WHITE PAPER

Developing Biosimilars in Emerging Markets: Regulatory and Clinical Considerations

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EXECUTIVE SUMMARY

Emerging markets in Asia Pacific, Latin America and Eastern Europe are increasingly important locations for biosimilars development as sponsors pursue multinational programs to gain efficient access to appropriate patient populations. Many emerging nations are establishing biosimilars regulatory pathways, and sponsors now have opportunities to select research sites strategically to optimize overall development timelines and achieve registration goals.

Multinational clinical programs have the added advantage of supporting biosimilars product registration in emerging economies with growing biologics markets. Multinational development strategies pose country-by-country challenges. Implementing studies across countries with varying regulations involves layers of complexity that demand in-depth knowledge of each local environment. In this paper, PPD discusses regulatory and clinical considerations for key emerging markets.

INTRODUCTION

In July 2012, South Korea approved the monoclonal antibody, Remsima™, a biosimilar version of the blockbuster rheumatoid arthritis product Remicade®. Remsima was developed by Korean manufacturer Celltrion.[1] Celltrion's news release noted that Remsima will also be introduced in Asian and South American markets. In the same year, the U.S. Congress enacted the Biosimilar User Fee Act of 2012, which ensures funding of the United States Food and Drug Administration (U.S. FDA) to support timely review of biosimilar applications under the new U.S. biosimilars development pathway per the Biologics Price Competition and Innovation Act (BPCIA) of 2009.[2] These events, half a world apart, point to the continuing evolution of a global biosimilars market and the major role emerging markets will play in its development.

A biosimilar is a biological product that is highly similar to an approved biologic and has no clinically meaningful differences in terms of safety, purity and potency, compared to the branded "reference" biologic product. 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.[3] 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.[4]

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 14 biosimilar products approved to date and seven now undergoing review.[5, 6] 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.

OPPORTUNITIES IN EMERGING MARKETS

More than 80 biosimilars are now in development, and the global biosimilars market is expected to reach $3.7 billion by 2015.[7] 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.

However, multinational programs require high levels of expertise and country-by-country planning to implement biosimilars studies across multiple locations with varying regulatory requirements and operational considerations.

EVOLVING REGULATIONS POSE CHALLENGES

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. Manufacturing processes also pose challenges related to quality assurance. Current regulations for biosimilar marketing approval require sponsors to demonstrate that the biosimilar is comparable to the reference biologic in analytic characterization and quality. Biosimilars also must demonstrate comparable clinical response—that is, developers must show that there is no clinically meaningful difference between the biosimilar and the reference product in terms of safety, purity and potency or effectiveness.

EMA, FDA and WHO Frameworks

Guidances developed by EMA, the U.S. FDA and the World Health Organization (WHO) set out general principles for demonstration of comparability in terms of quality, safety and efficacy.[8, 9, 10] These guidances generally recommend a risk-based, stepwise development approach that requires nonclinical *in vitro* and *in vivo* comparability studies as a first step. Evaluation begins with functional and physiochemical characterization and quality comparability assessments. Pharmacokinetic (PK) and pharmacodynamic (PD) studies are followed by clinical safety and efficacy trials. In certain cases, PK/PD studies may be sufficient to demonstrate comparability.

Although the EMA and U.S. FDA regulatory frameworks share many similarities, there are several differences. The U.S. FDA draft guidances state more explicitly that robust comparability of physiochemical, immunochemical and functional properties may enable a smaller or more focused clinical program with the potential, in some cases, to conduct clinical studies with reduced trial populations. Another difference is the question of interchangeability—the automatic substitution of a biosimilar for an originator biologic without prescriber input. Currently, EMA guidelines do not address interchangeability whereas interchangeability is clearly defined in U.S. law (BPCIA). However, the U.S. FDA has yet to issue specific guidelines on how it intends to implement BPCIA provisions on interchangeability. The U.S. FDA states that it will continue to consider the type of information sufficient to enable regulators to determination if a biosimilar product is

interchangeable with the reference biologic.

Patchwork of Rules Across Emerging Markets
Over time, the U.S. FDA, EMA and WHO regulatory frameworks will help to increase harmonization of biosimilars licensing pathways but regulation still varies widely across emerging nations. Some, notably India, Singapore, Malaysia and South Korea, have issued biosimilars guidelines consistent with the EMA model. Others, like Russia and China, have neither specific regulations nor guidelines; these countries regulate biosimilars in the same way as they do new biological products, requiring that they comply with similar requirements to earn market approval.

