

EGA Docket response
Docket No. FDA-2010-N-0477

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. FDA-2010-N-0477

Dear Sir/Madam:

Thank you for granting us the opportunity to provide the European Generic medicines Association's (EGA's) point of view on what has been learned in the European Union¹ and how FDA may consider our experiences useful for the implementation in the US of the new abbreviated biosimilar pathway, created in the Biologics Price Competition and Innovation Act of 2010.

EGA members have extensive experience with biosimilars and with biologics approved as originator products. Our members are the developers of all of the biosimilar products approved and marketed in the EU², and many also have products approved in other highly regulated markets, including Japan, Canada, Australia and the US³. Biosimilars have been in use in the European Union for over four years, the first having been approved in early 2006, and there have been no unexpected or unusual adverse events with any of them. A total of 13⁴ biosimilars are now approved, and they include somatropin, epoetin and filgrastim products.

The European Medicines Agency (EMA) involved EGA and its members closely in the development of the general and product class specific guidelines that were generated concurrently in regard to these products. The joint learning of industry side by side with our regulators, as well as with other stakeholders, was constructive and synergistic. This led to scientifically sound, experience-based guidance documents. Also, EMA did not require product specific guidelines to be in place before products were approved⁵.

Since 2007, in its position as a Non Governmental Organisation into official relationship with the World Health Organization (WHO), the EGA also worked with the WHO to develop their guidelines⁶, as we believe access by patients in the less regulated markets to high quality, affordable biologics is extremely important.

It is also important to EGA to set straight some of the misrepresentations that we believe have arisen at the FDA Public Meeting⁷, where at least one presentation⁸ did not accurately reflect what we have seen in the European Union. We consider such statements disrespectful to our regulators at EMA/EC. Reacting to similar anti-biosimilars statements, Nicolas Rossignol⁹, then Administrator of the EC's pharmaceuticals, made the following, forceful statement on questions of safety concerning EU biosimilars at EGA's 2008 Annual Meeting:

"I don't judge case by case, but I have a message: we have promoted and developed with the European Medicines Agency a special biosimilars framework. So we are confident that if a product meets all the requirements and gets a marketing authorization from the commission, it means that the product is as safe and effective as any other product authorized by the commission."

We believe that FDA, through their licensure of the originator biopharmaceuticals, already has all the expertise and experience necessary to review high quality, safe and effective biosimilars for the US market. EGA is confident that FDA will, in addition, leverage the experience gained in the EU and offers to broadly share these learnings with FDA. We also look forward to regulatory cooperation in the future for those products yet to be approved as biosimilars, such as Monoclonal Antibodies (mAbs)¹⁰.

A. Biosimilarity

1. *What scientific and technical factors should the agency consider in determining whether the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components?*
2. *What scientific and technical factors should the agency consider in determining the appropriate analytical, animal, and clinical study or studies to assess the nature and impact of actual or potential structural differences between the proposed biosimilar product and the reference product?*
3. *What range of structural differences between a proposed biosimilar product and the reference product is consistent with the standard “highly similar” and may be acceptable in a 351(k) application if the applicant can demonstrate the absence of any clinically meaningful differences between the proposed biosimilar product and the reference product?*
4. *Under what circumstances should the agency consider finding that animal studies or a clinical study or studies are “unnecessary” for submission of a 351(k) application?*

The fundamental scientific principle that underlies any biosimilar application in the EU is the demonstration of similarity at the analytical and biological levels. With this foundation, subsequent preclinical or clinical studies can be limited in extent and will largely be of a confirmatory nature.

Today the technologies exist to develop biosimilars whose molecular properties optimally match those of their reference products. EGA’s members have pioneered the development of these technologies.

The first step in developing a biosimilar is creating a thorough understanding of the molecular properties of the reference product. For this purpose, multiple lots of reference material are purchased over a number of years and subjected to thorough analytical and biological characterization. With the help of multiple powerful and orthogonal analytical methods and bioassays, even complex glycoproteins can be described in great detail. In the course of this process, the biosimilar developer learns much about the variability of the molecular properties of the reference product – both from batch to batch and over time. Manufacturing changes in the reference product are easily picked up by modern analytics and manifest themselves as pronounced quality shifts. This variability of the reference products defines the target ranges, or the “goalposts” for the molecular properties of the biosimilar.

Once the target ranges are defined, the company systematically engineers a cell line and a manufacturing process to create a biosimilar whose molecular properties optimally match those of the reference products, aiming to lie between the goalposts for all relevant properties. With modern technologies and the significant efforts of our members, this can be achieved with great success today.

