Biotechnology Industry Organization

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COMMENTS ON DRAFT GUIDELINE FOR IMMUNOGENICITY ASSESSMENT OF BIOLOGICS

The Biotechnology Industry Organization (BIO) appreciates the opportunity to formally respond to the Colombian Ministry of Health's Draft Guidelines for Immunogenicity Assessment of Biologics, which are necessary for the implementation of Decree 1782 of 2014.

BIO has noted several concerns with the introductory articles to the draft guidance, specifically regarding the scope of required immunogenicity testing in the pre-marketing and post-marketing settings. First, the articles of the proposed resolution depart from international regulatory norms in that they do not expressly require head-to-head clinical immunogenicity studies as part of the pre-marketing comparisons made between a competing biological product and a reference biologic. Second, the articles depart from international risk management practices to the extent that they would require routine post-marketing immunogenicity testing for most biological products.

In order to address these concerns, BIO would like to first reaffirm its overarching views on immunogenicity of therapeutic proteins and then share with the Ministry of Health a detailed assessment of our concerns with respect to specific articles of the draft resolution. Furthermore, BIO has provided the Ministry of Health with some suggested language to be incorporated into the draft guidance that may remedy some of the identified issues.

In addition, BIO applauds the Ministry of Health for translating and adapting the comprehensive scientific guidance from FDA and EMA immunogenicity guidelines and incorporating these guidelines by reference into the proposed resolution. However, select passages apparently deviate from the referenced documents with respect to their intended scientific meaning, due to translation errors, omissions and language edits. Accordingly, we have also provided some suggested language and clarifications on these matters.

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General Comments on Immunogenicity

Articles 6, 9 and 22 of Decree 1782 of 2014 refer to requirements for immunogenicity testing. It is noteworthy that the Ministry of Health recognizes that immunogenicity testing is an important issue for biologics and has committed to draft a separate guideline. In this regard, BIO is encouraged by the opportunity to engage with the Ministry of Health in a detailed consultation to share perspectives of industry stakeholders as these guidelines are being developed. This consultation is important to ensure that the experience gained by biologic and similar biologic product developers working under globally accepted scientific-based standards can be considered by the Ministry of Health.

With this in mind, and prior to discussing in detail the specific articles proposed in the Draft Guidelines for Immunogenicity Assessment of Biologics, BIO would like to make clear the following points on immunogenicity that summarize the industry's views on the matter, specifically on biosimilar products (referred to as "competitor products" in the Draft Guidelines) that are evaluated through the pathways established in either Article 8 or Article 9 of Decree 1782 of 2014:

1. The clinical immunogenicity profile of biologic products is largely unpredictable from pre-clinical studies. Immunogenicity should therefore be studied in the clinic for all new biologic products, including for intended copies of existing products. Differences in immunogenicity can result in differences in safety and efficacy in ways that cannot be predicted without clinical testing.

2. Design of the immunogenicity testing for biosimilar products should not be solely based on the characterization and complexity of the drug substance (referred to as "active pharmaceutical ingredient" in the Decree), but should also consider other factors such as immunogenicity for the reference biologic product.

   Moreover, referring only to the drug substance, instead of also including the drug product itself, is a concern. Many factors related to both the drug substance as well as to the drug product can influence its immunogenicity. Such drug substance factors include a protein's degradation, misfolding, microaggregation, oxidation, and glycoform microheterogeneity. Other drug product factors include, for example, its formulation (e.g. buffers) and primary package-related components (e.g. leachates, extractables).

   In addition, state-of-the-art analytical testing still has significant limitations, particularly with respect to qualitative and quantitative comparisons of higher-order aggregates that may possibly be associated with some immunogenicity risks. For example, these techniques have limited quantitative sensitivity for particles <1 micron, and limited ability to differentiate qualitatively among any particles of similar size, but different morphology, between 0.1 and 10 microns.

   Hence, for the aforementioned reasons, complexity alone, besides not being a

clearly definable concept, cannot be the only element considered for the design of an immunogenicity assessment.

