February 29, 2012

Submission of comments on 'Concept paper on the revision of the guideline on similar biological medicinal product.' (EMA/CHMP/BMWP/572643/2011)

Comments from:

Name of organisation or individual
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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Biotechnology Industry Organization (BIO) thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the "concept paper on the revision of the guideline on similar biological medicinal product." BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. The decision to revise the overarching guidance document for biosimilars is welcome for the reasons given in the problem statement and further commented on below. We recognize that updating the annex guidance documents will require alignment with the overarching guidance. Specific, detailed comments are included below. We would be pleased to provide further input or clarification of our comments, as needed.	

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	A discussion of the general principles of trials to demonstrate clinical equivalence should be included in the overarching document: • A formal demonstration of clinical equivalence with the reference product would be preferred, except where there is a scientific rationale for a non-inferiority design in an indication approved for the reference product. • If the study is being used for extrapolation, demonstration of safety and effectiveness in a sensitive population is necessary to inform safety and efficacy relevant to other indications. The mechanism of action should be the same in the indication in which the clinical trials are conducted and in the indication applied for by extrapolation. • Clinical justification and pre-specification of equivalence margins for the primary endpoint are required. • For biological products that are administered over a short period, efficacy trials are typically conducted with a single primary endpoint. • For biological products that are administered over a long period where the dose is titrated to effect, trials are typically conducted with co-primary endpoints to measure efficacy and dose. • Clinical equivalence studies are generally	

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	designed to demonstrate similar efficacy, and thus are not always statistically powered to demonstrate equivalent safety. While equivalent safety should be concluded based on a valid scientific rationale at the time of approval, in some cases, establishing clinical equivalence for safety may require additional or post-marketing safety studies. The biostatistical working party should consider writing a "Points to Consider" guidance on the design and analysis of trials with a clinical equivalence objective in a similar manner to the guidance that has been produced for the design and analysis of trials with a non-inferiority objective.	

2. Specific comments on text

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2. Problem statement, first bullet		*The principles of biosimilarity may have to be explained in a clearer way.* Comment: The ultimate aim of a biosimilar product development program is to establish the safety and efficacy of a product by establishing similarity to the reference medicinal product (RMP), rather than conducting a full clinical program to demonstrate safety and efficacy independently. This principle, together with other requirements for the demonstration of (bio)similarity to the RMP in terms of quality and safety, may permit consolidation and greater clarity on the basis of cumulative scientific advice, development and approval (and withdrawal/rejection) experience.	
2. Problem statement, third bullet		*Discuss the feasibility to follow the generic legal basis for some biological products.* Comment: **It is unnecessary to follow the generic legal basis for biosimilar products:** Since it is possible to adapt the type and quantity of data required for certain biosimilars without changing the current legal basis of Article 10(4) of Directive 2001/83/EC (and Section 4, Part II, Annex I to Directive 23001/83, as amended), there is no need to follow the generic legal basis for any biological product. Such adaptation could include	

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		changing the nature and amount of clinical data supporting the marketing application for a biosimilar product as appropriate on a case-by-case basis. EMA therefore already has the authority to assess whether a biological product is “simple” or “fully characterised” and adjust the nature and extent of supporting clinical data commensurate with the nature of the biological product in question and the supporting quality data. **It is inappropriate to follow the generic legal basis for biosimilar products:** As described in the existing guideline, "by definition, similar biological medicinal products are not generic medicinal products since it is expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products." Taking into account the "feasibility to follow the generic legal basis for some biological products" clearly undermines the scientific and legal basis for the biosimilar pathway. Indeed, biosimilars do not meet the conditions in the definition of generics. Article 10(4) of the Directive 2001/83/EC, as amended, defines a biosimilar as a product that "does not meet the conditions in the definition of generic medicinal products." When looking at such conditions, it is clear that no medicinal products developed from biotechnical processes that are similar to a reference biological product meet such conditions:	

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		I) Such products do not meet the (first) condition of Article 10(2) of the Directive 2001/83/EC, as amended, namely to have "the same qualitative and quantitative composition in active substances... as the reference medicinal product." II) Such products do not meet the (third) condition of Article 10(2) of the Directive 2001/83/EC, as amended, namely "whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies." Conventional pharmacokinetic bioequivalence studies alone cannot assure clinical safety and efficacy of biological products. Pharmacokinetic bioequivalency studies only provide a limited short term exposure to the active substance/ingredient, and would not provide sufficient information with regard to efficacy, safety, or immunogenicity. Current analytical and *in vivo* methods cannot fully predict the immunogenicity profile of a biological product, as the human immune system is more sensitive than existing nonclinical (*in vitro* and *in vivo*) techniques. Further, while current techniques may be able to show quality differences, they still cannot predict if such differences will manifest a different clinical outcome or immunogenic response in humans. **The distinction between (1) chemical drugs/generics, and (2) biotechnology-derived medicinal products/biosimilars is helpful and should be preserved:**	

