July 25, 2014

Colombia’s Fifth Draft Decree on the Registration Process for Biological Medications—PhRMA Comments

General Comments:

We appreciate Colombia’s release on July 10, 2014 of an updated draft decree on the registration process for biological medicines (“new draft”) for public comment. We support the Colombian government’s continued efforts to create a comprehensive framework for registration of biological medicines. We have significant concerns, however, about the decree’s continued inclusion of a proposed third route for registration (the “abbreviated route”). This route is contrary to World Health Organization (WHO) guidelines and guidelines proposed in the United States and Europe and is inadequate to protect patient welfare. We are also concerned that the new draft continues to appear to permit indiscriminate approval of a biological medicine for any indication for which another product with the “same” active ingredient is approved. We respectfully encourage the Colombian government to address these and the other issues discussed below to promote access to safe and effective biological medicines in Colombia.

Abbreviated Route:

We remain concerned that Colombia’s proposed abbreviated route for approval of biological medicines will not reliably ensure quality, safety, and effectiveness of these products. We believe biological medicines should be approved either on a stand-alone basis with a full dossier of supporting quality, preclinical, and clinical evidence (as reflected in Colombia’s “complete file” route), or on the basis of a robust analytical, preclinical, and clinical comparison with a previously approved innovative (reference) biological medicine (as reflected in Colombia’s “comparability” route). This dual approach promotes patient safety as well as access to lower cost biological medicines. We urge the Colombian government to eliminate the proposed third, abbreviated route.

The abbreviated route poses unnecessary risks to patients and conflicts with accepted international standards in several fundamental respects. First, Article 6 does not require an applicant using this route to demonstrate that its proposed product is similar to an already-approved product, but nonetheless permits the applicant to abbreviate its testing of the proposed product. Specifically, Article 6 requires an applicant using the abbreviated route to submit some information involving the proposed product, i.e., immunogenicity data, manufacturing information, purity information, biological identity and physicochemical data, and potency and biological activity data. It does not, however, require an applicant to compare this information with that of a reference product approved on the basis of a full dossier. As international standards recognize, robust comparative testing against a reference product is critical to ensuring that a proposed product with a less-than-full dossier is safe and effective. For example, without head-to-head testing of a proposed product against a reference product using the same assays, it is impossible to evaluate whether antibodies and immunogenicity detected in the proposed product fall within an acceptable range.
By not requiring head-to-head comparative testing, the abbreviated route also departs from the proposed approaches of the European Medicines Agency (“EMA”) and U.S. Food and Drug Administration (“FDA”) regarding biological medicines that are extremely well-characterized. The EMA and FDA have proposed that applicants for these products could submit more truncated biosimilar applications based on evidence from orthogonal, fingerprint-like analytical analyses showing that the proposed product and reference product are highly similar. This more truncated application could contain data from a more abbreviated nonclinical or clinical testing program than a typical biosimilar program. Both agencies have made clear, however, that this more abbreviated approach is appropriate only if an applicant first demonstrates a high level of similarity between the proposed product and a reference product through robust, comparative analytical testing that evaluates a variety of product attributes. Colombia’s abbreviated route does not include this prerequisite. It thus lacks the foundation essential to justifying scientifically a more truncated approach.

Second, the new draft does not appear to require an applicant using the abbreviated route to submit any clinical data evaluating its product. Inconsistent with international standards, the draft does not even explicitly require (at a bare minimum) clinical pharmacokinetic and immunogenicity testing. Clinical testing is critical to meaningfully assess a product’s bioavailability and clearance. And analytical and nonclinical testing cannot predict the immunogenicity of a particular product in clinical use; the only way to effectively reduce