3. Product differences that are difficult or impossible to detect analytically can lead to differences in immunogenicity *in vivo*. State-of-the-art analytical testing may be capable of showing that two complex protein products are very highly similar in structure, but such testing cannot always demonstrate that those products will produce similar immunogenic responses in humans, particularly in situations where complex protein products are derived from new processes and cell lines.

    i. The overall goal is to establish that there are no clinically meaningful differences in immune response between a proposed biosimilar product and the reference product. At least one head-to-head clinical immunogenicity assessment will be required in those settings that are more sensitive in detecting difference in immunogenicity, even if statistically underpowered.

    ii. Immunogenicity should be assessed in a sensitive patient population using a clinically relevant treatment regimen sensitive to the generation of antidrug antibodies (ADAs) taking into consideration high quality, evidence-based data from the reference product. A risk-based approach will dictate the type, amount and timing of the head-to-head clinical immunogenicity testing required.

4. Similar incidence rates of immunogenicity with an innovator biologic and a potential biosimilar do not necessarily mean similar immunogenicity. Two similar complex protein products may be immunogenic in different patients and/or elicit different antibodies isotypes to different epitopes, with different titers or kinetics (time to onset and transient/persistence), which is why appropriate head-to-head testing and characterization of immunogenicity is always necessary. Guidelines should include requirements to characterize any confirmed ADAs with respect to isotype, neutralizing potential, kinetics, etc. as well the establishing of possible clinical consequences thereof.

5. The Decree and the Guidelines recognize that risk management planning is needed in "all phases of development"; however, pre-market clinical testing is typically inadequate to exclude rare but clinically important differences in immunogenicity, particularly in situations where complex protein products are derived from new processes and cell lines. For chronically administered biologics it may be advisable to evaluate up to one year of comparative immunogenicity data prior to market authorization. Post-market surveillance measures will also be necessary, but cannot replace the need for premarket, head-to-head comparative immunogenicity testing. Although one year is generally recommended, the period for both pre-approval and post-approval testing for chronically administered agents could be reduced to 6 months, for example, if the shorter duration can be

scientifically justified based on the totality of the evidence to support biosimilarity or if there is an agreed upon commitment to present the additional data post-approval.

Specific Comments Addressing Immunogenicity Concerns in Preamble and Articles of Proposed Resolution

Preamble

Since biosimilars are within the scope of this Guideline, BIO recommends the inclusion of three other pivotal documents in addition the two FDA and EMA Guidances originally referenced in this Resolution:

"*Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use".*
24 May 2012
EMA/CHMP/BMWP/86289/2010
Committee for Medicinal Products for Human Use (CHMP)

"Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues"
30 May 2012
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

"Scientific Considerations in Demonstrating Biosimilarity to a Reference Product"
Guidance for Industry
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 2015

Besides the product-specific guidelines, these documents establish a clear and scientifically supported pathway for the evaluation of biosimilars.

Preamble, Articles 3 and 4 – Risk-Based Approach for Comparisons of a Competing Product

The pre-amble and Articles 3 and 4 taken together suggest that INVIMA may waive clinical immunogenicity testing as a required element for a comparison of a competing therapeutic protein (i.e. a candidate biosimilar product) to an existing reference product. Specifically, Article 3 states that physicochemical and functional comparability data may suffice to determine the need for *clinical* immunogenicity testing and Article 4 stipulates that sponsors may justify alternate approaches to immunogenicity testing to those described in the adapted FDA and EMA guidelines. The adapted guidelines recommend

clinical immunology testing in order to appropriately assess immunogenicity risks in patients, but the potential implication of Articles 3 and 4 is that alternate models may be sufficient to address the immunogenicity testing requirements of Article 6 of Decree 1782 of 2014.

BIO cautions the Ministry of Health and INVIMA that reliance on alternate *non*-clinical, *in vitro*, and/or *in silico* immunogenicity models is not supported by current science, and is in contradiction to the advice of the referenced FDA and EMA guidelines. Specifically, the referenced FDA and EMA guidelines caution that non-clinical models are generally not adequately predictive of the human clinical response. Although the adapted guidelines do not directly address the case of biosimilar development, the additional FDA and EMA guidelines recommended for inclusion above and that are related to biosimilar development specifically require clinical immunogenicity comparisons for all biosimilar products.[1]

BIO therefore seeks clarification that Article 4 refers to alternate approaches solely for *clinical* immunogenicity testing.