This way, a product is systematically designed, or reverse engineered, that can be expected to be equivalent to the reference product in both non-clinical and clinical terms (see Figure 1. below).

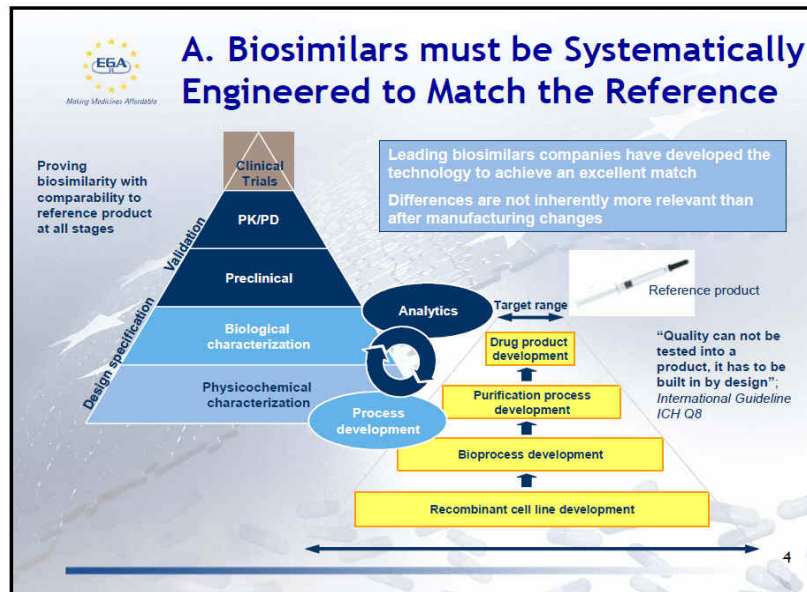


Figure 1. Summary of the development model for a biosimilar: Note the cycle of analytics and process development that is repeated for a biosimilar, and that would not be the case for an originator biologic

Should any minor differences remain, they have to be investigated analytically, in bioassays and, if necessary, in animal studies to rule out any potential clinical relevance. Figure 2 summarizes how a company can arrive at scientifically sound acceptance criteria for the molecular properties of its biosimilar product.

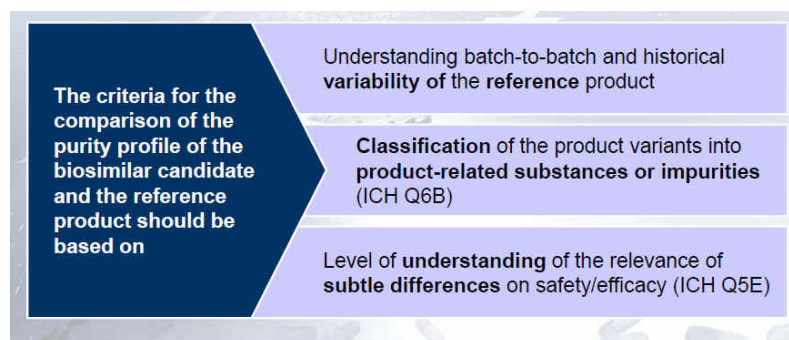


Figure 2. The criteria to establish comparability/similarity between two biologics

The theme of demonstrating similarity for a biosimilar is an extrapolation of the comparability principles initiated in the US¹¹, which were adopted with revisions in the EU¹², and formed the basis for ICH Q5E¹³ and subsequently for the EU regulations and guidelines on biosimilars¹⁴. It should be noted that the EMA never limited the application of comparability to a single company making manufacturing changes to its own product, instead it was held to be a scientific evaluation irrespective of the source (manufacturing change or biosimilar) of the two entities being compared¹⁵. Thus, while we all recognize that ICH Q5E defines comparable as having “highly similar quality attributes”, and limits its use to a single company with their own product, the EU guidelines use the

terminology of similarity and comparability interchangeably within the same regulatory documents, and recognizes that the two terms refer to the same scientific principles.

Also, it is critically important to note, that in all jurisdictions that use ICH standards, comparability when used as the basis for manufacturing changes, presupposes that the product before and after the change is fully substitutable/interchangeable, and the label on the product does not change. This also means that comparability is the basis for extrapolation between all the indications of the original, pre-change product, irrespective of whether the mechanism of action of the pre-change product is known or not. Besides this, health care providers and patients are not informed that any change has occurred¹⁶. Generally speaking, these same principles should also apply to biosimilars that have demonstrated a degree of similarity in line with that expected for comparability after a manufacturing change.

