Food and Drug Administration
Silver Spring, MD 20903

*UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES*

In response to a request for comment submitted by the Government of Colombia, the U.S. Government is pleased to provide information on FDA's approach to regulating biological medicines, including biosimilars, for the Colombian Ministry of Health to consider as it further develops its draft regulation on biological medications, including similar medications, as notified in the 4th draft of the document notified to the WTO as G/TBT/N/COL/196. FDA would like to thank Colombia for being receptive to comments submitted on the 4th draft. The present comments are directed to the 5th draft, published on July 10, 2014.

Comments on the regulation of biological medicines:

FDA considers the safety of patients who are taking any medical product to be of paramount importance. The U.S. FDA has a rigorous approval process for biological products as reflected in the regulations, guidance documents, and other information posted at www.fda.gov. There are two approval pathways for a biological product under the Public Health Service Act (PHS Act) in the U.S. A sponsor can submit a biological license application (BLA) under (1) section 351(a) of the PHS Act for a "stand-alone" biological product, which would contain a full complement (complete dossier) of data and information, or (2) section 351(k) of the PHS Act for a biosimilar or interchangeable data product, which would contain an abbreviated package of data and information. These two pathways have different requirements for approval and the types of data that would be expected would depend on whether the sponsor submitted a BLA under section 351(a) or section 351 (k) of the PHS Act.

For further information on FDA's current thinking on multiple key scientific and regulatory factors involved in submitting applications for biosimilar products to FDA for evaluation please reference the FDA draft guidance documents (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm).

Also, please note that FDA's thinking on these complex issues is evolving, and that the Agency expects further guidance documents on biologic similar products to be issued in the future.

Comments on the Colombia proposed regulations:

Draft 5 of the Colombian draft regulation includes three pathways to support a demonstration that a biologic medication is of the necessary quality, safety, and efficacy to be afforded market access.

The first Pathway is the complete dossier. This path appears to most closely align with the U.S. FDA 351(a) BLA approach outlined above.

The second is the Path of Comparability which appears to most closely align with the U.S. FDA 351 (k) BLA outlined above.

The third Pathway is the Abbreviated Pathway. FDA is concerned that while this draft better defines the necessary documentation that an applicant would need to use in order to apply under the Abbreviated Pathway, it is still unclear how the safety, purity, and potency of products in this Pathway would be assured.

Article 9 outlines the Data requirements for the abbreviated route. It is unclear if this abbreviated pathway is intended to describe the approval of a product based on comparison to a reference standard, rather than a reference product. If that is the intent, it is unclear what the scientific standard is when compared to a reference standard, or what the scientific standard of the reference standard is. As noted above, it is unlikely that a pharmacopeia monograph or reference standard will be sufficiently extensive enough to cover all aspects of characterization, testing, release and stability. Of note, the European Medicines Agency (EMA) and U.S. FDA do not have such a pathway. Comparable pathways in these regulatory regions include the complete dossier route and comparability route.

The last paragraph of Article 9 stipulates, "applicants may opt for this route only if the candidate medicinal product's active pharmaceutical ingredient has a previously defined and thoroughly documented safety and efficacy profile and has robust pharmacovigilance data." Unlike the previous paragraphs of Article 9, this stipulation appears to compare to a "reference product" and not a "reference standard."

FDA is concerned by Colombia's use of the term "same active pharmaceutical ingredient" in Article 4 of the draft decree. FDA does not use the "drugs", "API", or "active ingredient" terminology for biologics. In addition, it is unclear what is meant by "same active pharmaceutical ingredient." If they are referring to a similar biotherapeutic (a biosimilar), the standard for "same" is not the US or global standard. The U.S. standard is "highly similar' and the EMA/ WHO standard is "similar." This may be a translation issue, but a standard of "same" is not considered scientifically reasonable for biological products.

There are also concerns in Article 6 of the draft decree. FDA approves products based on the data and information provided by the applicant. The U.S. Pharmacopeia has developed few biological product monographs, and it unlikely that a pharmacopeia will be sufficiently extensive to cover all aspects of characterization, testing, release and stability using state of the art techniques and methods that are appropriate for the product. As the Article is written it is unclear that the application should not be exclusive to what may be in a pharmacopeia. Additionally, in the U.S. a sponsor must demonstrate that they are biosimilar to a licensed product, not similar to a monograph.

In Article 8 the decree allows for the applicant to justify differences found between the reference product and the applicant product. The U.S. statutory standard for a biosimilar is that (1) is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and (2) has no clinically meaningful differences from the reference product.

FDA's last concern is relative to Article 22 Guidelines on immunogenicity, risk management plans and stability. The draft decree only refers to clinical trial data being necessary to prove the immunogenicity of the active pharmaceutical ingredient. FDA firmly believes that both the drug substance and drug product should be adequately evaluated through the documented methodology to ensure the entire medication's immunogenicity.