Biosimilars 2.0
Guiding principles for a global “patients first” standard

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In the European Union, biosimilar products have been approved since 2006 under an abbreviated pathway that leverages their similarity to an existing “reference” biological product. The products approved to date are based on recombinant versions of endogenous proteins with well-understood structures and pharmacology, but complicated safety and immunogenicity profiles. The period during the 2000s that included the first reviews, approvals, sale and use of biosimilars is referred to herein as “Biosimilars 1.0.” Over the next several years, a new and advanced tranche of biosimilars will be developed for complex reference products, including medicines used in the treatment of cancer and autoimmune diseases. A global market for biosimilars is developing and this may well foreshadow the beginning of the second era of product development. This Biosimilars 2.0 period will likely be characterized by the development of complex products, global harmonization of standards and the increasing demand for long-term monitoring of pharmaceuticals. The products developed in this period should exhibit high levels of fidelity to the reference products and should be rigorously evaluated in analytical, non-clinical and clinical comparisons. Additionally, Biosimilars 2.0 manufacturers should strive for transparency in their labels and take proactive strides to be accountable to providers and patients for the quality of their products. An important opportunity now exists for the healthcare community, industry and regulators to work in partnership, to outline the appropriate standards for these products and to facilitate increased access while meeting patients’ needs.

Introduction

Over the course of the past decade, the European Commission and European Medicines Agency (EMA) established an abbreviated pathway for biologic medicines, and this pathway was used to launch the first generation of similar biological medicinal products, now widely referred to as “biosimilars.” According to EMA guidelines, the pre-approval evaluation of these products required robust, side-by-side studies of the analytical, non-clinical and clinical similarity of the biosimilar product to the reference product. The resulting “biosimilarity exercise” adopted components of a comparability exercise while acknowledging data deficiencies that result from the reverse-engineering of a finished reference product and production in a discrete manufacturing process. This early period, including the first reviews, approvals, sale and use is herein referred to as “Biosimilars 1.0.” Biosimilar 1.0 products were approved in the European Union (EU) beginning in 2006, and the products approved to date are based on recombinant versions of naturally occurring hormones and cytokines that have well-understood structures and pharmacology, but complicated safety and immunogenicity profiles. Many aspects of the European biosimilar pathway have also been adapted by policymakers around the world.

In the next several years, a large number of innovative biologic medicines will reach patent expiry. Within this group are...
complex and advanced medicines used in a wide range of therapeutic areas, including the treatment of cancer and autoimmune diseases, where they are often part of the existing standard of care. These complex and multifunctional molecules, including fusion proteins and monoclonal antibodies (mAbs) with targeted and cytotoxic mechanisms of action, will form a substantial portion of the new and advanced tranche of biosimilars.

Commensurate with the increased complexity of the reference products, questions about the standards required for demonstration of similarity and fidelity will emerge. Answers to these questions will likely be provided by an expanding group of regulators, acting nationally or internationally and facilitated by ever-increasing analytical, process development and manufacturing capabilities. In addition, a global market spanning the International Conference on Harmonisation regions, as well as the emerging markets, is now developing. The combination of these factors may well foretell the beginning of the second era of biosimilars, referred to herein as Biosimilars 2.0. While the Biosimilar 1.0 period was characterized by the definition of the initial framework, the Biosimilar 2.0 period will likely be marked by challenges in the manufacturing and clinical development of complex products, global harmonization of standards and the increasing demand for long-term safety and efficacy data for all pharmaceuticals.

In the past few years, global companies with differing levels of skill, experience and resource have begun to develop biosimilars of complex products. An important opportunity now exists for the healthcare community, industry and regulators to work in partnership to outline the scientifically appropriate standards for these complex products to facilitate increased access while meeting the increasingly discerning standards of regulators, physicians, payers and most importantly, patients.