REGULATORY CONSIDERATIONS IN EMERGING MARKETS

Key regulatory considerations pertaining to biosimilars development in emerging markets are as follows:

+ The selection of reference products for a given country
+ Data requirements necessary to demonstrate comparability for marketing approval
+ Whether clinical trials must be conducted in the country in order to obtain local marketing approval

Reference Product Considerations
Sponsors generally must demonstrate a biosimilar's comparability with a reference product licensed in the given country. Innovator companies sometimes market the same biologic under different brand names in different markets. For example, rituximab is marketed as Rituxan® in the U.S. and as MabThera® in other parts of the world. To address these differences, two reference products may be included in a single study. Selection of reference products is based on commercial opportunities in targeted markets and on goals for marketing approval in the U.S. and EU. The place of manufacture of the reference product is another important consideration. Availability of the reference product in a given country and the regulations governing the import and export of pharmaceuticals will impact clinical trial supplies, as will patent and exclusivity considerations. In addition, some countries permit the use of certain data generated with a comparator registered elsewhere if the sponsor can demonstrate that the comparator used in the study was manufactured at the same site as the reference product registered in the jurisdiction where the biosimilar application is being filed.

Requirements for Comparability Data
The strictest regulations, as promulgated by EMA and the U.S. FDA, 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.

When the innovator biologic is approved for more than one indication, sponsors may use data extrapolation to apply for regulatory extension of biosimilar indications. If comparability has been demonstrated for one indication, it may be possible to argue that the biosimilar will be comparable to the originator product's safety and efficacy profile in other indications that have a

similar mode of action, without conducting additional studies. EMA and the U.S. FDA permit extrapolation on a case-by-case basis. Most emerging countries allow extrapolation of data to streamline registration pathways. The potential for data extrapolation also impacts the strategic selection of indications for a biosimilar development program.

Requirements for Local Studies
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.

OPERATIONAL CONSIDERATIONS IN EMERGING MARKETS

Biosimilars studies are especially complex when conducted across multiple countries with non-standardized regulatory and research environments. Sponsors will encounter challenges, and successful programs require country-by-country expertise to design strategies and to manage team operations. In selecting sites for biosimilars development, sponsors must pay particular attention to investigator and patient recruitment and to issues surrounding clinical supplies.

Investigator Recruitment
Physician recruitment is one of the most challenging operational factors. In locations where the originator biologic is both approved and reimbursed, physicians may be reluctant to expose patients to potential safety risks or to lack of efficacy from an unapproved biosimilar for the purpose of developing a less expensive version. In emerging markets there is a higher likelihood for both physicians and patients to participate in biosimilars trials to gain access to otherwise unaffordable medicines. Even where branded biologics are approved, lack of reimbursement often limits access to these therapies. For example, rituximab is approved but not fully covered for reimbursement in Argentina and Brazil. Study participation gives patients access to free treatment, and care providers are likely to have greater interest in making cheaper versions available to clinical practice.

Research Incentives
Sponsors should understand how research incentives impact recruitment in different study locations. In a country such as Brazil, patients cannot be compensated for trial participation. Physicians, however, are eager for research experience and opportunities to bring funding to their institutions. In countries where all pharmaceuticals are distributed by hospitals and formularies dictate treatment availability, investigator incentives are all important.

Many emerging countries have adopted strict ethical practices to protect large segments of their populations that are vulnerable due to poverty and illiteracy. For example, some Latin American countries require sponsors to provide insurance to compensate patients harmed during research. In some countries, sponsors are required to provide beneficial drug treatment for the lifetime of trial participants.

Depending on the therapy, there may be intense competition for investigators and quality study sites in a given market. For example, many different biosimilar versions of rituximab are being developed for follicular lymphoma, putting great pressure on availability of qualified research sites.

Reimbursement

While regulatory pathways dictate the course of biosimilar development, the availability of reimbursement largely determines patient access to the biosimilar product and, ultimately, the product's market success. In emerging countries, reimbursement ranges widely. Government-sponsored reimbursement plans may cover all or some costs, depending on the given product, the indication or the region where it is dispensed. For example, no key emerging countries provide full reimbursement for rituximab. However, Argentina, Brazil, Mexico and Turkey reimburse for rituximab only when it is used for select indications. And patients pay total cost out-of-pocket in China, India and Russia.