This raises a critical point about the availability of the reference product only in the form of the drug product, and not in the form of the drug substance¹⁷. Some opposed to biosimilars have suggested that this makes it impossible to make a biosimilar because the active ingredient is not available to the biosimilar company for use during development, and others maintain that a different process will always make a different product. However, these are not valid arguments as it is the final product that is used by the patient and that is available for direct comparison using comparability principles. In most cases excipients do not interfere with analytics and the product can be analyzed directly. For those cases where excipients do interfere with analytics, methods for separating the drug substance from the interfering components can be developed, and it can be validated that this separation does not influence the properties of the drug substance.

As successfully used in the European Union, the scientific grounding of similarity and comparability is the same, and the regulators endeavor to apply these principles consistently to both, original biologics and biosimilars. A high degree of similarity forms the basis for abbreviated clinical programs, approvability, extrapolation of indications, interchangeability, and trust by patients and healthcare providers.

B. Interchangeability

1. *What factors should the agency consider in determining whether a proposed interchangeable biological product can be "expected to produce the same clinical result as the reference product in any given patient?"*
2. *What factors should the agency consider in evaluating the potential risk related to alternating or switching between use of the proposed interchangeable biological product and the reference product or among interchangeable biological products?*

EGA believes that a high degree of similarity, consistent with comparability after a manufacturing change, is the adequate scientific basis for interchangeability. Nevertheless, interchange has occurred broadly through tender systems. There have been no problems identified as a result of this *de facto* interchangeability.

The EU pharmaceutical legislation¹⁸ does not address interchangeability, which remains with the authority of the member states. As a result, EMA is not involved in determining interchangeability.

In some countries, through tender pricing methods (put in place by national, regional, or private healthcare insurers), *de facto* interchange of large patient populations occurs on a regular basis, and sometimes more than once¹⁹. Prominent examples are Germany, the UK, and Poland. One example of wholesale switching is Poland where somatropins have been routinely switched, based on who wins the annual nationwide tender²⁰. In all of these cases, there has not been any evidence of any problems due to switching, and, in particular, no immunogenicity concerns have been raised.

However, it is important that similarity/comparability is established as the basis for interchangeability. One leading originator company has argued for substitution between different erythropoiesis-stimulating

agents (ESAs) that have never been compared. They have argued that all ESAs, both first generation (Epoetins alfa, beta etc., such as Eprex[®], NeoRecormon[®], Epogen[®], Procrit[®]), second generation (Darbepoetin alfa, i.e. Aranesp[®]), AND third generation (Methoxy Polyethylene Glycol-Epoetin Beta - Micera[®]) are all interchangeable for the purposes of participating in the bidding for available tenders²¹.

"EPOs available in Germany could "generally all be used equally therapeutically for the treatment of anaemia," the originator company wrote in June in its petition to the Landgericht [Regional Court] Düsseldorf for an interim injunction.

And furthermore, the arguments made by the originator company were agreed by those responsible for the purchasing of the ESAs, with further clarification of what this meant in terms of interchangeability of the products:

"The Procurement Division agrees with [the originator company's] arguments, whereby EPO preparations on the market, i.e. also biogenerics, are "comparable to each other and interchangeable with one another" in terms of "indication, effect and therapy".

The originator company was specifically questioned as to how this compared to its positions elsewhere on comparability:

"[The originator company] does not acknowledge having breached any taboo and said, when asked, that although copies of biotech preparations that are no longer protected by patent were not identical to the originals, the comparability was large enough to put them on a common medical level and to demand more competition."

The scientific basis for interchangeability is a high degree of similarity, confirmed at the analytical, biological, non-clinical, and clinical levels. Such data are not available for all products mentioned by the originator company above. They are, by definition (and regulatory requirement), always available for a biosimilar in comparison to its reference product. Therefore, EGA is convinced that safe interchange is possible, and believes that the necessary high degree of similarity must be established in a thorough similarity exercise and confirmed by regulators first. This should equally apply to original products and biosimilars.