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		The fundamental distinction between (1) chemical drugs and generics, and (2) biotechnology-derived medicinal products and biosimilars that has been established in the EU legislative framework should be preserved in a clear and consistent manner. Such distinction is useful and necessary for the sake of (1) legal certainty and consistency in assessment of such products by the regulatory authorities, and (2) ensuring clear and correct functioning of such framework. It is inappropriate to refer to Article 10(2) of Directive 2001/83/EC, as amended (*i.e.* the generic legal pathway), as a potential legal basis for approving products developed from biotechnical processes, including biosimilars, as this Article is only concerned with the concept of essential similarity for generics of small molecules (chemical) drugs. As such, it is widely acknowledged that it is not possible for biological products to meet the criteria for inclusion in Article 10(2), *i.e.* have “the same qualitative and quantitative composition in active substance.” If biotechnology-derived products, including biosimilars, were authorized on the basis of Article 10(2) of Directive 2001/83/EC, as amended, as opposed to Article 10(4) (and section 4, Part II, Annex I Directive 23001/83, as amended, applicants would not be required to i)"provide results of appropriate preclinical tests or clinical trials"; ii) comply with Directive 2001/83, as amended, or iii) comply with existing EMA biosimilars guidelines. Then neither the CHMP/EMA nor the EC could require the applicant to provide any such data or,	

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		carry out any such test/trials, or refuse to grant marketing authorization on the ground that such data/justification or test/trials have not been provided. The enactment of Article 10(4) demonstrated clearly that such an outcome was not intended. Had there been a will that biosimilars be treated as generics, article 10(4) would not have been enacted. Proposed change (if any): remove bullet	
3. Discussion (on the problem statement), Paragraph 1		*The biosimilarity exercise follows the main concept that clinical benefit has already been established by the reference medicinal product, and that the aim of a biosimilar development programme is to establish similarity to the reference product, not clinical benefit. It may be of benefit to amend the guideline accordingly to make this principle, and its consequences, clearer to the reader.* Comment: The EMA draft mAb biosimilar guideline states that "[t]he focus of the biosimilarity exercise is to demonstrate similar efficacy and safety compared to the reference product, not patient benefit per se, which has already been established by the reference product." Perhaps the revised overarching biosimilar guideline should also describe the differences between the goals of the development plans for biosimilars vs. novel biologics.	

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3. Discussion (on the problem statement), Paragraph 2		*Numerous terms are in use for 'biosimilar' or 'similar biological medicinal product', and often the term 'biosimilar' has been used in an inappropriate way. It may therefore be prudent to discuss if a definition of 'biosimilar', in extension of what is in the legislation and relevant CHMP guidance, is necessary.* Comment: It is acknowledged that Article 10(4) of the Directive 2001/83/EC, as amended, defines a biosimilar by the fact that such product "does not meet the conditions in the definition of generic medicinal products." Similar to the World Health Organization (WHO) guideline, the EMA could recognize that other terms such as subsequent entry biologics, similar biotherapeutic products, etc. have been "coined by different jurisdictions to describe these products." However, the term "biogeneric" is a misnomer since the fundamental differences between biologics and traditional chemical pharmaceuticals preclude the extrapolation of regulatory processes used for traditional generics to these new biologic products.	
3. Discussion (on the problem statement), first bullet		*A discussion of equivalence of efficacy and safety aspects, should this be necessary and not be covered by the revision of the general non-clinical and clinical guideline.* Comment: Guidance on this issue is necessary. No robust or evidence-	

