

# Biosimilar regulation: important considerations and global developments

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During the past ten years, many stakeholders have expressed an interest in the availability of biologically derived medicines authorised on the basis of previously authorised biological reference products, that is, on the basis of a truncated dossier that includes a robust showing of similarity between the two products. These medicines are known as biosimilars in many parts of the world, including Europe and now the US. In other jurisdictions, they may have different labels. (Under Canadian law, for example, they are known as subsequent entry biologics.) An increasing number of countries have passed laws, implemented regulations, or developed regulatory guidelines to govern the authorisation of biosimilars, and many have begun authorising them. For example, as of January 2011, biosimilar human growth hormone has been authorised in Canada, the US, Australia, and Europe, and indeed the European Commission has authorised 14 biosimilars. Regulation of biosimilars is evolving rapidly, because of:

- Increasing pressure for lower cost versions of biological medicines.
- Scientific technology (particularly analytical technology) continuing to improve.
- Regulators and stakeholders gaining experience with these complex molecules and the issues they present.

Against this background, this chapter looks at the:

- Differences between biologically derived medicines and chemically synthesised medicines.
- Significant scientific and regulatory challenges posed by the authorisation of biosimilars and discusses how those issues have been addressed in Europe and the US.
- Recent global developments related to biosimilar regulation.
- Patent considerations for biologics marketed in the US.
- Developments expected in the next several years concerning the regulation of biosimilars worldwide.

## BACKGROUND

Most countries already have well-established scientific standards and legal mechanisms for authorising generic versions of chemically synthesised medicines. These medicines are usually authorised on the basis of abbreviated applications, demonstrating they are the same in structure as, and bioequivalent to, a previously authorised product. Non-clinical and clinical data are not usually required. Although the generic drug paradigm has been in place in much of the world for several decades, it has been generally recognised for some time that the paradigm will not work for biologically derived drugs.

The generic chemical drug model is unworkable for a number of reasons. For example, biologic medicines generally consist of large, complex proteins. They can be difficult or impossible to fully characterise. For both reasons, it is usually impossible to show that one biological medicine is the same as another through analytical testing alone. Biologics are extremely sensitive to changes and variations in manufacturing process, starting materials, and methods of control. Even where an applicant seeks to produce a version of another company's biological medicine, the inevitable use of different processes and methods is likely to yield a product that differs in structure or in clinically significant ways. Further, it may not be safe to dispense entirely with pre-market testing of biological medicines in humans. Biologically derived drugs have a much greater potential than chemically synthesised drugs to elicit immune responses. These responses can be rare, sometimes too rare to detect even with any reasonable premarket safety database, and the severity of response can vary considerably.

## SCIENTIFIC AND REGULATORY CHALLENGES

### Key questions for regulators

Biosimilar authorisation poses a number of substantial scientific and regulatory challenges for regulatory authorities. These include:

- **Reference product.** Against what innovative product(s) may a biosimilar be compared to support its authorisation?
- **Quality.** What data must a biosimilar application include and what showing must be made to demonstrate that a biosimilar's quality is sufficiently comparable to that of the reference product?
- **Non-clinical data.** What type and amount of non-clinical data (including data comparing a biosimilar to its reference product) are needed, and what showing must be made, to support biosimilar authorisation?
- **Clinical trials.** Under what circumstances is clinical data (including data comparing a biosimilar to its reference product) needed to support a biosimilar's authorisation? What type of data is needed (such as, pharmacokinetic, pharmacodynamic, efficacy, safety or immunogenicity)?
- **Extrapolation of indications.** Under what circumstances (if any) may a biosimilar receive authorisation for an indication of the reference product based on data that evaluate, and show comparable safety and efficacy of, the biosimilar for a different indication of the reference product?
- **Naming.** What proprietary and/or non-proprietary names should be permitted (or required) for biosimilars so that physicians may select among medications and dictate the specific product dispensed, and so that manufacturers



and regulators may distinguish among biologics for pharmacovigilance purposes?

