MinSalud
Ministerio de Salud y Protección Social

PROSPERIDAD PARA TODOS

Bogotá, August 2014

Doctor
MARGARET A. HAMBURG
Commissioner
US Food and Drug Administration

REF: Response to the comment submitted by FDA to Colombia's draft regulation of biologics.

Dear Dr. Hamburg

The Colombian Ministry of Health is very pleased to have the opportunity to engage in technical discussions regarding regulation of biologics with the US Food and Drug Administration (FDA). We have closely followed the debates regarding this issue in the US and were able to virtually attend the 2014 Federal Trade Commission (FTC) Follow-on Biologics Workshop.

From the beginning of the debate here in Colombia (almost 3 years ago) we had tried to engage in such dialogue, given the fact that the US health authorities have to deal with the same challenges posed by rising prices of biologics and have started a public debate to formulate public policy to tackle with them: Biologics Price Competition and Innovation Act (BPCI) and its implementation trough draft guide-lines published for comments by FDA.

In various meetings that the Ministry of Health has held with officers from the United States Trade Representative and the US Embassy in Bogotá, the offer to facilitate contact with the FDA was made in various times, and we are glad that it has finally materialized, even if it is at the end of the debate.

We now proceed to address the comments made in your letter.

First of all, we highly appreciate that FDA's comments are so constructive, questioning specific parts of our draft regulation. This gives us the opportunity to reflect on those issues and better formulate them in the definitive text. Some of the issues, as we explain below, are a matter of semantics and some others have to do with lack of precision in the language used in the 5th draft.

Nature of the draft decree

Like the FDA's, the Colombian Ministry of Health's thinking on issues regarding key scientific and regulatory factors of biologic medicines is constantly evolving, given the

speed of changes and advances in this realm of science. It is precisely because of this, that the Colombian regulation on biological medications is meant to be a broad enough regulatory framework that would allow for different approval pathways and gradually incorporate scientific developments. Like in the US, and after the approval of this framework regulation, specific immunogenicity and other guidelines will have to be produced and frequently updated. The draft decree has to be read as the general framework, i.e. equivalent to BPCI, and the guidelines to be issued once it is approved, would correspond to the FDA guidelines.

Comments regarding safety, purity and potency of products .

In the comment, you state: *"... 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 must be read in conjunction with article 6. Article 6 establishes requirements for purity, potency and safety (inmunogenicity) that sponsors must fulfill. The information to prove such attributes (and others listed in article 6) has to result from test carried out with the product that is the subject matter of the application. The information in article 6 is mandatory in all cases, and can never be waived.

Comments regarding pharmacopeia monographs

In your letter you mention: *"...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."*

We understand that a pharmacopeia monograph does not describe everything about biological activity, potency and safety. We also recognize that the way the 5th version is drafted is not clear about this, and could be understood as to mean that a monograph covers all aspects of characterization.

This is why we will modify article 6 as to clarify that a pharmecopeia standard, for the purpose of characterization, should be used for those aspects described in the monograph. We will also modify article 9 in order to specify that the existence of a monograph may be an indicator, among others, of a sufficient characterization of proteins.

Comments regarding reference standard

In the letter you say *"...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 a consequence, definition of reference standard will be included in the final version and it will clarify that we will understand "reference standard" to mean a pharmacopeia monograph for those aspects described therein or a product approved through a full dossier in Colombia or a reference country (reference countries are listed in article 8)

Comments regarding terminology and similarity

Your comments regarding terminology reads as follows: *"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."*

We are aware that in the realm of biologics, it is not possible to have two exact same proteins, in the literal sense of "same". Given this Colombian draft decree uses "same pharmaceutical ingredient" to mean that the applicant product should be "essentially the same" to the reference standard.

Nonetheless, given that the terms "similar" or "highly" similar constitute broadly used language, we are considering using them in our regulation in the context of characterization for all pathways.

Comments regarding guidelines on immunogenicity

You wrote: *"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."*

As per your comments we will include in article 22 the term "drug product" in addition to "drug substance".

Comments regarding the abbreviated pathway

You letter mentions that *"...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."*

While we understand this, we believe that our abbreviated pathway explicitly regulate discretion given to FDA by section 351(k)(2)(A)(ii) of the Public Health Service Act (PHS) that determines the following:

> "(ii) DETERMINATION BY SECRETARY.—The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(I) is unnecessary in an application submitted under this subsection".

Our abbreviated pathway describes the specific requirements and circumstances where such waiver is possible, for the purpose of transparency, reduction of discretion by sanitary authority and predictability by applicants. It is also indicative about which elements described in clause (i)(I) can be waived: only pre-clinical and clinical information. Unlike PHS Act, our draft decree does not allow for waivers of analytical studies.

Another difference between PHS Act and our draft regulation, is our broader understanding of the term "comparability", because it allows for the usage of pharmacopeia monograph where available (and not only references products) for characterization.

Finally, like PHS Act, our decree allows usage of publicly available information about products with a common pharmaceutical ingredient (i.e. highly similar) to support an application. 351(k)(2)(A)(iii) reads:

> "(iii) ADDITIONAL INFORMATION.—An application submitted under this subsection—
> "(I) shall include publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent; and
> "(II) may include any additional information in support of the application, including publicly-available information with respect to the reference product or another biological product.

Sincerely,

Alejandro Gaviria Uribe
Ministry of Health

Elaboró: **CGOMEZM/CVACA/TANDIA**