific principles for the evaluation of biotherapeutics as standalone products.

In conclusion, the rapidly evolving regulatory science in the biosimilar area would benefit from better cooperation, information exchange and collaboration from different NRAs. It is important for all NRAs to work together to have proper regulatory oversight on the clinical use of biosimilar products. Also the sponsor's/applicant should meet and discuss about their development plan with respective NRA in appropriate interval for their acceptance. This will help to ease the NRA review process and early product approvals.

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