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		based consensus standards are available for the acceptable limits of similarity or difference between a biosimilar and its reference product in comparative studies of their non-clinical and clinical safety and efficacy attributes. It is recognized that the margins of similarity or difference will likely vary between product classes depending on the state of knowledge and experience, and the particular circumstances of the indication, patient population, and the characteristics of the product class. These considerations will therefore need to be addressed at the level of the product specific guidance for the development of biosimilar products. Presently, the overarching general guideline states: "The requirements to demonstrate safety and efficacy of similar biological medicinal products have to comply with the data requirements laid down in Annex I to Directive 2001/83/EC. General technical and product-class specific provisions are addressed in EMEA/CHMP guidelines (see Section 3.2). For situations where product-class specific guidance is not available, applicants are encouraged to seek scientific advice from EU Regulatory Authorities."	
3. Discussion (on the problem statement), second bullet		*There is mention of pharmaceutical form, strength and route of administration, which should be the same for biosimilar and reference medicinal product. The current text specifies if these are not the same then there should be additional data in the context of a "comparability exercise". It has to be reviewed if such a scenario is at all possible for a biosimilar.*	

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		Comment: This could be covered by providing the more detailed definition of a biosimilar. These aspects should be covered within the definition. The text from the initial adopted version of the guideline should be revised in relation to the issues of the pharmaceutical form and the route of administration. Pharmaceutical form and route of administration are addressed separately below. • *Pharmaceutical form*: the standard terms for pharmaceutical form describe the way and form in which the product is administered. All approved and current candidate biosimilars and their respective reference products are parenteral products; all of them are administered as solutions by injection or infusion. A change in the pharmaceutical form would therefore require a different route of administration to accommodate a non-solution form. The notion that a biosimilar product could have a different route of administration from its reference product is highly problematic in both scientific and regulatory aspects. Scientifically, the different routes of administration would lead to non-comparable bioavailability and pharmacokinetic (ADME), pharmacodynamic toxicokinetic, and immunogenicity profiles, which would confound any demonstration of biosimilarity. In regulatory terms, the inevitable consequence is that the biosimilar would be	

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		seeking an approval for a previously unapproved mode of use (*posology and method of administration* in the SmPC) of the reference product. In addition, where different routes of administration of existing products have been approved, these approvals have been of entirely new products on the basis of complete dossiers in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended (cross-referencing to the common quality, safety and efficacy elements of the original filing). This option is not available to the biosimilar, which does not have the right of cross-referral to data of the reference product in this way. As such, the inference in the original text of the pharmaceutical form of a biosimilar being “not the same” as its reference product, with or without provision of supporting data, should therefore be removed. We agree with the CHMP that this scenario is not at all possible for a biosimilar in the EU. We note that this scenario, if retained in the EU guidance, would conflict with the principles of biosimilar product development applicable in other jurisdictions. For example, the U.S. Biologics Price Competition and Innovation Act of 2009 (BPCIA) requires that “the route of administration, the dosage form, and the strength of the (biosimilar) biological product are the same as those of the reference product.” In cases where the reference product has multiple routes of administration approved, the biosimilar applicant should assess all routes of administration for safety, and the route of administration that is most sensitive for PK, efficacy, and safety	

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		(including immunogenicity) should be evaluated (in the clinical trial(s)). • *Route of administration*: the consequences of having a different route of administration have been discussed above (see Pharmaceutical Form). Therefore the inference in the original text of the route of administration of a biosimilar being "not the same" as that of its reference product, with or without provision of supporting data, should be removed. We agree with the CHMP that this scenario is not at all possible for a biosimilar in the EU. Moreover, this scenario, if it were to be retained in the revised EU guidance, would conflict significantly with the principles of biosimilar product development applicable in other jurisdictions. For example, the U.S. BPCIA requires that "the route of administration, the dosage form, and the strength of the (biosimilar) biological product are the same as those of the reference product." Furthermore, it would be valuable to stakeholders for EMA to confirm in the guideline that the dose of the biosimilar product must be the same as that of the reference product.	
3. Discussion (on the problem statement), third bullet		*The current guideline gives a long collection of guideline references, including outdated ones. It should be discussed if this is useful and feasible, given the fact that many more guidelines have meanwhile been drafted. Consideration should be given as to whether the scope of the document should*	

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		move away from this particular aspect. Comment: Users of guidelines are greatly aided by the referencing of related and relevant guidance documents. These serve to set the regulatory and scientific context in many instances, and to allow readers to compare and contrast texts to derive a better understanding of the expectations of regulators in different circumstances. This information is very useful for regulators and for industry in countries outside the EU that are not familiar with the European regulatory environment. In the particular case of guidance for the development of biosimilars, the body of EU regulation referenced in individual guidance documents sets clear standards against which regulators in other jurisdictions are able to develop their own regulatory frameworks and technical guidance. The continued accessibility of, and direction to, current related guidance is supported. The issue of outdated or withdrawn guidance can be addressed either by the use of a cautionary statement to invite the reader to check current guidance on the EMA website, or perhaps by the use of a hyperlink in the document to direct readers to a maintained up to date list of relevant guidance documents on the EMA website. This section of the guideline also provides exclusionary/exceptional language for vaccines & allergens, blood products, and gene or cell therapy products, which should be retained in the revised overarching guideline.	