- **Labelling.** How will biosimilars be labelled? For example, what information from the reference product's label may or must appear in the biosimilar's labelling? Must a biosimilar's labelling indicate that the product is a biosimilar?
- **Pharmacovigilance and risk management.** What (if any) post-marketing monitoring and safety-related requirements should be imposed on biosimilar applicants (such as, special requirements related to safety reporting, post-marketing studies, or information that must appear in labelling for physicians or patients)?
- **Interchangeability and substitution.** What data must be provided and what showing must be made for a regulatory authority to conclude that a biosimilar is interchangeable with its reference product (that is, to determine that the two products have acceptably similar therapeutic results and safety risks such that one can be used in place of the other in a given patient, or a given patient can switch back and forth between them, and the same clinical outcome can be expected)? As a legal or policy matter, under what circumstances (if any) can automatic substitution take place (that is, when can, or must, a pharmacist dispense a biosimilar in place of the biologic medicine prescribed by a physician, without the consent of the physician or patient)?
- **Data protection.** To help innovators recoup their investment and to encourage continued medical innovation, should innovators be afforded a period of time during which a biosimilar applicant cannot rely on the innovator's proprietary data to support authorisation of the biosimilar? If so, what length of data protection should be provided?

### The EU approach

The EU was the first to develop a robust regulatory framework for the authorisation of biosimilars. In 2001, much of the EU's directive-based legislation concerning medicines regulation was codified as Directive 2001/83/EC. In 2003, the European Commission concluded that its existing procedures for authorisation of medicines based on abbreviated applications (known as abridged applications and bibliographic applications), would not ordinarily be appropriate for biologic medicines. This was due to the difficulty in determining whether biologic active ingredients are the same as those of the reference product (in the case of abridged applications) or those of the products described in published literature (in the case of bibliographic applications).

The Commission therefore amended Annex I of Directive 2001/83/EC to create a new marketing authorisation procedure for similar biological medicinal products. The procedure, which applied to biotechnology-derived medicines and certain other biological products such as low molecular weight heparins, required medicines agencies to demand safety and efficacy data in addition to the bioequivalence studies that would normally support a generic application. The amendments to Annex I took effect in October 2003 and were subsequently reinforced by an amendment to the main body of Directive 2001/83/EC.

The European Medicines Agency (EMA) has developed the regulatory scheme for biosimilar authorisation through a relatively transparent process. The EMA has issued concept papers and draft guidances and held public scientific workshops. It has issued guidelines that describe general principles and provide an over-arching framework for authorisation of biosimilars. The EMA's

Committee for Medicinal Products for Human Use (CHMP) has also issued several product class-specific guidance that sets out product requirements in greater detail. The CHMP has issued guidelines for recombinant erythropoietin, granulocyte-colony stimulating factor, recombinant human soluble insulin, low molecular weight heparins, somatropin, and recombinant interferon alfa.

### The US approach

**New law.** On 23 March 2010, the US President signed into law a bill governing the regulation of biosimilars. The Biologics Price Competition and Innovation Act of 2009 (BPCIA) permits the licensing of biological products that are shown to be biosimilar to previously licensed reference products. A biological product is considered biosimilar to a reference product if it is highly similar to the reference product, notwithstanding minor differences in clinically inactive components and if there are no clinically meaningful differences between the products in terms of safety, purity, and potency. The law does not require the US Food and Drug Administration (FDA) to issue any regulations or guidance to implement its provisions or FDA's new authorities.

**Outstanding implementation issues.** Although more detailed than the corresponding European law, the BPCIA leaves many issues to FDA to resolve. The agency might choose to address these issues prospectively and systematically, or it might proceed on an *ad hoc* basis as issues arise. In addition, it may proceed through more formal mechanisms (such as regulations) or less formal mechanisms (such as guidance documents or even internal policies). It may decide to resolve some issues with over-arching decisions and others on a product-by-product, or even class-by-class, basis.