**Biosimilars 1.0**

In the EU, biosimilar products have been approved since 2006 under a specially adapted pathway designed to abbreviate the development and approval of medicinal products claiming to be similar to an existing or “reference” biological medicines product authorized in the European Community. The EU biosimilar pathway is distinct from the rules governing the approval of generic medicines. The biosimilar pathway was framed to address the “advances as well as the limitations of methods and techniques available today for the full characterization of such medicinal products” that include a recombinant protein as the active substance.

To date, 14 biosimilar marketing authorizations have been granted: two human growth hormones, five erythropoietins (comprising two distinct products) and seven granulocyte-colony stimulating factors (comprising three distinct products; Table 1). These 14 biosimilar products have seen varying degrees of uptake, depending on country and product class. These factors have resulted in differing levels of long-term safety and efficacy data in patients treated with biosimilars.

Biosimilar 1.0 products were, in many cases, developed by European biotechnology companies (e.g., Hexal, Stada, Arzneimittel, Sicor, Pliva and Ratiopharm) before the European approval pathway was established. Once innovator patents for products such as human growth hormone, epoetin alfa and filgrastim approached expiry, large generic firms began to in-license biosimilar versions of these products or to acquire the companies developing the biosimilars. Generic companies such as Sandoz, Teva and Hospira entered the recombinant biotechnology market during 2006–2008.

The key features of Biosimilar 1.0 products relate to the circumstances in which they came to market. They are primarily European in origin, were developed and evaluated under the EMA biosimilar review process and were approved following innovator patent expiries. These products are exclusively marketed by generic drug companies (or generic divisions of pharmaceutical companies such as Novartis) and are approaching three to five years of clinical use in some countries.

Biosimilar 1.0 products are structurally related to naturally occurring growth factor proteins and, overall, have well-understood mechanisms of action. This, combined with the ability to study the pharmacodynamics (PD) of these products in rodents, has facilitated the assessment of their pharmacology in non-clinical studies. Robust and sensitive endpoints of efficacy exist for Biosimilar 1.0 products, which allows applicants to effectively compare the biosimilar products’ efficacy in abbreviated clinical trials. Furthermore, based on the known mechanisms of action and risk-benefit profiles in different patient populations, selective extrapolation to additional approved indications for the reference product was approved by EMA for Biosimilar 1.0 products.

Experience with Biosimilar 1.0 products to date has been generally positive and has served to both elevate the stature of the European regulatory approach, as well as to substantiate the potential of biosimilars in the market. However, some concerns related to biosimilar product regulation have arisen and been evaluated in the European scientific community. These concerns include the limits that currently exist on the ability to identify all critical quality attributes or define the extent of acceptable differences in comparison to the reference product. This has resulted in failures on the part of some manufacturers to achieve comparable drug products that show equivalence in dose, concentration or response in all of the reference products’ routes of administration. For example, unexpected differences were observed in exposure for one biosimilar filgrastim product and in titrated dose for one biosimilar epoetin. Although regulators determined that these differences had no effect on the overall conclusions on the safety or efficacy of these biosimilar products, the unexpected differences demonstrate that clinical studies are a critical component of biosimilar evaluations and can be sufficiently sensitive to detect differences in dose-concentration-effect between structurally related biologics.

Experience with several of the approved biosimilars has also reinforced that valid concerns remain about divergent immunogenicity profiles for similar biologics. One biosimilar product exhibited elevated incidence of anti-product antibodies during clinical development. After identification this issue was resolved through a
manufacturing change. Another biosimilar product being studied in a post-marketing clinical trial was associated with cases of anti-product neutralizing antibodies in nephrology patients treated using the subcutaneous route of administration. Although concerns about using the subcutaneous route of administration in nephrology patients treated with cases of anti-product neutralizing antibodies in marketing clinical trial was associated with similar product being studied in a post-clinical studies, so the importance of assuring unique identification of a particular marketed product in order to facilitate accurate attribution of adverse events cannot be overstated.