In addition, these concerns are also present in Article 3 where there is significant discretion afforded as so far as to the necessity, scope and time of clinical immunogenicity studies.

The necessity of a clinical immunogenicity study is not something that is optional if a regulatory body is to adequately assess the safety profile of a biologic drug.

Article 3 –Biosimilar Immunogenicity Clinical Testing is not the same as Risk-Assessment for routine Manufacturing Changes

Article 3 addresses risk-based assessment for routine manufacturing changes in the same context as the risk-assessment for a biosimilar product that has been reverse

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[1] See *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, U.S. Department of Health and Human Services, FDA, April 2015, page 16 ("*Structural, functional, and animal data are generally not adequate to predict immunogenicity in humans. Therefore, at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product will be expected. FDA encourages that, where feasible, sponsors collect immunogenicity data in any clinical study, including human PK or PD studies*") and page 18 *("As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there is residual uncertainty about whether there are clinically meaningful differences between the proposed product and the reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment*").

engineered with an entirely new cell line and process. These two concepts are entirely different and should not be addressed in the same context.

The incremental process changes that may occur over time with an innovator biologic due to manufacturing modifications are not equivalent to the process differences that exist between a biosimilar manufacturing process and its reference product manufacturing process. For the latter, a clinical study comparing immunogenicity will always be required since a biosimilar manufacturer develops a different manufacturing process to that used by the innovator for the reference product (since the manufacturing process used by the innovator is proprietary information). Therefore, due to different manufacturing processes there is likely to be small differences which must be assessed for any clinically meaningful differences by way of a comparative clinical study.

A single manufacturer who makes a change to their process can directly compare their product pre and post change with a full history of their product and manufacturing process (including results from in-process controls), meaning there is less of a knowledge gap compared to a biosimilar developer where the manufacturer has no knowledge of the originator manufacturing process. Comparability of a product before and after a manufacturing change may not require a comparative clinical study.

Articles 2 and 5 – Active Surveillance Post-Approval Framework

The requirements listed in Articles 2 and 5 for active post-approval surveillance would require significant clarification in terms of how such measures would be applied case-by-case basis. For example, clarification is needed on whether they can be limited and time-bound for new biologic products, whether they apply to biosimilar products that already showed comparable immunogenicity in pre-marketing studies, and whether they integrate with a risk management plan (RMP), for example.

It is also prudent to point out that from a clinical and public health standpoint it is inadequate to measure adverse events only through laboratory tests, given that not all adverse events will necessarily have a reflection on these tests. In actuality, many adverse events reported, particularly those reported spontaneously, do not come with laboratory results. Furthermore, whether an adverse event has a clinical laboratory correlate will relate to the test's specificity, sensitivity and positive and negative predictive values, among other factors. Clinical lab reports, in short, will not provide all the necessary elements for an efficient pharmacovigilance system for these products. Rather, a complete post-marketed pharmacovigilance approach, which takes into account the nuances specific to biologic products, should be enacted including both passive and active pharmacovigilance measures, including RMPs.

A general requirement for post-marketing clinical immunology testing would set Colombia apart from pharmacovigilance requirements in other jurisdictions, including in Latin America. For example, several countries now require "intensive pharmacovigilance" for new biologic products, but these measures are primarily based on increasing awareness and participation of patients and providers in voluntary case

reporting. Post-approval anti-drug antibodies (ADAs) testing in the commercial population exposes patients to invasive procedures that may or may not lead to clinically meaningful results. Therefore, in the absence of a specific safety signal, post-approval safety assessments are generally sufficiently detailed in the harmonized ICH E2C Periodic Benefit-Risk Evaluation Report. In conclusion, requirements for post-marketing immunogenicity testing could be very difficult to implement and would undermine efforts to harmonize regulatory standards in Latin America.

