Novartis Services, Inc.

July 19, 2019

SUBMITTED ELECTRONICALLY VIA www.regulations.gov

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2019-D-2102 Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Dear Madam/Sir,

Novartis Services, Inc. is submitting this letter on behalf of Novartis Pharmaceuticals Corporation (NPC) and Sandoz Inc. (Sandoz). NPC researches, develops, manufactures, and markets innovative medicines aimed at improving patients' lives. We offer a broad range of medicines, including small molecule drugs and biological products (including cell & gene therapies) for cancer, cardiovascular disease, inflammatory disease, infectious disease, neurological disease, eye disease, organ transplantation, respiratory disease, and skin conditions.

Sandoz is a leader in generic pharmaceuticals and biosimilars, providing access to a broad portfolio of high quality, cost-effective prescription medicines. Sandoz launched the first biosimilar approved under the Biologics Price Competition and Innovation Act (BPCIA) pathway in the United States (U.S.) and now has three biosimilar products approved in the U.S.

We refer to NPC and Sandoz collectively herein as "Novartis" and therefore offer a balanced view from the perspective of a company that develops and markets both originator biologic and biosimilar drugs.

Novartis appreciates FDA's approach to revise the Biosimilar Quality Guidance from 2015[1], and adding sections on the comparative analytical assessment. This provides a fully integrated guidance document on these topics, which we believe, is superior to having separate quality and statistical guidances. We especially appreciate FDA's reconsideration of its statistical approach in favor of using quality ranges, which is a practical approach that is consistent with current regulations as they are applied to biologic manufacturing processes. We respectfully offer the following comments that we believe would further enhance the utility of the guidance.

1. REQUIREMENTS FOR QUALIFICATION AND USE OF REFERENCE STANDARDS

[1] FDA guidance "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" April 30, 2015

The section referring to the qualification of reference standards provides criteria for the assignment of a 100% potency value for methods where the result is reported relative to the reference standard. Given that we interpret relative potency unitage as percentage of units per milligram compared to a reference standard, this guidance helps control against potential drift when different lots of a product with a defined structure are expected to have a constant potency.

However, for products where potency can vary between different lots, e.g. glycosylation dependent ADCC or CDC, different reference standard lots may also differ in their relative potency. This issue is not biosimilar specific but is relevant for all biological drugs. In biosimilar development a change of the relative potency of representative product lots is especially common to the point where it is almost inevitable when the manufacturing process of such biosimilar candidates is modified in the course of development to resolve differences observed in the comparative analytical assessment (see Lines 905 and 906).

The guidance currently does not contain recommendations on how to assign the potency of reference standards for products which show lot-to-lot variation in potency, and specifically discourages the use of correction factors to account for differences in potency between reference standards.

Therefore, we propose to clarify that for products with variable potency, different reference standards can be assigned by a stated potency that may deviate from 100 %. We believe that this is an important addition which enables assignment of an appropriate potency value for subsequent reference standards. By applying similar criteria of stringency as prescribed for the assignment of 100% potency (e.g. the 95 % CI is included in a sufficiently narrow interval), this proposal is also suitable to help control for drift.

2. USE OF DATA FROM NON-U.S.-LICENCED COMPARATOR PRODUCT

The draft guidance states that as a scientific matter, it is not acceptable to pool data obtained with U.S. and non-U.S.-licensed products when determining the acceptance criteria or when performing the comparative analytical assessment. We propose the Agency to strike the phrase “as a scientific matter” since we believe that this requirement represents regulatory policy and is not a scientific matter. In cases where U.S. and non-U.S.-licensed product are made by the same process and employ the same control strategy, they provide a single data population with respect to quality attributes.

Therefore, we believe that pooling of data should be allowed in cases where it is possible to provide evidence that the manufacturer of the reference product is using the same manufacturing process for the U.S. reference product and the non-U.S. comparator product.

Specifically, we propose to add to the guidance the following criteria that could justify the pooling of data obtained with US and non-US reference product material:

a. Demonstrate by multivariate data analysis of the analytical data package that the US reference and the non-US comparator is one population.
b. Use state-of-the-art analytical technology to demonstrate on the level of product related substances (e.g. quality and quantity of low-level variants and impurities) and process related impurities (e.g. host-cell proteins) that U.S. and non-U.S. material are indistinguishable

c. Public information that the manufacturer of the reference product uses one manufacturing process for U.S. and non-U.S.-licensed products.

3. CONSIDERATION OF DATA ANALYSIS – DISTRIBUTION OF ATTRIBUTES

The Agency recommends that a biosimilar manufacturing process should target the center of distribution of the quality attributes of the reference product as closely as possible. However, the center may change over time in the course of development when new reference product lots become available for analysis. We have observed this phenomena multiple times when developing biosimilars. Nevertheless, we believe and agree that this represents good practice and is therefore appropriate advice for the purpose of this guidance.