The issues that FDA will need to address include:

- What analytical data are necessary to show that a biosimilar is highly similar to its reference product (notwithstanding minor differences in clinically inactive components) and what constitute minor differences.
- What type and how much non-clinical and clinical data it requires in applications.
- Whether and when it will permit extrapolation from one reference product indication to another.
- Whether and when it will exercise the discretion to permit omission of data otherwise required in biosimilar applications.
- Whether it will exercise its option, granted by statute, to declare that certain products or product classes are not yet suitable for biosimilar applications.
- How biosimilars will be labelled, including whether and how the labelling will indicate that a product is a biosimilar and whether a biosimilar's labelling will be permitted or required to include information from clinical studies of the reference product conducted by (or for) the reference product sponsor.
- What data or other showing is necessary for a biosimilar to be found interchangeable with its reference product.
- Whether biosimilars should have non-proprietary names that are distinct from the non-proprietary names of the reference products on which they are based.
- Whether and when information concerning a reference product could lead the agency to take action to revoke or suspend the authorisation of products biosimilar to that reference product.

### Comparison of EU and US approaches

The following table summarises features of the approaches taken by the EU and US to resolve some of the challenges relating to biosimilar authorisation.

Topic	EU	US
Key guidelines or law	<p>Directive 2001/83/EC, as implemented by various CHMP guidelines, including:</p> <ul style="list-style-type: none"> <li>■ Guideline on Similar Biological Medicinal Products EMEA/CHMP/437/04.</li> <li>■ Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues EMEA/CHMP/BMWP/42832/2005.</li> <li>■ Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues EMEA/CHMP/BWP/49348/2005.</li> <li>■ Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins EMEA/CHMP/BMWP/14327/06.</li> </ul>	<p>The Biologics Price Competition and Innovation Act of 2009 (sections 7001 to 7003 of the Patient Protection and Affordable Care Act, Pub. L. 111-148 (2010)).</p>
Scope of guidelines or law	<p>Whether a biological medicinal product can be regulated as a biosimilar depends on the ability to sufficiently characterise the product and therefore to demonstrate the similar nature of the product to its reference product.</p> <p>Vaccines and allergen products are considered on a case-by-case basis.</p> <p>Blood or plasma-derived products and their recombinant alternatives are excluded.</p> <p>Gene and cell therapy medicinal products will be considered in the future.</p>	<p>Any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesised polypeptides), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound).</p> <p>The regulatory authority (the Secretary of the US Department of Health and Human Services or Secretary) may indicate in a product class-specific guidance that current science and experience do not allow approval of biosimilar applications with respect to a particular product or product class (except for recombinant proteins).</p>
Reference product	<p>Must be authorised in the EU based on a complete dossier.</p>	<p>Must be licensed under a full biologics licence application (under section 351(a) of the Public Health Service Act).</p>
Quality	<p>For recombinant proteins, an extensive comparability exercise is required. Quality aspects of comparability must be considered in relation to implications for safety and efficacy. Purity and impurity profiles of the active substance and medicinal product must be assessed qualitatively and quantitatively for the biosimilar and the reference product.</p>	<p>Unless the Secretary makes a determination that it is unnecessary, an application must contain data from analytical studies demonstrating that the biosimilar is highly similar to the reference product (notwithstanding minor differences in clinically inactive components).</p>
Non-clinical data	<p>Non-clinical studies for biosimilar versions of recombinant proteins should be comparative in nature, designed to detect differences in response between the biosimilar and the reference product. In vitro studies, in vivo studies in relevant animal species, and at least one repeat-dose toxicity study in relevant animal species normally should be conducted.</p>	<p>Unless the Secretary makes a determination that it is unnecessary, an application must include data derived from animal studies (including the assessment of toxicity) to help demonstrate that the product is biosimilar to a reference product.</p>