Considerations for post-marketing surveillance could more effectively be addressed in the separate, planned risk management guideline where they could be placed within the overall context of a product-specific risk assessment and RMP. As part of a standard RMP, agreed upon case-by-case, adverse events are monitored and reported. Ongoing post-marketing collection and testing of patient sera for analysis of potential ADAs is not a common requirement for RMPs, even for new biologics, although it may be warranted in certain select circumstances.

The draft guideline appears to base the need for post-marketing clinical immunogenicity studies on the presence or absence of detectable ADAs in the pre-marketing studies. However, the detection of ADAs during clinical development is common for many biologic products, while their correlation with serious adverse events is relatively rare. Therefore, considerations for the potential needs for ongoing active surveillance should be based on more stringent criteria related to defined risks (e.g., potential for cross-reaction to a non-redundant endogenous protein as described in the draft guideline Section III.B-5 and Annex A). Even in such cases the need for active post-marketing surveillance should be time-bound (for example, via a Phase IV study or registry), linked to the RMP, and designed to assess a specific safety risk that would inform subsequent risk minimization measures.

Of further concern, Article 2 refers to assessment of risks in the "exposed population", but is not clear regarding whether this is specific to Colombian patients or to the global safety database of the sponsor. Due to limitations in access to patient health records and reimbursement claims, as well as the low rate of spontaneous adverse event reporting in Colombia, it may be very difficult for sponsors to perform a Colombia-specific assessment of immunogenicity in the exposed population. In addition, there is a current limitation of commercially available assays for the detection and measurement of ADAs in Colombia and throughout Latin American, thus further complicating how one would effectively conduct this sort of assessment.

A further consideration is that patient consent is always required for immunogenicity testing. Such consent is routinely obtained for interventional clinical studies, but it is not typical in the post-marketing setting outside of Phase IV studies or registries. Occasionally, health care providers may obtain such consent and request that a manufacturer provide specific diagnostic support to facilitate individual patient care (e.g., to determine whether the therapy should be switched to another medication, whether doses should be changed, or whether concomitant medications should be introduced). Such measures are not originally taken to support pharmacovigilance. The

draft guideline would appear to put the onus on the manufacturer to solicit such testing on a routine and ongoing basis for the purposes of compliance with post-marketing commitments.

Suggested Modifications to Articles 2, 3, 4 and 5

Please consider below some recommended changes (**in bold**) to some key articles of the proposed resolution. Language which we suggest to be deleted has been struck through (~~example~~) and language that we propose to be included is in bold (**example**).

Article 2, paragraph 3:

BIO recommends modifying Article 2 to remove the implication that confirmed diagnostic association of adverse events with anti-drug antibodies is required during post-marketing surveillance. As aforementioned, such clinical diagnostic testing is extremely rare, requires prescriber and patient consent, and is typically not required as part of risk management.

> In addition for the renewal of a registration, the post-marketing information of the exposed population and adverse events that have been presented and ***their potential association with immunogenicity*** ~~an immunogenicity assessment that meets the management and minimization of such adverse events following the guidelines of this guide~~ ***must be provided and addressed in accordance with agreed risk management and risk minimization commitments described in the associated guideline***.

Article 3:

BIO also recommends the following language for Article 3 and the inclusion of a new subparagraph in this Article:

> Scope of clinical studies of immunogenicity when comparisons are made ***for a manufacturing change***. The need, extent and timing of clinical immunogenicity studies in the context of the effects assessment of a change in manufacturing will depend on the degree of physicochemical and functional ~~similarity~~ **comparability** of the therapeutic protein before and after the changes. **Generally, immunogenicity testing is not required for manufacturing changes when analytical comparability studies demonstrate that there has been no adverse impact to quality, safety and efficacy.** ~~This principle also applies to the immunogenicity assessment of a competing therapeutic protein with the reference protein.~~
>
> **Subparagraph** [New]
>
> **Comparative clinical immunogenicity testing is generally required for development of a competing therapeutic protein. Physicochemical and**

functional similarity studies comparing the competing protein with a reference protein may inform the extent and timing of these comparative clinical immunogenicity studies, as informed by the product and patient-related risk factors described in the adapted guidelines.