C. Patient Safety and Pharmacovigilance

- 1. What factors unique to proposed biosimilar or interchangeable biological products and their use should the agency consider in developing its pharmacovigilance program for such products?*
- 2. What approaches can be undertaken by the agency, industry, or health care community to ensure appropriate pharmacovigilance for biosimilar and interchangeable products?*
- 3. Assuming each product is given a unique nonproprietary name, should a distinguishing prefix or suffix be added to the nonproprietary name for a related biological product that has not been demonstrated to be biosimilar, a biosimilar product, or an interchangeable product to facilitate pharmacovigilance? What factors should be considered to reduce any negative impact on the health care delivery system related to unique nonproprietary names for highly similar biological products?*
- 4. What safeguards should the agency consider to assist the healthcare community when prescribing, administering, and dispensing biological products to prevent inadvertent substitution of products not identified as interchangeable without the intervention of the prescribing health care provider?*
- 5. What are some mechanisms that FDA may consider to communicate findings that a particular product is or is not biosimilar to or interchangeable with a given reference product?*

Suitable pharmacovigilance and risk management systems are in place in the US and the EU today, and no new systems specific to biosimilars are needed. Traceability can be ensured using the currently required and available information. The use of separate non-proprietary names in different territories would lead to confusion rather than to transparency.

In the EU, the current Volume 9A²² stipulates that any adverse reaction report for *ANY BIOLOGICAL* has to mention the approved name and the batch number. This is sufficient to fully identify a product and trace the adverse reaction back to the correct lot. The same approach has now been put into the new pharmacovigilance legislation.

On 29 November 2010, the EU Council, representing the 27 Member States, adopted a regulation and a directive aimed at strengthening the EU system for the safety monitoring of medicinal products for human use ("pharmacovigilance"), hereby better protecting public health²³. The EU institutions have not proposed a distinct International Non-proprietary Name (INN) for biosimilars because it is not needed to uniquely identify products and it is therefore neither required for pharmacovigilance purposes. The text agreed by the EP and the Council will now be transformed into hard law at the beginning of 2011²⁴.

In the European Union, all biosimilars are subject to an EU Risk Management Plan (EU-RMP), which may include Post Approval Safety Studies (PASS), as well as specific educational and pharmacovigilance measures. The detail and extent required by EMA is that appropriate to what is known about the medicinal product at the time of its approval. Thus, biosimilars include elements learned with the use of the originator biologic over its lifetime, and the biosimilar company does not have to unnecessarily repeat any studies²⁵.

EGA fully supports the collaboration of EU/EMA/FDA on product specific Risk Management initiatives, further convergence of Risk Management formats, and the FDA/EMA collaboration on biosimilars under the EU-FDA Transatlantic Administrative Simplification Action Plan²⁶. Indeed, as already laid down on FDA's website, there is already a specific element that addresses "Collaboration on biosimilar medicinal products / follow on biologicals", which we anticipate will continue.

EGA agrees that it is important to clearly identify all biologics and be able to state the name and the batch number in case a suspected ADR is reported. However, we see no basis for any changes to the current US system. Improving the quality of reporting and data collection would solve this issue. The payers who spoke appeared confident at their ability to trace products to the individual lot of the concerned product²⁷, including for small molecule drugs where vastly more volume of product is in use. We defer to their US experience and their confidence in the current system. Rather than inventing new systems, it must be ensured that the available information, which is fully sufficient to clearly identify each product and lot, is reliably captured by the existing systems²⁸.

Naming is *NOT* an issue actually addressed in BPCIA, but is a topic around which there has been much recent international debate. In the EU, companies do not have to apply for an INN from WHO for any medicinal product. The use of the same INN for a biosimilar is based on EMA's scientific assessment as part of the review process and EMA's finding that the biosimilar exhibits an adequately high degree of similarity to its reference product. EGA believes that a company should be entitled to use the same INN for its biosimilar based on the demonstration of similarity.

Similarly, as we understand, the US has always adhered to the INN process, and FDA has informed WHO, as well as the international community more broadly, of its intention to continue that policy in the context of biosimilars on the basis that demonstrably comparable products should share identical names²⁹. EGA knows of no reason for FDA to change this sound and well-considered approach. Requiring a non-proprietary name different from that used for the same product in the EU would indeed introduce greater naming complexity and would seriously undermine the international exchange of pharmacovigilance data.

Furthermore, requiring a non-proprietary name different from that of the reference product, then all products subject to a manufacturing change would also have to be issued new non-proprietary names.

Thus, EGA knows of no changes that are needed as the current system works well when the data is reported. Indeed not only are there no changes needed that are specific to biosimilars in the US, but were the US to adopt a different policy with the USAN³⁰ (recognizing that in the US naming is ultimately a USP responsibility³¹), it would undermine the fundamental value of the INN system as a way to inform

healthcare providers worldwide about the active ingredients in the medicines they give their patients. We are confident that FDA will take this into account when making its decision on non-proprietary names for biosimilars.