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1 FDA, “Draft Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product” (May 2014) at § III.C. (“[In some cases] the proposed biosimilar product [may meet] the statutory standard for analytical similarity based on integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences. [If the] results of these fingerprint-like analyses permit a very high level of confidence in the analytical similarity of the proposed biosimilar and the reference product, … it would be appropriate for the sponsor to use a more targeted and selective approach to conducting animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity.”); EMA, “Draft Guideline on Similar Biological Medicinal Products,” CHMP/437/04 Rev 1 (May 22, 2013) at § 3.3 (“In specific circumstances, e.g. for structurally more simple biological medicinal products, a comparative clinical efficacy study may not be necessary if similarity of physicochemical characteristics and biological activity/potency of the biosimilar and the reference product can be convincingly shown and similar efficacy and safety can clearly be deduced from these data and comparative PK data. Such an approach may have to be supported by additional data, for example in vitro and/or clinical PD data from a comprehensive comparative PD fingerprint approach.”).

2 Moreover, the abbreviated route is in some respects even less rigorous than the generic approval route in the United States and Europe for chemically synthesized medicines. This is because an applicant seeking approval under Colombia’s abbreviated route need not submit clinical data (e.g., comparative PK data) establishing bioequivalence of the proposed product and a reference product.

3 See, e.g., WHO, “Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)” (2009) (“WHO Guidelines”) at § 10.6 (“Immunogenicity of biotherapeutic products should always be investigated preauthorization. Even if efficacy and safety of [a biosimilar] and [reference product] have been shown to be similar, immunogenicity may still be different. The immune response to a biotherapeutic is influenced by many factors including the nature of the drug substance, product- and process-related impurities, excipients and stability of the product, route of administration, dosing regimen, and patient-, disease- and/or therapy-related factors. … Immunogenicity of a biotherapeutic should always be investigated in humans since animal data are usually not predictive of the immune response in humans.”).
uncertainty about whether features unique to a specific product may affect its immunogenicity is through clinical testing.

**Third**, to be eligible to use the abbreviated route, the proposed product must be (among other things) “adequately described.” Under the new draft, a product is adequately described in two circumstances. One circumstance is if an applicant submits information that permits detailed knowledge of its product’s identity, biological activity, physiochemical properties, and purity and explains why any differences from the reference standard used are “not … substantial.” This provision does not require an applicant to justify its claim of insubstantial differences using any particular kind of testing or to compare the product to a reference product (approved on the basis of a complete dossier). Further, even state-of-the-art analytical technology might not identify all clinically relevant differences between two biological medicines; and even seemingly minor analytical differences can have important clinical implications. Because the clinical implications of differences that do not appear “substantial” (however that term may be interpreted) — and of undetected differences — cannot be predicted with certainty, residual uncertainty about product similarity will exist after analytical characterization. This uncertainty can be addressed only through additional (clinical) testing.

According to the new draft, the other circumstance in which a proposed product will be deemed adequately described is if its active ingredient is included in a pharmacopoeial monograph. Because of the complexity of biological medicines, however, it is currently not possible to establish that two products from different manufacturers have the “same” active ingredient. Any single monograph claiming to provide identity standards for multiple biological products would almost certainly permit a wider range of specifications than those for any particular product. The WHO, the EMA, and FDA thus take the position that the comparison of a proposed product to a public reference standard or a pharmacopoeial monograph is not sufficient for approval of a biological medicine with a less-than-full dossier.

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4 Ministry of Health and Social Protection, Republic of Colombia, Draft Decree (“Draft Decree”) at Article 9.
5 Id.
6 Id.
7 See, e.g., WHO Guidelines at §§ 4 (“A reference biotherapeutic product is used as the comparator for head-to-head comparability studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a [reference product]. It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.”), 8.2.2 (“International standards and reference reagents are intended for calibration of national reference standards. … They are not intended for use as a [reference product] during the comparability exercise.”), 8.3 (“Specifications are employed to verify the routine quality of the drug substance and drug product rather than to fully characterize them. … International standards and reference reagents are intended for calibration of national reference standards. … They are not intended for use as a [reference product] during the comparability exercise.”), 8.3 (“It should be noted that pharmacopoeial monographs may only provide a minimum set of requirements for a particular product and additional test parameters may be required.”); EMA, “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1),” EMA/CHMP/BWP/247713/2012 (May 22, 2014) at §§ 1 (“A comparison of the biosimilar to a (continued…)