Article 4:

In order to address previously discussed concerns regarding the need for alternative approaches to solely be based on *clinical* immunogenicity testing, BIO recommends the following language in Article 4.

> Standardization and validation for immunogenicity testing. It may be accepted an alternative approach for **clinical** immunogenicity assessing proposed in the guidelines of the guidance adopted by this resolution, as long as the information provided demonstrate that the materials and the testing used were standardized and validated. Also, any ***non-clinical*** model **used to inform the extent and timing of clinical immunogenicity studies** must be justified in the alternative approach for immunogenicity assessing. The Specialized Chamber for Drug and Biological Products of INVIMA (hereinafter the Specialized Chamber) may request additional information that it deems necessary.

Article 5:

Finally, please modify Article 5 to clarify that post-marketing immunogenicity testing should be contingent on a RMP and by exception.

> ***The applicant should consider the potential need for post-marketing clinical immunogenicity evaluation as part of the risk management plan. Such requirements, if any, should be based on specific, identified risks that cannot otherwise be addressed through more common pharmacovigilance measures.***
>
> ***When post-marketing immunogenicity testing is included in the risk management plan*** a clinical testing report must be submitted to INVIMA, including the assessment of anti-drug antibodies (ADA) in the context of a relevant and validated model for such assessment of the adverse events and aggregate consumption data and the population exposed.
>
> The clinical testing and frequency of its realization should be defined and informed by the applicant of sanitary registration certificate in accordance with the approach of the clinical immunogenicity assessment adopted. The Specialized Chamber may modify the package of laboratory testing and the frequency of its execution.
>
> ***This article should not be interpreted in such a manner to conflict with the ethical consideration that a patient receiving a licensed biologic therapy for its approved use in the post-marketing setting is under no obligation to consent to clinical immunogenicity testing.***

The applicant shall submit periodic reports to INVIMA, containing the analysis of aggregate information of the clinical testing performed, as established by the INVIMA.

Observations on Guidelines for Immunogenicity Assessment – Sheets 4-38

BIO again applauds Colombia's MoH for translating and adapting the comprehensive scientific guidance from FDA and EMA immunogenicity guidelines. We have noted that in selected passages the adapted versions apparently deviate from the referenced documents with respect to their intent, due to translation errors, omissions and language edits. These differences at times render the document misleading and inadequate on providing clarification on key points.

Please consider below some recommended changes to the Guidelines to better reflect the intended effect of the referenced FDA and EMA Guidelines on Immunogenicity. Language to be struck from the document will be crossed out and language to be included in the resolution is in bold.

a) Post-Marketing Immunogenicity Requirements

BIO would like to comment on three specific issues in the guidelines that relate specifically to post-marketing immunogenicity requirements and how some language deviates from current FDA and EMA guidelines. These modifications adapt FDA and EMA guidelines to align with Article 5's apparent requirement for post-marketing immunogenicity testing. These passages should be modified, as suggested below, to reflect that such testing is the exception, as indicated by the RMP.

Section	Suggested Language

Section IV, Product-Specific Antibody Sampling Considerations (Sheet 10)	In addition to a pre-specified sampling schedule, unscheduled sampling triggered by suspected immunologically related adverse events, is necessary for establishing the clinical relevance of ADAs. **In cases where the risk management plan requires post-marketing evaluation of immunogenicity** the applicant must submit a sampling plan for the detection of ADA ~~in the post-marketing phase in cases where the trial end obtained positive results,~~ so that the clinical significance of these is analyzed, if there is any. Post-marketing sampling in patients who participated in the pre marketing clinical trial must have informed consent. Similarly, banking of serum samples from clinical trials under appropriate storage conditions following standard procedures for future testing is always advisable.
Section IV Post-marketing monitoring (Sheet 11)	Robust post-marketing safety monitoring is an important component in ensuring the safety and effectiveness of therapeutic protein products. The potentially serious and rare safety risks (e.g. adverse effects related to the immune response) could not be detected during clinical testing done before approval, because the size of the exposed population may not be large enough to value them. In some cases, it may be necessary to evaluate these risks through the post-marketing surveillance, clinical studies and / or phase IV studies. Because some aspects of post-marketing safety are specific for each product, applicants must submit a plan for post-marketing safety monitoring. **In cases where immunogenicity testing is required**, submitting periodic laboratory tests is recommended as part of the Risk Management Plans (RMP), including ADA clinical evaluation within a relevant and validated model, adverse events and aggregated of consumption and exposed population information
Section VIII Appendix B (Sheet 30)	The neutralizing capacity of antibodies present in positive samples needs to be established as this often correlates with diminished clinical responses