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3. Discussion (on the problem statement), final paragraph		*Discussion is needed to clarify if in exceptional situations, e.g. where a very simple biological fully characterised on the quality level, a biological medicinal product could be authorised based on a bioequivalence study only combined with an extensive quality comparability exercise.* Comment: As discussed above in the context of the problem statement, third bullet, for legal, scientific, and practical reasons we do not believe it is appropriate or necessary to permit biological products to qualify under the generic pathway. As such, this topic should not be addressed in the revision of the guideline.	
Other Aspects of the initial guidance not referenced in the concept paper on which comment could be made:		*The chosen reference medicinal product must be a medicinal product authorised in the Community, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended.* Comment: We support the statement that the reference medicinal product must be a medicinal product authorised in the Community, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. However, considerable challenges exist for companies developing biosimilar products on a global basis, *i.e.*, challenges with respect to the need to address the use of a suitable reference product. For biosimilar development two practical issues arise:	

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		a. The use of data generated with non-EU reference products to support biosimilar authorization in the EU. In the EU, the reference product for biosimilars is defined under Directive 2001/83 Article 10(2) (a) which means that the reference product has to be authorized in the EU on the basis of a full dossier. Guidance would be welcome on when the use of data on non-EU sourced reference products (RPs) could be acceptable, and in particular what scientific justification should be provided to support the use of data on non-EU sourced RPs. Although it is understood that EU law apparently demands the biosimilarity exercise being conducted versus a EU reference product, and that data generated with a non-EU reference product will be only seen as supportive and censored from the final primary data analysis, flexibility on this issue is necessary to ensure the feasibility of global biosimilar development programmes. b. The use of non-EU reference product for bridging studies conducted in the EU. The FDA requires a strict legal definition of the reference product as being licensed in the USA but is open to consideration of non-US licensed product as being the comparator in global clinical trials providing that the non-US and US reference products are comparable	

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		and an appropriate reference product "bridging" exercise is successfully conducted. This consideration provides the potential for the EU reference product to be used globally in phase 3 clinical studies, upon the demonstration of pharmacokinetic and -dynamic comparability between the licensed products. We ask EMA to consider a similar approach. **Pharmacovigilance Monitoring:** The existing guideline sets an expectation that, "in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified." We recommend that, with this revision of the guideline, the EMA provide clarity on the expectations for how to achieve this objective, *i.e.* methods or processes that must be established to ensure that the biologic administered is clearly identified for the patient. There may be other methods or processes, but certainly unique nomenclature (including the assignment of a non-proprietary name or INN), readily distinguishable from that of the innovator's version of the product, ensures accurate traceability and identification of adverse events that may be attributable either to the innovator product or a given biosimilar version of it. Accurate identification of the product(s) associated with a suspected adverse event is fundamental to a reliable pharmacovigilance system. The lack of accurate identification of biologics could create public health concerns and potential safety risks. Use of the brand name	

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		when recording adverse events could support sound pharmacovigilance. In addition, for a period of time after the approval of any new biologic, including all biosimilars, the safety database will be limited and lack long term safety data. Thus, reliance on the unique brand name as a means for fully elaborating the safety profile for newly approved biologics during that time is essential. If two different biologic medicines have the same INN, and only the INN is indicated on the medical prescription, it is extremely challenging to determine which product was administered to the patient on the basis of the prescription. The INN is not a unique identifier, and may not reliably distinguish one product from another, which is critical where biologics with potential differences have been authorized with the same INN. Additionally, biologics sharing the same INN may have distinct characteristics that need to be clearly identified to healthcare professionals, and the INN does not convey distinguishing information about a product use. Furthermore, reliance solely on the INN for different biologics may lead healthcare professionals and patients to infer incorrectly that such products can be safely interchanged, while this may not be the case. The EU pharmacovigilance legislation stresses the importance of the brand name as a fundamental identification requirement in order to ensure the best means of accurate identification and traceability. Therefore, it is important that the EMA recognize that while prescribing guidelines are an EU Member State competency, unique nomenclature (*i.e.*, unique brand	

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		name) is an essential component to generate meaningful pharmacovigilance information and ensure accurate product identification/traceability.	

Please add more rows if needed.