Biosimilars 1.0 has served as an insight into the need for high-resolution technologies for screening molecules in the future, they will have the means to achieve a higher standard of analytical similarity to their reference products than was feasible in the past. Advances in protein engineering, understanding of critical quality attributes and the development of high-throughput, high-resolution technologies for screening process conditions will enable Biosimilar 2.0 manufacturers to achieve high similarity to complex reference products.

Increasingly, “flexibility” is discussed as a regulatory approach for biosimilars; however, alterations to host cell expression

| Table 1. Biosimilar product marketing applications submitted to the European Medicines Agency |
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| Trade name | Generic/common name | Owner of trade name | Reference product | Decision | Decision date |
| Omnitrone® | somatropin | Sandoz | Genotropin® | Approved | April 12, 2006 |
| Valtropin® | somatropin | BioPartners | Humatrope® | Approved | April 24, 2006 |
| Alpheon® | interferon alfa-2a | BioPartners | Roferon-A® | Rejected | June 28, 2006 |
| Binocrit® | epoetin alfa | Sandoz Hexal Medice | Eprex® | Approved | Aug. 28, 2007 |
| Retacrit® | epoetin zeta | Hospira Stada | Eprex® | Approved | Dec. 18, 2007 |
| Insulin Rapid Marvel | soluble insulin | Marvel | Humulin® | Withdrawn | Jan. 16, 2008 |
| Insulin Long Marvel | isophane insulin | Marvel | Humulin® | Withdrawn | Jan. 16, 2008 |
| Insulin 30/70 Marvel | biphasic insulin | Marvel | Humulin® | Withdrawn | Jan. 16, 2008 |
| Tevagrostim® | filgrastim | Teva Ratiopharm Ratiopharm CT Arzneimittel | Neupogen® | Approved | Sep. 18, 2008 |
| Zarzio® | filgrastim | Hospira | Neupogen® | Approved | Feb. 6, 2009 |
| Nivestim® | filgrastim | Hospira | Neupogen® | Approved | June 10, 2010 |

Note: Some products are marketed in different jurisdictions under different brand names. Data source: European Public Assessment Reports published on European Medicines Agency website; www.ema.europa.eu/pdfs/human/press/pr/4031706en.pdf
systems, formulations and containers will introduce new variables with the potential to affect efficacy, safety and product stability. While Biosimilar 2.0 companies may pursue such strategies, development costs and risks will increase with each additional variable introduced. Many companies may seek approval of potentially differentiated products through original marketing applications rather than as biosimilar products. Regulators will need to determine which alterations are acceptable for a product to qualify as a biosimilar.

At a minimum, biosimilar products must have identical primary structures to their reference products and very close fidelity in post-translational modifications that could affect the safety or efficacy of the medicine. In contrast to generic drugs that are required to have identical molecular structures to their reference products, a similar biologic medicine may be permitted to have some differences in structural variants. For example, small differences in the nature or distribution of glycosylation structures or glycoforms may be acceptable, but in some cases differences in such structures could affect a product’s function or pharmacokinetics (PK). 28,29

Furthermore, structural variations not present in the reference product (e.g., distinct post-translational modifications or alterations that occur during purification, formulation, storage or shipping) may have a profound impact on the efficacy, safety or immunogenicity of biologics. 22,23 The relevance of these variations compared to the innovator product can only be confirmed in clinical studies.

A particular challenge for the Biosimilar 2.0 era will be the successful development of biosimilar mAbs that can have multiple structural variants influencing their binding affinity, PK, stability and immunochemical parameters. 24 This may result in a greater number of critical structural attributes compared with simpler protein products and makes it more likely that a manufacturer will have to accept tradeoffs in the degree of similarity of some attributes in order to assure similarity in others. Technology now allows high throughput screening of cell lines and process variables. Coupled with high throughput analytics, these scientific advances can help biosimilar manufacturers in the Biosimilar 2.0 era address the complex optimization problem.