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Fourth, an applicant using the abbreviated route relies on evidence from specified health authorities outside Colombia indicating that the “active pharmaceutical ingredient” has a well-documented safety and effectiveness profile and is supported by considerable clinical experience and robust safety information.8 This global evidence may consist entirely of information concerning products marketed by manufacturers other than the applicant.9 As noted above, however, it is not possible to demonstrate that active ingredients in two biological medicines made by different manufacturers are the “same.” And characteristics such as immunogenicity can vary due to subtle product-specific differences (for example, differences in inactive ingredients or container closures), leading to product-specific safety and effectiveness profiles. Generalizations derived from other products within the same class of medicines therefore may have only limited relevance to the safety, effectiveness, and quality of a proposed product. Thus, as WHO, EMA, and FDA guidelines recognize, head-to-head comparative studies between a reference product and the proposed product are always essential.

For the above reasons, we strongly urge the Colombian government to eliminate the abbreviated route. This action would promote the public health and help bring Colombia’s laws for biological medicines in line with international standards. Doing so is all the more pressing in light of the World Health Assembly’s (WHA’s) recent resolution on biotherapeutics. This resolution urges Member States to develop regulatory frameworks that “promote access to quality, safe, efficacious and affordable biotherapeutic products, including similar biotherapeutic products.”10 The resolution notes the continued importance of the WHO’s 2009 guidelines on similar biotherapeutic products (biosimilars) in contributing to the development of scientifically-based regulatory frameworks, and it states that the WHO intends to update the guideline (particularly to account for technological advances in characterization). Colombia’s proposed abbreviated route contravenes the central principle of the WHO guidelines: an applicant seeking approval of a biological medicine on the basis of a less-than-full dossier must demonstrate high similarity in quality, safety, and efficacy to a reference product that has been approved on the

publicly available standard, e.g. a pharmacopoeial monograph, is not sufficient for the purpose of comparability.”), 5.1 (“Publicly available reference standards (e.g. Ph. Eur.) cannot be used as the reference medicinal product for demonstration of biosimilarity.”); FDA, “Draft Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product” (Feb. 2012) at § VI.G (“A thorough physicochemical and biological assessment of the reference product should provide a base of information from which to develop the proposed biosimilar product and justify reliance on certain existing scientific knowledge about the reference product. … In addition, even when multiple approved products are on the market, a sponsor must demonstrate that the proposed product is biosimilar to a single reference product that previously has been licensed by FDA. … If there is a suitable, publicly available and well-established reference standard for the protein, then a physicochemical and/or functional comparison of the proposed biosimilar product with this standard should also be performed.”).

8 See Draft Decree at Article 9.

9 Id. at Article 10.1 (“For purposes of the abbreviated route, it is possible that the global evidence may only make reference to information regarding medications that contain the same active pharmaceutical ingredient.”).

10 WHA, “Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy,” WHA67.21 (May 24, 2014). See also WHA, “Regulatory system strengthening for medicinal products” WHA67.20 (May 24, 2014) (noting that the WHA is concerned about “the impact on patients of medical products of compromised quality, safety and efficacy”).
basis of a full dossier. And it contravenes the basic purpose of the WHA’s resolution: promoting access to biotherapeutic products while ensuring their quality, safety, and efficacy.

**Indication Approval:**

Article 4 of the new draft states that “[t]he approval of indications must always be supported by evidence regarding safety and effectiveness, both the medication that is the subject of the evaluation and those that contain the same active pharmaceutical ingredient.”