Topic	EU	US
Clinical studies	<p>For recombinant proteins, comparative efficacy clinical trials usually are necessary to demonstrate clinical comparability. The clinical requirements depend on the existing knowledge about the reference product and the claimed therapeutic indication(s).</p> <p>For recombinant proteins, a biosimilar's immunogenicity must always be investigated. Immunogenicity risks in different indications should be considered separately.</p>	<p>Unless the Secretary makes a determination that it is unnecessary, an application must include data derived from a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used. The purpose of these data is to help demonstrate that the product is biosimilar to a reference product.</p>
Extrapolation of indications	<p>For recombinant proteins, in certain cases, it may be possible to extrapolate therapeutic similarity to other indications. Justification of extrapolation depends on clinical experience, available literature, whether the same mechanism of action or receptor is involved in both indications, and possible safety issues in different subpopulations.</p>	Not addressed.
Naming	<p>To support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified. The name, appearance, and packaging of a biosimilar medicine should differ from those of the reference product.</p>	Not addressed.
Labelling	Not addressed.	Not addressed.
Pharmacovigilance and risk management	<p>By law, a risk management plan or pharmacovigilance plan must be submitted for biosimilars as for other medicines. The plan should take into account risks identified during product development and potential risks and how those risks will be addressed after authorisation</p> <p>For recombinant proteins, clinical safety must be monitored closely after authorisation. The application should include a risk specification and pharmacovigilance plan.</p>	<p>The Secretary's existing authority to require a risk evaluation and mitigation strategy (REMS) for drugs applies to biosimilars (a REMS documents requirements designed to minimise risk associated with a drug).</p> <p>In addition, the Secretary's existing authority to mandate post-market studies and clinical trials as well as post-market labelling changes applies to biosimilars.</p>
Interchangeability and substitution	<p>Substitution is determined at the member state level, and therefore this topic is not directly addressed in EMA guidance.</p> <p>EMA guidance states that biosimilars are not generic medicinal products and that the decision to treat a patient with a reference product or a biosimilar should be made following the opinion of a qualified healthcare professional.</p>	<p>Substitution is determined at state level in accordance with state pharmacy laws.</p> <p>FDA must find a biosimilar to be interchangeable with its reference product if the information submitted by the biosimilar applicant demonstrates that:</p> <ul style="list-style-type: none"> <li>■ The applicant's product is biosimilar to the reference product (under the law's standard for biosimilarity).</li> <li>■ The applicant's product can be expected to produce the same clinical result as the reference product in any given patient.</li> </ul> <p>For products administered more than once to an individual, the applicant must also demonstrate that the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar and use of the reference product is not greater than the risk of using the reference product without such alternation or switch.</p>

Cross-border



Topic	EU	US
Data protection for reference products	For a reference product for which the application for approval was submitted in October or November 2005 or later (different rules apply to a reference product for which the application for approval was submitted earlier), a biosimilar may not be marketed until ten years after authorisation of its reference product that is a new active substance. This period may be extended for an additional year, if within eight years after reference product authorisation, the reference product is authorised for a new therapeutic indication that constitutes a significant clinical benefit in comparison with existing therapies.	<p>A biosimilar may not be approved until 12 years after the date on which the reference product was first licensed under section 351(a) of the Public Health Service Act.</p> <p>The date of first licensure does not include the date of approval of a supplement to the reference product application or the date of approval of a subsequent application for either:</p> <ul style="list-style-type: none"> <li>■ A change to the reference product, other than a structural change, that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength.</li> <li>■ A structural modification to the reference product that does not result in a change in safety, purity, or potency.</li> </ul>

## GLOBAL DEVELOPMENTS

Recently a number of countries issued final guidance addressing the regulation of biosimilars and the content of biosimilar applications. The World Health Organisation (WHO) has also issued guidelines for local regulatory authorities that are seeking

to develop national standards. The following table describes features of biosimilars guidance adopted by the WHO, Canada and Japan. Japan issued its final guidance in March 2009, followed by the WHO in October 2009 and Canada in March 2010.

Topic	WHO	Canada	Japan
Primary biosimilar guidelines	WHO, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs).	Health Products and Food Branch, Health Canada, Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs).	Ministry of Health Labor and Welfare, Pharmaceutical and Food Safety Bureau, Guideline for Ensuring Quality, Safety, and Efficacy for Biosimilar Products, PFSB/ELD Notification No. 0304007.
Scope of guidelines	Well-established and well-characterised biotherapeutic products (such as, DNA-derived therapeutic proteins). Excludes vaccines, plasma-derived products, and their recombinant analogues.	Biologic drugs that contain well-characterised proteins derived through modern biotechnological methods (such as, recombinant DNA and/or cell culture).	Recombinant proteins (including simple proteins and glycoproteins) that have been produced using micro-organisms or cultured cells, have been highly purified, and can undergo characterisation by means of a series of appropriate analytical procedures. Polypeptides and their derivatives. Potentially other categories of products that have been highly purified and can undergo quality characterisation (such as, non-recombinant protein products produced using cell culture or proteins and polypeptides that have been isolated from tissue or body fluids).