D. The Use of Supportive Data and Information

From a scientific perspective, to what extent, if any, should animal or clinical data comparing a proposed biosimilar product with a non-U.S.-licensed comparator product be used to support a demonstration of biosimilarity to a U.S.-licensed reference product? What type of bridging data or information would be needed to scientifically justify the relevance of the comparative data?

Global development for biosimilars is an essential prerequisite for ensuring affordability and patient access, which was the key motivation of US legislators in creating the BPCIA. If there is sufficient evidence that a reference product from another ICH region (esp. the EU) is equivalent to the US reference product, the repetition of nonclinical and clinical studies should not be required.

The spirit of the BPCI Act is to enhance the affordability of and patient access to often life saving biologics. Efficiency of the development programs is an important prerequisite for being able to offer these important drugs at lower prices. This would be compromised, however, should full development programs have to be repeated for each and every country or region. Requiring the use of a nationally licensed reference product for every comparative study in the program would *de facto* lead to such a situation for purely legalistic reasons.

In addition, conducting animal studies and human clinical studies comparing biosimilars with reference products sourced from different jurisdictions in situations where these reference products are known to be equivalent, would raise ethical concerns, and thus run against international guidelines for the conduct of animal and human studies.

It has proven very resource intensive to harmonize regulations after they have already been adopted in separate jurisdictions, even for the highly regulated markets³². Thus, biosimilars offer the excellent opportunity to coordinate regulatory requirements from the beginning and for each jurisdiction to learn from each other, as suits their individual statutory and public health situation.

A conservative implementation of the statutory language by FDA could create an artificial problem with respect to the originator reference product for a biosimilar. While in the European Union an EU licensed reference product is required for a biosimilar application³³, and in the US a US licensed reference product is required³⁴, in neither jurisdiction does the law state that every study included within the biosimilar application has to be conducted with the domestically-sourced product.

Thus, EGA supports scientifically appropriate bridging between applications for each jurisdiction, not only because in some cases the difference between the EU and US reference product is the label on the vial or syringe, not its contents. It is up to the company to provide the data that bridges the two reference products, but they should be allowed to do so as is appropriate to the available science.

The clearest demonstration of equivalence can be obtained from documentation available in the public domain, and/or analytical data demonstrating a high level of similarity between reference products from different jurisdictions. In cases where, for example, a different formulation is used in the US reference product compared to, e.g., the EU licensed reference product, additional proof of the equivalence of the two reference products may have to be provided in the form of rigorous comparative clinical phase I PK/PD studies. See Figure 3.

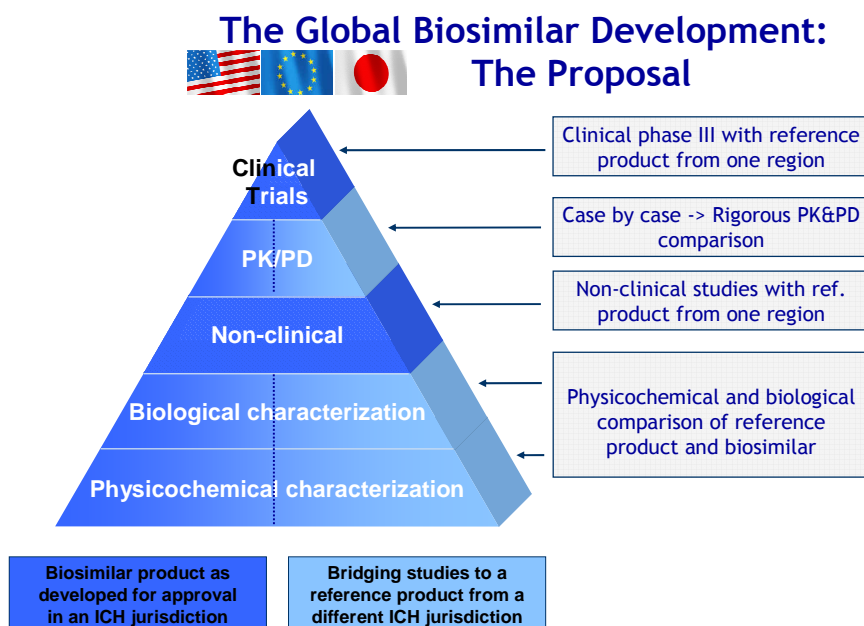


Figure 3. A science-based strategy for the concurrent development of a biosimilar in two highly regulated (ICH) markets.