A comparison between human growth hormone (hGH) and immunoglobulin (Ig) G highlights the difference in scale and complexity of protein-based medicines. HGH has a single-chain primary structure consisting of 191 amino acids with two intramolecular disulfide bonds and no glycosylation. 25 In comparison, IgG is a glycoprotein with a primary structure consisting of two light chains and two heavy chains (approximately 220 and 500 amino acids respectively depending on subclass) that are bound by a complex and variable series of disulfide linkages and electrostatic interactions both within and between the four chains. 26

The field of analytical technology is advancing quickly, which will serve as both an asset and liability to Biosimilar 2.0 manufacturers. The technology will reveal more information about the reference product, but will commensurately show more differences that exist in a biosimilar product during comparative analysis. More knowledge, however, is being generated and published about the relevance of certain structural variants to the bioavailability, safety and efficacy of biologics, including mAbs. 27,28 This knowledge can be leveraged for a particular biosimilar product to prioritize development efforts towards those attributes that are likely to be critical to safety and efficacy. Prior to conducting expensive clinical studies, sponsors of Biosimilar 2.0 products will likely demonstrate a robust knowledge of known critical quality attributes in order to prevent failed studies.

**Holistically Evaluated**

As with Biosimilar 1.0, manufacturers in the Biosimilar 2.0 era should convincingly establish the existence of a highly similar dose-concentration-effect of the biosimilar to that of the reference product through a combination of non-clinical studies followed by PK, PD where applicable and clinical efficacy and safety studies in patients. These principles for a holistic non-clinical and clinical evaluation of similarity of safety and efficacy are articulated in the various guidelines for biosimilars that have been adopted by multiple regulatory authorities. 19

A sophisticated and comprehensive analytical comparison will increasingly be reinforced with highly sensitive pharmacology and an informative PK equivalence evaluation en route to clinical trials evaluating for the equivalent efficacy and non-inferior safety of the biosimilar product. Experience shows that some effects of relevant differences in structure or formulation can be detected at early stages like PK and hence, these results should be considered the first gate in a demonstration of similarity or cause for remediation before evaluations of clinical performance are initiated. 29

A unique characteristic of Biosimilar 2.0 products in comparison to their Biosimilar 1.0 predecessors is that many of these products will be mAbs, which are structurally more complex and may have more than one mechanism of action involved in their pharmacological effect through target-antigen binding, Fc-effector function(s) or Fc-receptor binding. Due to this structural and functional complexity, it is critical that any differences that exist between the various structural attributes of a biosimilar fusion molecule or mAb and its reference product are evaluated in nonclinical in vitro or in vivo pharmacology studies. Such studies should compare binding affinities to the target and to Fc receptors, as well as to complement. They should also compare biological activities mediated by target binding and any relevant immunochemical functions such as antibody-dependent cell-mediated cytotoxicity and complement dependent cytotoxicity.

A further challenge with some mAb therapeutics is that there is no established in vivo pharmacology model other than non-human primates. Biosimilar 2.0 manufacturers should evaluate the in vivo toxicology of their products in primates, if necessary, prior to proceeding with human clinical studies. Toxicology studies are warranted because alterations to various regions on some mAbs, including post-translational modifications, can affect the safety profiles of these products, resulting in off-target adverse effects including thrombocytopenia and anemia associated with monocyte activation and phagocytosis (unpublished results) and thrombocytopenia associated with
platelet activation.\textsuperscript{30} However, it may not be ethical to perform a statistically powered, comparative evaluation of PD in non-human primates if data derived from the study will not be material to the biosimilarity exercise. Therefore, the evaluation of functional similarity for such products will rely to a greater extent on in vitro studies and clinical studies. This is in contrast to the Biosimilar 1.0 products for which it was possible to compare PD in statistically powered rodent models prior to proceeding with clinical studies.