Item 2.3.1	to biological product. It should be noted that neutralizing activity does not necessarily correlate with binding antibody content i.e. samples containing significant or high amounts of binding antibodies may fail to neutralize biological activity. This may depend on product, but must be determined empirically **through clinical studies** ~~, hence the immunogenicity should be studied, also and especially during the marketing phase and biotherapeutic use~~. Screening neutralizing antibodies samples by cross-neutralization of other products based on the same protein and the endogenous protein is important as it may have possible implications for clinical efficacy and safety.

b) Omissions and Translation Errors

In addition to the aforementioned concerns regarding post-marketing immunogenicity requirements, BIO has identified areas of the regulation where matter from the FDA and EMA guidelines have been excluded from the current proposed resolution or where translation errors may create technical uncertainties with respect to how to effectively implement the regulation. Accordingly, BIO would like to recommend the inclusion of language in order to more clearly align the proposed regulation with the true intent of the cited FDA and EMA guidelines.

Section	Suggested Language
Section I, Introduction (Sheet 5)	El Anexo A provee información suplementaria para el diagnóstico y fisiopatología de las consecuencias adversas particulares de respuestas inmunes a proteínas terapéuticas y una breve discusión de los usos de los ensayos en animales y la realización de pruebas de inmunogenicidad**, incluyendo aquellas de carácter comparativo**.
Section II, Background (Sheet 6)	… ~~aplasia de células rojas puras~~ **aplasia pura de células rojas**
Section Iv, Development of Assays for ADAs (Sheet 9)	Applicants should develop and implement sensitive immunoassays commensurate with the overall product development program. **These assays should have design and performance**

	parameters that are in line with current industry best practices.
Section IV, Development of Trials for ADAs (Sheet 10)	Los solicitantes deben desarrollar e implementar inmuno-ensayos sensibles adecuados a la totalidad del programa de desarrollo del producto. Se debe realizar una valoración concomitante de los niveles de la proteína terapéutica en la muestra, para valorar el potencial de que la presencia del producto ~~de~~ **pueda** interferir con la detección de anticuerpos en el ensayo.
Section IV Adverse Events (Sheet 11)	...~~enmascare signos tempranos y síntomas de eventos adversos~~ **enmascare signos y síntomas tempranos de eventos adversos**...
Section IV Scope of Clinical Studies (Sheet 11)	En los casos en los que se realicen estudios de inmunogenicidad comparativos (por ejemplo aquellos que comparan los eventos adversos inmunológicamente relacionados, incidencia de anticuerpos, título o actividad neutralizante al producto antes y después de los cambios en el proceso de manufactura). *BIO suggests that this text should also include those cases with products adopting the Comparative Pathway (article 8 of Decree 1782) or the "Abbreviated" Pathway (article 9 of the Decree 1782).*
Section IV Post-marketing monitoring (Sheet 12)	...~~estudios clínicos y/o estudios fase IV~~ **y/o estudios clínicos (incluyendo estudios fase IV**)
Section V Immunologic State (Sheet 12)	...~~en pacientes sanos~~ **en voluntarios sanos**
Section V Immune Tolerance State (Sheet 14)	...~~de ambas proteínas especificas de células T y B~~ **de células T y B proteína-específicas**