Global development is critical to expedite development and to maximize competition in the biologics market. It is the only way to improve worldwide availability, affordability and patient access to high quality biopharmaceuticals. At the same time, ethical issues related to the unnecessary repetition of animal and human studies would be avoided, especially in cases in which the originator product is equivalent in different ICH countries.

F. Guidances

1. *What types of guidance documents for industry should be a priority for the agency during the early period of implementation?*
2. *Section 351(k)(8)(E) of the PHS Act permits the agency to indicate in a guidance document that the science and experience, as of the date of the guidance document, with respect to a product or product class (not including any recombinant protein) does not allow approval of a 351(k) application for such a product or product class. What scientific and technical factors should the agency consider in determining if the existing science and experience are sufficient to allow approval for a product or product class under section 351(k) of the PHS Act?*

EGA believes the best way of developing guidance documents is by basing them on the experience gained during the course of the review and approval of biosimilar products. Approvals should not be held up by the lack of written guidance.

In the EU, guidelines do not need to be final for the EMA to evaluate and the European Commission to approve a biosimilar. The only block on biosimilar applications is the regulatory data exclusivity on the reference product³⁵. By way of example, the EMA guideline on somatropins was adopted after the Omnitrope[®] and Valtropin[®] approvals.³⁶

Some of the guidelines are under revision because extensive experience has been gained through Scientific Advice Procedures and Marketing Authorisation Application (MAA) assessments by the EMA, as well as progress in the collective understanding as to what is needed in biosimilar dossiers. The revised EPO guideline recognizes that the guideline needed refinement to take into account several practical considerations relating to the development of biosimilar epoetins³⁷. The EU will continue to collect experience with the biosimilars already approved using the current CHMP guidelines, and with which no unexpected quality, safety or efficacy issues have arisen.

We also expect the EMA and FDA to update each other regularly using their existing channels (under the permanent confidentiality agreement). EGA supports other efforts for international regulatory exchange and cooperation, especially between ICH regions, as this is becoming increasingly important to reduce duplication of effort and preserve scarce resources.

In the meantime, we have great confidence that FDA can review and approve biosimilars in the absence of general and product-specific US guidance. We believe that FDA, through its licensure of the originator biopharmaceuticals, already has all the expertise and experience necessary to review high quality, safe and effective biosimilars for the US market.

CONCLUSIONS:

EGA has welcomed the opportunity to participate at the start of FDA's implementation of the BPCIA, and its new statutory authority, to review and approve biosimilars and interchangeable biosimilars. In this document, we submit the following facts and convictions to FDA for consideration:

The fundamental scientific principle that underlies any biosimilar application in the EU is the demonstration of similarity at the analytical and biological levels. With this foundation, subsequent preclinical or clinical studies can be limited in extent and will largely be of a confirmatory nature.

EGA believes that a high degree of similarity, consistent with comparability after a manufacturing change, is the adequate scientific basis for interchangeability. Interchange has occurred broadly through tender systems. There have been no problems identified as a result of this *de facto* interchangeability.

Suitable pharmacovigilance and risk management systems are in place in the US and the EU today, and no new systems specific to biosimilars are needed. Traceability can be ensured using the currently required and available information. The use of separate non-proprietary names in different territories would lead to confusion rather than to transparency.

Global development for biosimilars is an essential prerequisite for ensuring affordability and patient access, which were the key motivation of US legislators in creating the BPCIA. If there is sufficient evidence that a reference product from another ICH region (esp. the EU) is equivalent to the US reference product, the repetition of nonclinical and clinical studies should not be required.

EGA believes the best way of developing guidance documents is by basing them on the experience gained in the course of the review and approval of biosimilar products. Approvals should not be held up by the lack of written guidance.

EGA is confident FDA will build the new pathway based on sound science and its vast experience in biologics. We look forward to continuing to share our experience with these increasingly successful products in the European Union, and we invite FDA and other US stakeholders to contribute to our efforts in the EU regarding those products yet to be approved as biosimilars, such as Monoclonal Antibodies (mAbs)³⁸.