Topic	WHO	Canada	Japan
Reference product	Should be authorised in the country or region in question (or, where the licensing country lacks an authorised reference product, should be authorised and widely marketed in another jurisdiction with a well-established regulatory framework for and experience in evaluation and post-market surveillance of biotherapeutics).	<p>Should be authorised for sale and marketed in Canada based on a complete data package and have significant accumulated safety and efficacy data.</p> <p>If a product that is not authorised in Canada is used in comparative studies, then among other things:</p> <ul style="list-style-type: none"> <li>■ The applicant must show that the non-Canadian product is a suitable proxy for the version of the product authorised in Canada.</li> <li>■ The Canadian and non-Canadian products must be marketed by the same company and in same dosage form.</li> <li>■ The non-Canadian product must be widely marketed in a jurisdiction that formally adopts the International Conference on Harmonisation (ICH) guidelines and has regulatory standards and postmarket surveillance activities that are similar to those in Canada.</li> </ul>	Must be authorised in Japan.
Quality	Comprehensive physicochemical and biological characterisation of the biosimilar in head-to-head comparisons with the reference product is required, and all aspects of quality and heterogeneity should be assessed.	A complete chemistry, manufacturing, and controls data package is required along with data demonstrating similarity with the reference product (including comparative characterisation studies).	A biosimilar must be fully characterised, including by conducting studies comparing the structure and composition, physicochemical properties, bioactivity, and immunologic properties of the biosimilar against its reference product.
Non-clinical data	<p>The non-clinical evaluation should include pharmacodynamic, pharmacokinetic, and comparative repeat-dose toxicity studies in a relevant species. The amount of additional non-clinical data required is dependent on product-specific factors.</p> <p>In vitro assays like receptor-binding studies or cell-based assays should normally be conducted to establish comparability of pharmacodynamic activity. Animal studies in a relevant species should generally be conducted.</p>	Appropriate non-clinical studies that are comparative in nature and designed to detect significant differences between the biosimilar and reference product should be conducted before the initiation of clinical studies. In vitro receptor binding studies or cell-based assays should be conducted when appropriate. In vivo studies should include animal pharmacodynamic studies relevant to the clinical application(s) and at least one repeat-dose toxicity study conducted in a relevant species.	<p>Before performing clinical studies, the biosimilar applicant must conduct non-clinical studies to verify that the product can be safely administered to humans. Before conducting non-clinical studies, a biosimilar must be subjected to a full quality characterisation.</p> <p>The pharmacological action of the biosimilar and its reference product should be compared through non-clinical pharmacological studies, and repeat-dose toxicity and toxicokinetic studies may be useful.</p>