	… ~~genéticas asociadas con las proteínas no expresadas ellos pueden~~ **genéticas que confieren un fenotipo que no expresa la proteína ("knock out") pueden**
Section V Immune Tolerance State (Sheet 15)	… ~~incluyendo polimorfismos con un solo nucleótido en poblaciones~~ **incluyendo polimorfismos de nucleótido único en poblaciones…**
Section V Product Origin (Sheet 15)	… ~~su fuerza~~ **su potencia…**
Section V Product Origin (Sheet 16)	… ~~al usar fagos~~ **al usar muestrario de fagos…** ~~bio-especificos~~ **bi-especificos**
Section V Primary Molecular Structure (Sheet 16)	… ~~para eliminar epitopes en células Th inmunogénicas~~ **para eliminar epitopes reconocidos por células Th inmunogénicas** o ~~la adición de epítopes en células T tolerogénicas~~ **la adición de epitopes reconocidos por células T tolerogénicas** **…** en la ~~región de unión~~ **región bisagra**…
Section V Primary Molecular Structure (Sheet 17)	… y la~~ presencia~~ **presentación…** … la susceptibilidad ~~de~~ **a** tales modificaciones **…**~~pero que no sean reactivas con ninguna de las proteínas asociadas pueden no tener como blanco epítopes novedosos en la región de fusión~~ **pero que no sean reactivas a alguna de las proteínas que la componen pueden tener como blanco epitopes novedosos en la región de fusión (o bisagra)**… … por ejemplo en ambientes inflamatorios ~~en~~ **o a** pH fisiológico…

Section V Quaternary Structure (Sheet 17)	... ~~de receptores de células B; activación eficiente de células B~~ **de receptores de células B causando su eficiente activación...** … de las señales ~~peligrosas~~ **de peligro**… **...**~~para la generación de anticuerpos IgG de alta afinidad o diversos isotipos~~ **para la generación de transición de isotipos hacia anticuerpos IgG de alta afinidad...**
Section V Quaternary Structure (Sheet 18)	... de la pérdida **o** ~~de~~ preservación **de**… … de las **primeras** preparaciones ~~recientes~~ de… **...** epítopes degradados **que** causan anafilaxia**...** ... ~~de que agregados de altos pesos moleculares y partículas~~ **de que agregados y partículas de alto peso molecular**...
Section V Impurities with Coadjuvant Activity (Sheet 19)	La actividad ~~auxiliar~~ **coadyuvante**… …~~por medio de los receptores tipo peaje u otros patrones de receptores de reconocimiento presentes en las poblaciones~~ **por medio de receptores *toll-like* u otros receptores reconocedores de patrones presentes en las poblaciones**…
Section V Immunomodulating Properties (Sheet 20)	**...** a otras proteínas terapéuticas co-administradas**,** ~~con~~ proteínas endógenas...
Section V Formulation (Sheet 20)	… tapones de caucho poseen actividad inmune ~~auxiliar~~ **adyuvante...**
Section V Product Storage (Sheet 22)	… de una ~~proteína~~ **epoyetina** alfa**...** **...** aplasia pura de células rojas ~~medida~~ **mediada**…

Section VII Annex A (Sheet 24)	… por ejemplo ~~piquiña generalizada~~ **ampollas generalizadas…** **…**(por ejemplo ~~piquiñas generalizada~~ **ampollas generalizadas**, enrojecimiento con ~~piquiña~~ **prurito…** **…**Síntomas gastrointestinales ~~pertinentes~~ **persistentes**… Presión **arterial** baja… **…** determinar el nivel ~~específico~~ de anticuerpos IgE **específicos** dirigidos…
Section VII Annex A (Sheet 25)	…potencial de mediar ~~reacciones~~ **la union** cruzadas~~~~ de receptores**…** Tales ensayos deben discutirse con ~~la FDA~~ **el INVIMA** antes… ~~El impacto de la reactividad cruzada de receptores celulares del producto debe considerarse en tales estudios~~. **El impacto del enlace cruzado de receptores celulares provocado por el producto debe considerarse en tales estudios.**
Section VII Annex A (Sheet 26)	…~~brote~~ **erupcion…** ~~Existen reportes de casos de enfermedades inmunes complejas con respuestas inmunes.~~ **Existen casos de enfermedades por complejos inmunes con respuestas inmunes**… **…** síntomas que sugieran una enfermedad **por complejos inmunes** ~~compleja inmune~~… … ~~sito~~ **sitio** catalítico.. … en las células que son su blanco**, y facilitación de la diseminación** ~~facilitando la generación~~ de epítopes, permitiendo… … caso de la hemofilia A **o** las enfermedades de depósito lisosomal…