Clinical Supplies Considerations

Clinical supply logistics can be complicated by the choice and number of reference products and their manufacturing sources. It is important to involve clinical supplies experts early to plan and manage regulations and operations within each country and across multinational programs. Key areas to consider are as follows:

+ Product Sourcing - Multiple product sources will be necessary to support international development programs, and strategies surrounding reference product selection should consider manufacturing sources and availability.
+ CMC - Chemistry, manufacturing and control (CMC) regulations are often more detailed in emerging countries as a result of their generics-driven environments. Developers should be aware of stability testing requirements in countries where they plan to do research.
+ Disclosure and Intellectual Property Issues - Though most countries in emerging regions adhere to globally recognized intellectual property (IP) protections, some countries require sponsors to make their confidential information public. Legal experts should be included on biosimilar project teams in the planning stages.
+ Import/export Licenses - Import/export regulations and licenses pertaining to experimental and reference products must be planned and managed on a country-by-country basis. In most countries, the clinical trial must be approved before licenses can be granted.
+ Supply Chain Sensitivities - Supply chain issues are particularly critical for biologics. Research teams must be experts in managing multiple vendors and local infrastructures to ensure on-time deliveries of heat- and humidity-sensitive product across challenging environments.

OVERVIEW OF KEY EMERGING MARKETS

In the following section, a closer look will be taken at key countries in emerging regions.

ASIA PACIFIC

China

China has not established a regulatory pathway for biosimilars development, although there are 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

Table 1: Overview of Key Asia Pacific Countries

	POPULATION	BIOSIMILARS GUIDANCE	TRIALS*
China	1,343.3 m	No	12
India	1,205.0 m	Yes	37
South Korea	48.8 m	Yes	23

* Number of biosimilars trials conducted. SOURCE: Citeline Trialtrove

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.[11] Regardless of project registration, China is an attractive location for sponsors eager to take advantage of quality sites and rapid, efficient patient enrollment.

Investigators have strong incentives to participate in research, but there are long IND lead times. IND approval currently takes from 15 to 18 months. Sponsors can reduce delays by taking advantage of pre-IND consultations when possible and filing near-final protocols. Sponsors should plan two to three months for careful dossier preparation, including preparation for a quick and accurate response to queries which usually come about five months after submission. Using manufacturing sites in China also speeds timelines, and if sponsors plan to market in China, the product must be manufactured in China. Full disclosure of product and study information is required, and China requires sponsors to submit the investigational product to government laboratories for quality testing before study approval. China does not allow import or export of biological samples; all laboratory work must be done locally.

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 biologic.

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.

India's generic-driven domestic biopharma industry has created a strong foundation for biosimilars development, and Indian companies are positioned to become major players in the global biosimilars market. By the time its biosimilars regulatory pathway was issued in 2012, India had already approved more than 25 products designated as 'similar biologics'.[12] A number of Indian companies are well ahead of their regional competitors. Ranbaxy Ltd, for example, announced plans to launch at least three biosimilar cancer products in India by 2015.[13]

With its history of high-quality generic development and manufacturing, India has deep experience in global drug development. India offers large patient populations, quality investigators and efficient timelines, making it one of the most attractive locations for multinational studies. However, biosimilars sponsors will find intense competition from domestic companies, in both research operations and in India's growing biopharma

market. India has large populations of treatment-naïve patients, but sponsors must select study sites carefully in India's large, diverse research landscape. Although English is commonly accepted, translations into diverse languages are necessary for local review boards and informed consent.

South Korea, Taiwan and ASEAN

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. South Korea's growing biosimilars environment includes 11 biosimilars development companies and 13 IND approvals as of 2012.[14]

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.[15] The South Korean government has announced its goal to control a 22-percent share of the global biosimilars market by 2020.[16]

Taiwan and Singapore offer smaller patient populations but have excellent healthcare systems and a generally favorable regulatory environment. Taiwan has established a regulatory pathway for biosimilars registration. The application process and timeline are the same for biosimilars as for new biologics, but submission documents are slightly different. Taiwan requires comparison study data. Clinical trials may be waived if sponsors demonstrate comparability of PK and toxicity data to the reference product.