Cross-border



Topic	WHO	Canada	Japan
Clinical studies	Clinical studies should be designed to demonstrate comparable safety and efficacy of the biosimilar and reference product. Clinical trials are required to demonstrate similar efficacy. Immunogenicity should always be investigated in humans before authorisation.	Comparative clinical trials to evaluate safety and efficacy are critical. Sponsors should also evaluate immunogenicity.	Clinical studies should generally be required, but they may not be required where non-clinical data are sufficient to assure bioequivalence and quality equivalence (if bioequivalence and quality equivalence have been demonstrated). Pharmacokinetic or pharmacodynamic study results are, however, inconclusive concerning clinical efficacy. Clinical studies should be conducted to verify efficacy for the specific indications for which the biosimilar applicant seeks authorisation. Sponsors should also conduct studies to evaluate immunogenicity.
Extrapolation of indications	Extrapolation may be possible if a sensitive clinical test model has been used that is able to detect potential differences between the products, that the mechanism of action and/or receptors are the same, and that the safety and immunogenicity of the biosimilar have been characterised and there are no special safety issues expected with the extrapolated indication.	Extrapolation may be justified based on the mechanism of action, pathophysiological mechanisms of disease, safety profile in the intended indications and/or populations, and clinical experience with the reference product.	Extrapolation may be permitted if the mechanism of action is not unclear, the applicant can show that a similar pharmacological result can be expected for the relevant indications, and the mechanism of action does not differ among indications.
Naming	Biosimilars should be clearly identifiable by a unique proprietary name. Where an international non-proprietary name (INN) is defined, that name should be stated and the WHO's policy on INNs should be followed.	Not addressed.	Notification PFSB/EKD No. 0304011 regulates the naming of biosimilars and states that the non-proprietary names and proprietary names of biosimilars should be readily distinguishable from the names of reference products and other biosimilars. For non-proprietary names, the following should be added to the end of the non-proprietary name: Follow-on 1 [2, 3, and so on]. For proprietary names, the letters BS should be added to the end of the name, along with the dosage form, dosage, and name of the manufacturer.

Topic	WHO	Canada	Japan
Labelling	<p>The prescribing information for the biosimilar should be as similar as possible to that of the reference product, except for product-specific information, such as different excipient(s).</p> <p>If the biosimilar has fewer indications than the reference product, the information related to those indications may be omitted unless it is considered important to inform doctors and patients about certain risks. In these cases, the prescribing information should clearly state that the biosimilar is not indicated for use in the specific indication(s) and the reasons for it.</p> <p>A national regulatory authority may choose to require prescribing information to mention the product is a biosimilar, discuss the studies performed with the biosimilar, and/or include instructions to the physician on how to use the biosimilar.</p>	<p>A biosimilar may not use the product monograph (labelling) of the reference product in its entirety.</p> <p>A biosimilar's product monograph must include, among others, a statement that it is a biosimilar, key data on which the decision for marketing authorisation was made, and tables that show the results of comparisons between the biosimilar and its reference product.</p>	Not addressed.
Pharmacovigilance and risk management	A pharmacovigilance plan is required when an application is submitted and a risk management plan may be necessary in some cases.	An applicant should provide a risk management plan and pharmacovigilance plan before marketing authorisation.	A post-marketing safety surveillance plan and a risk management plan for biosimilars is required and should be submitted with the application.
Interchangeability and substitution	Not addressed.	<p>Authorisation of a biosimilar is not a declaration of pharmaceutical or therapeutic equivalence to the reference product.</p> <p>In addition, Health Canada stated in a letter to provincial and territorial drug plan directors in July 2010 that the agency does not support automatic substitution of a biosimilar for its reference product.</p>	Substitution of a biosimilar for, or the combined use of a biosimilar with, a reference product should be avoided during the postmarketing surveillance period.
Data protection for reference products	Not addressed.	By regulation, a drug containing a new medicinal ingredient not previously authorised in a drug by Health Canada and not a variation of a previously authorised drug is entitled to an eight-year period of data exclusivity that runs from the date of authorisation of the innovative drug, and an applicant relying on data of the innovative drug cannot file its application for the first six years (as of September 2010 Health Canada's authority to promulgate these regulations, however, was the subject of litigation).	A biosimilar application cannot be approved until the innovative product on which the application relies has completed an eight-year re-examination or post-marketing surveillance period.

Cross-border

## PATENT CONSIDERATIONS IN THE US

In the US, some biologically derived drugs have been approved under the Federal Food, Drug, and Cosmetic Act (FDCA). Most biologically derived drugs, however, have been approved under the Public Health Service Act (PHSA). (Under the new biosimilar law, beginning on 23 March 2020, new drug applications (NDAs) for biologically derived drugs approved under the FDCA will be deemed to be licences under the PHSA.) The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, established a patent litigation scheme for drugs approved under the FDCA.