Section VII Annex A (Sheet 27)	…~~mAbs~~ **anticuerpos monoclonales…** Se recomienda considerar la profilaxis ~~de~~ **mediante** inducción de tolerancia,…
Section VII Annex A (Sheet 28)	… desarrollo a través de la **leche** materna.
Section VIII Annex B (Sheet 30) Item 2.2.4	**Validación de ensayos** ~~Ensayos de Validación~~
Section VIII Annex B (Sheet 32) Item 3.1.4	~~Para analizar las células B de memoria (y a veces las células T de memoria) los ensayos pueden proporcionar la información útil en cuanto a la naturaleza de la respuesta inmune y pueden contribuir a la predicción del desarrollo de problemas de inmunogenicidad.~~ **Los ensayos para células B de memoria (y algunas veces para células T de memoria) pueden aportar información útil sobre la naturaleza de la respuesta inmune y pueden contribuir a la predicción del desarrollo de problemas de inmunogenicidad**.
Section VIII Annex B (Sheet 32) Item 3.2	**Características de los ensayos** ~~Ensayos Caracteristicas~~ ~~Por ejemplo para un producto biológico que se usará en pacientes que reciben la terapia prolongada puede no ser necesaria un ensayo de gran sensibilidad para detectar la cantidad de anticuerpos.~~ **Por ejemplo, para un producto biológico en particular usado para la terapia de pacientes y que puede inducir una cantidad elevada de anticuerpos, puede no ser necesario el uso de ensayos de alta sensibilidad.**
Section VIII Annex B (Sheet 33) Item 3.3	~~y su empleo quedar limitado a los estudios preparativos de referencia con humanos, por ejemplo, procedimientos de inmunohistoquímica, que implican el empleo de un reactivo de inmunoglobulina anti-humana, de fuentes fidedignas no responderá a anticuerpos no humanos y la respuesta en todos los ensayos, puede ser diferente a las respuestas a anticuerpos humanos en muestras humanas.~~ **y su uso es más limitado que para preparaciones de referencia de origen humano; por ejemplo,**

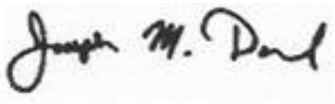
	procedimientos inmunohistoquímicos, que implican el empleo de un reagente tipo inmunoglobulina anti-humana, no responderá de manera confiable a anticuerpos no humanos y las respuestas en todos los ensayos puede ser diferente en sus características de aquellas respuestas a anticuerpos humanos en muestras humanas
Section VIII Annex B (Sheet 34) Item 3.3	...establecer líneas de base ~~de~~ para caracterizar/validar los ensayos. … la medición de la respuesta ~~de~~ **al** ensayo… Sin embargo, este resultado ~~no~~ puede **no** representar la respuesta

Conclusion

BIO again applauds the Ministry of Health for the opportunity to comment on the Draft Guidelines for Immunogenicity Assessment of Biologics and hopes that the Ministry of Health will address some of the clarifications and questions outlined in this document.

As always, BIO is ready and able to support the Ministry of Health and INVIMA should further information be required or should there be interest in utilizing our global expertise and resources. Please reach out to Justin Duarte Pine on my staff at jpine@bio.org or +1 (202) 962-6694 with any inquiries, comments, or questions.

Sincerely,



Joseph M. Damond
Senior Vice President
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cc:
Enrica Alteri, Head of Human Medicines Evaluation, EMA
Public Health Section of the European Commission
Ruchi Nanda, Senior Policy Adviser, Department for Business, Innovation and Skills, United Kindgdom
John Melle, Assistant US Trade Representative for the Western Hemisphere, Office of the United States Trade Representative
Mark Abdoo, Director for Public Health and Trade, U.S. Food and Drug Administration