It also states that “[a]ll indications approved for each active pharmaceutical ingredient shall be included in the pharmacological norms.” These statements appear to suggest that safety and efficacy in an indication may be established on an active ingredient-by-active ingredient basis, rather than on a product-by-product basis. In other words, they suggest that any product with a given active ingredient is necessarily safe and effective for all indications approved for other products with the “same” active ingredient. Assuming this is the intent of the quoted language, we believe such an approach is inappropriate as a scientific matter. As noted above, it is not possible to demonstrate that products manufactured by different manufacturers have the “same” active ingredient. Moreover, biologics with similar active ingredients can have vastly different clinical effects. And product-specific characteristics unrelated to active ingredient also may affect a particular product’s safety and effectiveness profile. Thus, the fact that an indication and active ingredient are listed together in a compendium or that a similar product is approved for an indication is not sufficient evidence, standing alone, for approval of any particular biological medicine for an indication.

We suggest that the final decree describe factors that the regulatory authority will consider when determining whether to approve a product under the comparability route for an indication for which the applicant did not provide supportive clinical safety and efficacy data. Factors may include, for example, whether the mechanisms of action of the product across the different diseases is the same, and whether the patient population tested is the most adequate and sensitive to detect potentially clinically meaningful differences between the proposed product and its reference product.

**Other Issues:**

**Immunogenicity Testing**

Article 6 states that for purposes of determining immunological effects, the applicant must always submit the results of immunogenicity tests performed with the proposed product in accordance with forthcoming immunogenicity guidance. The previous draft had referred instead to immunogenicity tests “including clinical tests.” We strongly recommend that the final decree clarify that clinical immunogenicity testing will always be required, regardless of the approval route.

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11 Draft Decree at Article 4 (emphasis added).
12 *Id.*
13 The sentence refers to the immunogenicity guidance discussed in Article 25 of the Decree. It should instead refer to the guidance discussed in Article 22.
Vaccines

The new draft decree no longer includes an article addressing the approval of vaccines (Article 8 in the previous draft). Due to the complexity of these products, we recommend that the final decree state that vaccines may be approved only under the complete file route.

Pharmacological Evaluation

Article 4 identifies attributes of a proposed product that the regulatory authority will consider as part of the pharmacological evaluation. We support the new draft’s statement that the regulatory authority must consider quality information as part of its evaluation of safety and effectiveness.

We note that Article 4 characterizes contraindications, interactions, and warnings as effectiveness information. We believe it would be more appropriate to characterize these features as safety information.

Naming and Labeling

The new draft still does not address naming or labeling for biologics. We understand that, by default, the rules that currently apply to drugs apply to biological medicines as well. We do not believe this is appropriate. In particular, because a product approved under the comparability route will not be the “same” as the reference product, it should have a nonproprietary name that is similar to, but not the same as, that of the reference product and other products approved under the comparability route. This, along with any traceability technology established by guidance, will help ensure that adverse events can be correctly traced to the responsible product. Providing a means for robust product traceability and pharmacovigilance is a key component of regulatory oversight for all biological medicines.

Similarly, a product approved under the comparability route should not automatically have the same labeling as the reference product (as is generally the case for generic drugs). Product labeling should inform healthcare professionals and patients about any observed differences between the products, as well as the testing that was actually performed on the biosimilar (as opposed to on an innovative product). We suggest making these points in the final decree.

Interchangeability and Substitution

The new draft also remains silent on the interchangeability or substitution of biological medicines. Currently, there is no scientific, regulatory, or medical consensus regarding the requirements to demonstrate the interchangeability of two biological products. We continue to suggest that the final decree state that biological medicines should not be substituted for one another in the absence of regulatory determination of interchangeability and/or a clinical determination that substitution is appropriate in a particular patient’s treatment.

14 Draft Decree at Article 24.
Incentives for Innovation

The new draft still does not discuss regulatory data protection. We understand that Colombia grants five years of data protection to innovative drugs and biologics alike (i.e., five years during which a follow-on applicant cannot rely on approval of a prior innovative biological product to receive approval). This five-year period helps ensure that there is an opportunity for sponsors to recoup their investment and helps protect incentives for companies to develop innovative new therapies. We believe it would promote transparency and be useful for applicants if the final decree stated that a product may not be approved via the comparability route (or the abbreviated route, if it is not eliminated) until five years after approval of the reference product.