The new biosimilar law has established a scheme for resolving challenges of patents for innovative biologics approved under the PHSA. This scheme is designed to enable the resolution of patent disputes before a biosimilar enters the market. Under this scheme, the reference product sponsor and biosimilar applicant must privately exchange information about relevant patents. The law provides default provisions for maintaining confidentiality during this exchange, but the parties may agree to an alternative arrangement. The parties then negotiate to identify patents that will be litigated through an immediate litigation procedure.

Unlike the Hatch-Waxman Act's patent litigation scheme, the scheme created for biosimilars:

- Includes no provision preventing FDA from approving a biosimilar if the biosimilar applicant indicates it will wait for patent expiry before commercial marketing.
- Provides no stay of FDA approval of a biosimilar where a patent infringement suit has been brought.
- Provides no special incentive for biosimilar applicants to challenge or design around innovator patents (that is, there is no incentive like 180-day exclusivity, the period of marketing without competition from other generic products that the first generic applicant to submit an application to FDA and challenge a patent of the particular reference product is eligible for under the Hatch-Waxman Act).

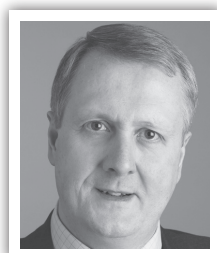
## CONSIDERATIONS FOR INDUSTRY

Some developments expected in the next several years concerning the regulation of biosimilars are described below. Stakeholders may want to consider monitoring or taking actions to influence these developments.

- Regulatory authorities worldwide must address how to effectively trace adverse events that are experienced by patients to the use of specific biologic products, in light of the availability of biosimilars and individual countries' policies related to naming. This may entail significant re-evaluation of current post-market safety surveillance requirements. The EU or US may decide, or be encouraged, to take the lead on developing standards that potentially could be applied on a global scale.
- Regulatory authorities must determine when they will conclude that a biosimilar is interchangeable with its reference product. Countries must also develop laws or policies concerning if and when a pharmacist may automatically substitute a biosimilar for a prescribed biologic medicine. In some cases, these laws or policies may be evaluated in conjunction with evaluation of a country's medicines reimbursement regime.
- As more biosimilars reach the market, stakeholders will learn more about how quickly these products will be authorised in specific countries, how rapidly they will be accepted by physicians and patients and gain market share, and how much cost savings they will in fact provide.
- As FDA addresses the scientific, legal, and regulatory issues raised by BPCIA, the agency may provide opportunities for public comment through rulemaking or guidance-making processes. In addition, some companies may wish to proactively engage FDA on specific topics through other means such as meetings or the submission of citizen petitions.
- Issues related to the implementation of the BPCIA's provisions concerning the resolution of patent disputes is likely to be addressed by the courts through litigation.
- Regulators who review biosimilar applications often have fairly broad discretion to determine whether to authorise a product for marketing. Countries may consider adopting procedures to provide reference product sponsors an opportunity to comment on biosimilar applications.
- The distinction between a biosimilar and a biologic product approved on the basis of a full, self-standing application may not always be clear. Policymakers or regulators in some countries may need to address under what circumstances a biologic will benefit from a period of data protection.



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#### Recent transactions

- Regulatory planning for a new advanced therapy medicine, including orphan designation and hospital practices.
- Litigation on supplementary protection certificates before the European Court of Justice and at national level.
- Legislative and regulatory aspects of the distribution systems for medicines within specific member states and the interconnection with parallel trade.
- Detailed input into the legislative process for the new Directive on Falsified Medicines.



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Advising drug, biologic, device, and food manufacturers and trade associations on a range of regulatory and consumer protection issues involving the US FDA, US Consumer Product Safety Commission and US Department of Agriculture.



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#### Recent transactions

- Working with a number of trade associations and ad hoc coalitions, and many major biopharmaceutical companies and numerous smaller companies on regulatory and policy issues globally.
- Deeply involved in developing the BPCIA and is working on the development of biosimilar policy worldwide.
- Regulation of:
  - clinical trials;
  - drug safety (such as, risk management plans and pharmacovigilance); paediatric and orphan exclusivity; advertising and labeling;
  - interactions with healthcare professionals;
  - importation;
  - counterfeiting;
  - online pharmacies;
  - generic drug approval;
  - comparative effectiveness research.

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