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- ¹ Similar biological medicinal products, now commonly called 'biosimilars' became possible in the EU under DIRECTIVE 2004/27/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0034:0057:EN:PDF> (accessed 17 December 2010)
- ² One company that is the license holder to a biosimilar approved with the same dossier is not a full member of EGA, but all of the other companies that sponsor successfully marketed EU biosimilars are EGA members.
- ³ The first EU approved biosimilar, Omnitrope®, was approved in the US as a FD&C Act 505(b)(2) biologic drug. The Low Molecular Weight Heparins in the EU must follow the biosimilars pathway, but the US has approved one already as a fully substitutable Abbreviated New Drug Application (ANDA or 505(j) application), or "generic biologic".
- ⁴ There have been 18 biosimilar products' submissions. 13 received approval, one received a positive scientific opinion but had to be withdrawn by the applicant before approval by the EC due to the lack of a license partner, 3 were withdrawn before CHMP scientific opinion and one has been rejected by the CHMP.
- ⁵ The first biosimilar approved in EU was Omnitrope® (somatropin) and a positive CHMP opinion and the EC marketing authorization occurred prior to finalization of the EU Somatropin guideline.
- ⁶ EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION, Geneva, 19 to 23 October 2009. GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs). Available at: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf (accessed 17 December 2010)
- ⁷ See Agenda, Approval Pathway for Biosimilar and Interchangeable Biological Products Public Meeting, Part 15 Public Hearing, November 3, 2010 Presentations, available at www.fda.gov/downloads/Drugs/NewsEvents/UCM230995.pdf (accessed 17 December 2010)
- ⁸ See Agenda for Approval Pathway for Biosimilar and Interchangeable Biological Products Public Meeting, Part 15 Public Hearing, November 3, 2010 Presentations (Presentation by Richard Kingham, Covington & Burling LLP). Available at: <http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm> (accessed 17 December 2010); also the presentation given is available at <http://www.regulations.gov/search/Regs/home.html#searchResults?N=0&Ne=11+8+8053+8098+8074+8066+8084+1&Ntk=All&Ntx=mode+matchall&Ntt=FDA%202010-N-0477> (accessed 17 December 2010)
- ⁹ SCRIP World Pharmaceutical News 24 April 2008, reporting on EGA Meeting, London
- ¹⁰ EMA Draft Guideline on similar biological medicinal products containing monoclonal antibodies. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf (accessed 17 December 2010)
- ¹¹ FDA Guidance "Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products", Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), published April 1996. Available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm> (accessed 17 December 2010)
- ¹² 2003 EU Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substances: Quality issues (CPMP December 2003). Available at: <http://www.emea.europa.eu/pdfs/human/bwp/320700en.pdf> (accessed 17 December 2010)
- ¹³ ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CPM, December 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted 26 April 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, pages 37861-37862. Available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf
(accessed 17 December 2010)

- ¹⁴ EU Homepage on Biosimilar Medicines: Available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac0580281bf0 (accessed 17 December 2010);
EMA Homepage for Guidelines on Biosimilars. Available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c (accessed 17 December 2010)
- ¹⁵ 2003 EU Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substances: Quality issues (CPMP December 2003). Available at:
<http://www.emea.europa.eu/pdfs/human/bwp/320700en.pdf> (accessed 17 December 2008)
- ¹⁶ The use of comparability is made public in Europe as EMA publishes information on each product on its website, but this does not link the change to batch number, and is not routinely accessed by physicians and their patients. Our understanding is that the FDA does not publish this information at all, and healthcare providers and patients could not therefore access it even if they wanted to.
- ¹⁷ Unlike small molecule drugs where active pharmaceutical ingredients are readily available, for biologics, very few standards are available through the pharmacopeia's (EU, US and Japan) or elsewhere. However, by definition the marketed product is available commercially and ultimately it is this that the biosimilar must be shown to be similar to, and not the drug substance.
- ¹⁸ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use, as amended, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf (accessed 18 December 2010)

Official Journal L – 311, 28/11/2004, p. 67 – 128
- ¹⁹ Poland issues national tenders for Somatropin – All Polish patients on Somatropin have been switched from Genotropin® to Omnitrope® and back to Genotropin®
- ²⁰ Poland, through use of tenders, routinely switches all the patients needed somatropin from one product to another and back again, and there have been no safety or efficacy problems
- ²¹ Amgen's statements in the context of the German Baden-Wuerttemberg tenders (all epoetins are the same). Amgen and Roche Battling about Patent Protection: In the fight for German discount contracts, a US pharmaceutical group is demanding a European-wide invitation to tender - Original preparation and copies should be placed on an equal footing. Certified translation of Article from the FINANCIAL TIMES Deutschland, Wednesday, 20 August 2008 Daily paper Internal publication no.: 146200 [Attached]; Also see FOBs Amgen 1112-Ruling-BKA **Extract (page 7) of** FEDERAL CARTEL OFFICE, Kaiser-Friedrich-Str.16, 53113 Bonn 3rd Awarding Chamber – Ref. No. VK3 – 107/08 R U L I N G [Attached]
- ²² Volume 9A – Pharmacovigilance for Medicinal Products for Human Use (version September 2008), available at:
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm (accessed 17 December 2010)