Singapore initially established guidance on registration of similar biological products in August 2009. The guidance is based largely on the EMA framework. It is important to note that if a particular biosimilar product is already approved by one of Singapore's "reference agencies", namely Australia TGA, Health Canada, EMA or the U.S. FDA, then an abbreviated license pathway can be followed. Otherwise, a complete data package would be required.

Efficient trial approval and relatively short timelines make Singapore an attractive option. Singapore is the most mature research environment among the 10-member nations of ASEAN (Association of Southern Asian Nations), which is evolving a common platform for global clinical research. The economically vibrant ASEAN region is well positioned to offer major biosimilars research and market opportunities.

LATIN AMERICA

Brazil

In 2010, Brazil adopted legislation on biologics that also defines the approval pathway for biosimilars. It should be noted that the term "biosimilar" is not used in Brazil; instead, regulators use the concept of comparability to characterize the scientific comparison between a biologic product and a "comparable" biological product, and to detail requirements that show no detectable differences exist in terms of quality, safety and efficacy in non-clinical and clinical information.

Brazil's regulations provide two pathways available for approval of "comparative biological products" (also called "similar biotherapetuic products" in some

Table 2: Overview of Key Latin American Countries

	POPULATION	BIOSIMILARS GUIDANCE	TRIALS*
Argentina	42.2 m	Yes	14
Brazil	199.3 m	Yes	7
Mexico	114.9 m	Yes	8

* Number of biosimilars trials conducted. SOURCE: Citeline Trialtrove

instances) namely the individual development pathway and the comparative pathway. For the individual development pathway, 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.[17]

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.

The Brazilian biologics market is estimated at USD$5.1 billion. Reimbursement is available in Brazil. Quality investigators and large treatment-naïve patient populations offer an attractive environment for clinical research, but studies conducted in Brazil generally do not enjoy faster timelines or a more favorable regulatory environment compared to other emerging markets. Historically, long delays in trial approval have been a problem. Brazil is instituting an electronic submissions platform and new regulations have been issued to speed startup. In addition, rapid enrollment can compensate for delays.

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.[18] 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.

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 will 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.

Further guidance was issued in June 2012 on the registration process for biocomparable products. To establish the biocomparability of biotechnological products, preclinical and clinical studies are required to be carried out in appropriately qualified specialized research centers, as well as PK/PD, clinical safety, quality and safety studies of the product.

In addition, life sciences and biotechnology have been identified as a key development sector for the Mexican government, which should make Mexico more and more appealing for biosimilars development.

Argentina

In Argentina, the term "biosimilar product" is not officially recognized. For registration, a "similar prod-

uct" is defined as a product that is equivalent to other products approved and marketed either in Argentina or in any Annex I country (including Austria, Belgium, Canada, Denmark, France, Germany, Israel, Italy, Japan, Netherlands, Spain, Sweden, Switzerland, United Kingdom and United States) in terms of the active therapeutic component, formulation, pharmaceutical presentation, dosage, indications, warnings, precautions, adverse reactions, dissolution tests and other correlative data. Differences are allowed regarding size and shape, inactive ingredients, shelf-life and primary packaging. Although this regulation allows the registration of 'biosimilars' using a comparability approach, the details are yet to be determined and provided in a detailed technical guidance.

EASTERN EUROPE

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.

Table 3: Overview of Key Eastern European Countries

	POPULATION	BIOSIMILARS GUIDANCE	TRIALS*
Russia	142.5 m	No	19
Turkey	79.7 m	Yes	5

* Number of biosimilars trials conducted. SOURCE: Citeline Trialtrove

It is advisable for developers to fulfill 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.

Turkey

Turkey published a guidance for biosimilars development in 2008, with requirements that generally follow the EMA framework. The reference product may be registered in Turkey or in other countries. Biosimilars applications must include preclinical data, toxicology and/or clinical documentation. Sponsors must submit Phase I and Phase III clinical data and a risk management plan for each indication. Regulatory review times range from 15 to 18 months. There is a provision to request priority review.

The biosimilars regulatory pathway in Turkey is evolving quickly, and developers will need to stay up-to-date as they consider including this country in their development plans.

CONCLUSION

As the global biosimilars market continues to grow, emerging regions play an increasingly important role. 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.

Regulatory and operational hurdles remain. 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.

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