A demonstration of equivalent PK in humans is normally a required component of a biosimilar development program. Development programs for innovator products, including mAbs, have revealed unexpected changes in PK following manufacturing process changes.\textsuperscript{31-33} Just as these originator drug development findings have undermined early confidence in the ability to bridge to earlier findings of safety, efficacy or appropriate dose, a finding of non-equivalent PK of a purported biosimilar could give pause to further development of the biologic using an abbreviated pathway.

However, a combination of equivalent non-clinical pharmacology and equivalent human PK is insufficient to infer similar efficacy and safety of biologics in humans. To supplement this gap, PD markers, when validated and robust, will provide evidence of biosimilarity through predetermined equivalence margins. Where validated PD markers do not exist, clinical efficacy studies are needed to confirm performance. In all cases, non-inferior safety and immunogenicity should be demonstrated in patients before submission of an application to rule out major differences and, like all biologic products, biosimilars should be evaluated in post-approval setting to confirm equivalent benefit-risk profiles and to evaluate rates of serious but infrequent adverse events.

The need to perform statistically sensitive comparisons of PK, PD or clinical outcomes poses challenges in circumstances where there is a high level of variability in bio-absorption, elimination or PD response within and between subjects.\textsuperscript{29,34} This will be the case for many Biosimilar 2.0 products for inflammation or oncology wherein there may not be relevant PD markers and the clinical response can be highly variable. Indeed, in these situations the challenge of demonstrating an equivalent clinical response of two similar products may be more significant than that of demonstrating efficacy per se against a placebo control.

To address these situations, the EMA draft guideline for development of bio-similar mAbs issued in November 2010 suggests selecting relatively homogenous, sensitive subpopulations for the comparative evaluations of clinical efficacy biosimilarity. Using this strategy, Biosimilar 2.0 manufacturers should carefully select such populations such that conclusions of similarity in efficacy might be appropriately extrapolated to broader populations or additional conditions of use. Sponsors will need to consider, however, that while a particular patient population may be the most sensitive for a comparative assessment of efficacy, a different population may be the most sensitive for an assessment of safety or immunogenicity. Surrogate endpoints for clinical efficacy should only be considered when they provide a scientifically robust alternative versus the standard efficacy measurement and where biosimilarity can be demonstrated accurately. Biosimilar 2.0 manufacturers should pursue appropriate endpoints and proper assessments as opposed to using surrogate endpoints simply as a trade off for lower development effort. Biosimilars fulfill a valid need in the healthcare system, but do not meet requirements for accelerated approval.\textsuperscript{35}

The final challenge in Biosimilar 2.0 development will be to define the appropriate safety and immunogenicity data set required prior to registration. Reliance on PD or surrogate endpoints in selected subpopulations for the efficacy component of the exercise would commensurately reduce the nature and amount of clinical experience. The extent to which a biosimilar product can rely on a prior finding of safety and effectiveness should be dependent on the structural, functional and clinical similarity to the reference product. The Biosimilar 2.0 manufacturer will need to develop additional clinical data supporting conditions of use where this reliance is not fully justified and where immunogenicity and other adverse drug reactions should be evaluated in a comparative study using sensitive patient populations. Biosimilar 2.0 manufacturers should confirm the safety profile of the product with post-approval monitoring as a component of a robust risk management plan.

Globally Developed

Given the new expansion of the biosimilar marketplace to include Canada, Japan, Australia, the United States and others, manufacturers in the Biosimilar 2.0 era will likely seek harmonization of global approval requirements and will propose global development programs, where scientifically justified by a consistent reference product, to achieve development efficiencies and avoid duplicative clinical studies. Foreign clinical data often helps assure that medicines are evaluated in diverse but representative patient populations before approval. A unique challenge, however, will be in how to define a “global” reference product and demonstrate that comparator products sourced from various regions are suitable to represent the reference product that a patient in a given region might receive.\textsuperscript{36}

Because biologic products are sensitive to differences in cell lines, cultivation, harvest, purification and packaging, products manufactured and distributed in disparate regions can differ significantly or drift apart through manufacturing changes after once being comparable to each other.\textsuperscript{37} Products that are sold by independent manufacturers or that have drifted from comparability can exhibit differences in key quality attributes, including the structural properties of the product. Additionally, differences in raw materials and manufacturing equipment will frequently exist. In some cases, there are differences in specifications and methods for intermediate or final product evaluation, as well as formulation and filling for varied product presentations. If manufactured by different companies, the product and quality control standards will likely differ.