Chapter 4.1. : For adverse reaction reports relating to biological products, the definite identification of the product with regard to its manufacturing is of particular importance. Therefore, Marketing Authorisation Holders should give advice to reporters to provide the name of the medicinal product (in accordance with Article 1(20) of Directive 2001/83/EC, see Annex 1.3) and the batch number and should follow up the reports where this information is missing for completion
- ²³ Council Press Release. Available at:
http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/118080.pdf (accessed 17 December 2010)

²⁴ New Article 102 (3) of Directive 2001/83/EC, as amended : Member States shall make sure, through the methods of collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report; with due regard to the name of the medicinal product (in accordance with Article 1(20)) and the batch number.

source: 2008/0260 (COD)

²⁵ Certain adverse events were not predicted when the originator product was approved, but observed when it was marketed; specific requirements may then be applied to the biosimilar in terms of monitoring for these responses too.

²⁶ EU-FDA Transatlantic Administrative Simplification Action Plan, available at <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/EuropeanUnion/EuropeanCommission/ucm114338.htm> (accessed 17 December 2010)

²⁷ Agenda at Approval Pathway for Biosimilar and Interchangeable Biological Products Public Meeting, Part 15 Public Hearing, November 3, 2010 - Presentations by Presentation of Steve Miller, MD, MBA, Express Scripts, Inc.; See Presentation of Scott Reid, PharmD, CVS Caremark Corporation; Steve Russek, RPh, Medco Health Solutions (includes Accredo). Available at: <http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm> (accessed 17 December 2010)

²⁸ A minimum of **two** data elements are necessary for effective track and trace. These are: Brand name or manufacturer, plus INN or New Drug Code number (NDC#), plus lot number. If there is a Brand name, the INN is known by default, so Brand name plus lot number will suffice, however redundancy creates additional checks for the system.

²⁹ U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Nonproprietary Name (INN) Policies for Biosimilars September 1, 2006. We ask that the entirety of this statement also be entered into the docket FDA-2010-N-0477.

³⁰ United States Adopted names (USAN) Home page. Available at: <http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council.shtml> (accessed 17 December 2010); USAN Naming Biologics. Available at: <http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/naming-biologics.shtml> (accessed 17 December 2010)

³¹ USP General Information 1121 Nomenclature. Available at <http://www.usp.org/pdf/EN/USPNF/1121Nomenclature.pdf> (accessed 17 December 2010)

³² International Committee Harmonization; <http://www.ich.org/home.html> (accessed 17 December 2010)

³³ DIRECTIVE 2004/27/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0034:0057:EN:PDF> (accessed 17 December 2010)

³⁴ BPCIA - "(4) The term 'reference product' means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)."

³⁵ Article 10 of [Directive](#) 2001/83/EC as amended lays down the new EU protection rules:

- 8 years data exclusivity for the reference product calculated from the date of first MA (i.e. a biosimilar application can be filed for approval any time after 8 years) but
- 10 years market exclusivity for the reference product, respectively
- 11 years market exclusivity maximum if the MAH of the reference product obtains one or more new indications within the first 8 years of authorisation. The additional one year of market exclusivity on the whole product is only granted if these additional indication(s) are held to bring a significant clinical benefit.

These new rules of protection apply to all reference products submitted for approval on and after 30 October 2005. For the reference products approved before this date, 10 years data exclusivity applies.

- ³⁶ Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Somatropin came into effect in June 2006. Omnitrope® was approved on 12 April 2006 and Valtropin® on 24 April 2006 i.e. before coming into force of this guideline. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50003956.pdf
(accessed 17 December 2010)
- ³⁷ Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision) Came into effect 1 October 2010. This guideline replaces the Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products containing Recombinant Erythropoietins (CHMP/94526/05). Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089474.pdf
(accessed 17 December 2010)
- ³⁸ EMA Draft Guideline on similar biological medicinal products containing monoclonal antibodies. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf
(accessed 21 December 2010)