Regulatory agencies will likely be cautious when accepting data from comparative studies using foreign comparator products as they may differ substantially from the locally approved reference products.
products in manufacturing, processing or evaluation. Subject to this need for caution, in certain circumstances it may be acceptable for regulatory agencies to accept and review the comparative non-clinical and clinical data generated using a reference product sourced in a region different from the one in which approval is sought. First, biosimilar manufacturers in the Biosimilar 2.0 era should not rely on any data relating to a foreign product that is not manufactured by the same company that holds the license in the region for which approval is sought. Additionally, Biosimilar 2.0 manufacturers should convincingly establish a scientific basis for relying on tests with a foreign product and a lack of any relevant differences between the comparator products. When a global reference product is not available, Biosimilar 2.0 manufacturers should develop an original marketing application or perform additional clinical studies to ensure that every patient, regardless of region, receives biosimilars that exhibit no differences in safety or efficacy from that which they would experience with their regional reference product.

**Accurate and Transparent**

Biosimilar 2.0 manufacturers must develop products that are of the same dosage form, for the same route of administration and, most importantly, designed and formulated to achieve the same strength as that of the reference product. With skill in the art, a Biosimilar 2.0 manufacturer will know that the “strength” of a biologic must be evaluated in both its concentration (just as with a generic), but also in its potency. The challenge of achieving this standard is illustrated by the fact that not only some follow-on biologics sold in emerging markets, but also some EU biosimilars approved during the Biosimilar 1.0 era have demonstrated differences in strength or potency relative to their reference products even though they are labeled with the same nominal strength and dose.

Biosimilar 2.0 manufacturers should ensure that a quality biosimilar product exhibits the same concentration as and equivalent potency to, the reference product so that the biosimilar product can be assured of providing a similar clinical effect at a given dose. Dose conversions or adjusted concentration or formulation to match the strength or potency of the reference product should never be permitted. Each of these instances would be cause to terminate development or to remediate the situation. Differences in strength pose a clear risk for medication errors and should not occur in the Biosimilar 2.0 era.

Additionally, biosimilar sponsors should advocate transparency of data generated with their product to both providers and patients. They will want both parties to know the extent to which their products have been evaluated clinically before approval and in which indications. Unlike generic drugs that do not undergo clinical testing, medicines in the Biosimilar 2.0 era will be evaluated clinically for both efficacy and safety and manufacturers will openly and accurately present this information in the product insert and label.

Ultimately, when payers, doctors and patients decide among therapeutically similar biologics, whether a lack of clinical data or the existence of differences in product strength or potency should not confound their decision.

**Accountable**

Biosimilar 2.0 manufacturers must always be accountable for the quality of their product and should exhibit a patient-focused commitment to upholding the highest standards. All biologics manufacturers should stand behind their products and should not adopt identification mechanisms that risk confounding pharmacovigilance data with those of other manufacturers. The accountable biosimilar sponsor should do whatever is necessary to allow reliable and rapid tracing of adverse drug reactions (ADRs) to the actual biologic product, especially once single-source manufacturing is no longer an aid to event attribution.

Biologics have a unique risk profile compared with traditional pharmaceuticals in that ADRs can occur as a result of the interaction of specific structural differences with the physiology of individual patients. Because these structural attributes can be process-specific, highly similar biologics could diverge in terms of prevalence or severity of ADRs. The most common manifestation of this phenomenon has been observed with unwanted immunogenicity profiles that have differed substantially among closely related biologics. For example, incidence of pure red cell aplasia in nephrology patients treated with subcutaneous erythropoiesis stimulating agents has varied over time and between members of the product class, presumably due to process-specific factors. Similarly, the incidences of neutralizing antibodies in interferons diminished over time as a result of changes in the manufacturing process and formulation. It is the potential for process-specific ADRs, in addition to class effect ADRs that necessitates enhanced accountability of innovator companies and Biosimilar 2.0 manufacturers once multiple versions of a biologic are on the market.

Given that differences between products can occur because the biosimilar and reference products are prepared under different conditions such as different manufacturing and formulation processes, Biosimilar 2.0 manufacturers should seek unique brand and non-proprietary names for their products because these are the most common means for a patient or physician to accurately communicate his or her experience to an accountable manufacturer. It is essential that adverse events be linked to the associated product and manufacturer; without such a link, unique ADRs or a disproportionate prevalence of ADRs for a given product, could be missed in the overall surveillance dataset or attributed to the wrong manufacturer.

For product classes known to exhibit clinically-relevant unwanted immunogenicity, manufacturers of approved biologics, including biosimilars, should make available anti-drug antibody testing, in accordance with regulatory requirements of the country, so that doctors and patients can make the right decisions about ongoing therapy. For example, loss of efficacy to anti-tumor necrosis factor biologics can be attributed to either the underlying disease or to the immunogenicity of a specific product. Doctors and patients need the right information to determine whether to switch to a structurally distinct member of the class or to a different therapy.
If a disproportionate risk of immunogenicity is detected for a given marketed biologic via pharmacovigilance or antibody testing data, this should be of concern to a manufacturer and to regulators since some patients could be unnecessarily denied the benefits of the therapeutic class.

Traceability of an adverse event to the correct product is especially important because the effects of differences in quality attributes of biological products on their safety profiles are not completely understood. Without traceability, adverse safety outcomes related to differences in quality could go unrecognized or undetected, thus increasing the likelihood that emerging adverse events would not be recognized as being uniquely related to a particular product. If the relationship between a significant event and a particular product is unrecognized, appropriate clinical, manufacturing and, potentially, regulatory actions cannot be taken.

**Conclusion**

The Biosimilar 2.0 era can be characterized by high-quality products and data-rich global development programs. Patients have a right to demand highly similar and holistically evaluated products and the organizations, infrastructure and expertise to meet these requirements efficiently and effectively now exist.

Regulators and manufacturers will learn from experiences of the Biosimilar 1.0 product approvals and marketing to drive efficient and science-based comparative evaluations in the non-clinical and clinical settings. As the healthcare community, industry and regulators consider appropriate standards for Biosimilar 2.0 products, a few considerations stand out:

1. The evaluation of functional similarity for some Biosimilar 2.0 products will rely to a greater extent on in vitro studies and clinical efficacy studies given limitations in animal testing of these complex molecules; (2) Where there are no appropriate and validated PD markers and the clinical response can be highly variable, the challenge of demonstrating an equivalent clinical response of two similar products may be higher than that of demonstrating efficacy per se against a placebo control; (3) Surrogate endpoints for clinical efficacy should only be considered when they provide a scientifically robust alternative versus the standard efficacy measurement and where biosimilarity can be demonstrated accurately; (4) It will be a challenge to demonstrate that comparator products sourced from various regions are suitable to represent the reference product a patient receives in a given region, but may be justifiable if certain conditions are satisfied; (5) A quality biosimilar product must exhibit the same concentration as and equivalent potency to, the reference product so that the biosimilar product can be assured of providing a similar clinical effect at a given dose; (6) Biosimilar 2.0 manufacturers should provide the needed clinical diagnostic support so that the doctor and patient can make the right decisions about ongoing therapy.

Biosimilar manufacturers in the 2.0 era should embrace pharmacovigilance systems and programs that will enable regulators and the public to have confidence in the risk–basis extrapolation of product safety. These attributes will bring choices to patients, prescribers and payers in many markets without asking them to make trade-offs between cost and the benefit-risk of a biologic.

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