However, we are concerned about the statement in the draft guidance that "*distribution of a bias towards one side of the reference product distribution may raise concerns*" and that it may require appropriate justification. This poses a very real risk that manufacture of biosimilars will be held to stricter requirements than those that are applied to their respective reference products. Depending on the degree by which this potential requirement is applied by the Agency, this may, in the worst case, lead to an unintentional bias in market competition between companies that may ultimately limit patient access to biologic medicines.

To avoid this risk, we therefore propose to clarify this issue. We believe that the entire range of a given quality attribute of the reference product, as approved by the Agency, represents equally acceptable quality.

From our perspective, the following clarification would eliminate the risk for inconsistent regulatory requirements between biosimilar and reference products and associated risks for competitive bias (see also our specific line edits in Table 1):

a. Including a statement that for the final biosimilar evaluation, the entire range of the reference product distribution reflects acceptable quality
b. Include the following two examples of how it may be possible to justify a bias of the biosimilar distribution to one side of the reference product distribution:
   (1) Sufficient knowledge of the clinical impact of the respective quality attribute to exclude clinically meaningful difference;
   (2) A biosimilar control strategy that ensures containment of the biosimilar lots within the reference product distribution for the respective quality attribute

Table 1. Comments and Recommendations for Specific Lines of the Draft Guidance

Please note: new text is in bold

IV. General Principles		
Line Numbers	**Comment and Rationale**	**Proposed Change**
Lines 206-207	The qualifier word "some" in this sentence is not appropriate because	"Advances in analytical sciences (both physicochemical and biological) enable ~~**some**~~ protein

	all protein products can be extensively characterized.	products to be characterized extensively in terms of their physicochemical and biological properties."
Lines 218–220	Clinically relevant structures certainly must be characterized, but there is much less of a need to characterize structures known not to be clinically relevant.	"Despite improvements in analytical techniques, current analytical methodology may not be able to detect or characterize all **clinically** relevant structural and functional differences between the two protein products."
Lines 263-264	Many healthcare professionals and patients are under the misconception that the reference product is a single homogenous entity but a biosimilar is subject to variability. We encourage the FDA to clarify this point in this location.	"Because therapeutic proteins are made in living systems, ~~there may be~~ heterogeneity **is expected** in certain quality attributes of ~~**these**~~ **protein** products, **including both, reference product and biosimilar product**."
Lines 289–292	The second sentence can be understood as contradicting the first sentence. We propose to replace the "define" in the first sentence by "describe"	"Using multiple, relevant, state-of-the-art methods can help **describe** ~~define~~ tertiary protein structure and, to varying extent, quaternary structure, and can add to the body of information supporting biosimilarity. At the same time, a protein's three-dimensional conformation can often be difficult to define precisely using current physicochemical analytical technology."
Lines 339–344	The phrase "fingerprint-like similarity" is used in the reference cited. However, the term "fingerprint-like similarity" is not defined in that reference. As the sentences can be readily understood without the term "fingerprint-like similarity" we propose it to remove it from the draft guidance.	"It may be useful to compare differences in the quality attributes of the proposed product with those of the reference product using a meaningful ~~**fingerprint-like**~~ analysis algorithm that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods. Enhanced approaches in manufacturing science, as discussed in ICH Q8(R2), may facilitate production processes that can better match a reference product's ~~**fingerprint**~~ **quality profile**."

V. Factors for consideration in performing the comparative analytical assessment		
Line Numbers	**Comment and Rationale**	**Proposed Change**
Lines 393-397	The inability to reference a DMF is due to a reasonable regulatory expectation, rather than a matter of science.	**~~"As a scientific matter, as~~ <u>As</u>** with biological products originally licensed under section 351(a) of the PHS Act, an application for a biological product submitted for licensure under section 351(k) of the PHS Act may not incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a Master File (MF) because a license holder is generally expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license"
Lines 504-507	It should be possible to forego pharmacological/toxicological testing if impurity levels are lower in the proposed biosimilar. Therefore we propose to add clarification that "similar levels" includes the meaning of "lower levels."	"If a comparative physicochemical analysis reveals comparable product-related impurities at similar **<u>(including lower)</u>** levels between the two products, pharmacological/toxicological studies to characterize potential biological effects of specific impurities may not be necessary."
Lines 570-572	For initial reference standards, alternative approaches are possible that include (i) pooling of reference product lots, (ii) use of early technical biosimilar product lots generated before availability of clinical material. Inclusion of such practices into this section would be desirable	"(...) a reference product lot, **~~or~~** a lot of a non-U.S.-licensed comparator product (...), **<u>or a pool of several reference product or comparator product lots</u>** is typically qualified as an initial reference standards. **<u>Early technical material derived from biosimilar product development may also be used as an initial reference standard. "</u>**
Lines 582-586	Subsequent reference standards in many cases have different potencies, e.g. glycosylation dependent ADCC or CDC. This issue is not biosimilar-specific but is relevant for all biological drugs. In biosimilar	"For all methods where the result is reported relative to the reference standard, the assignment of a potency of 100% should include a narrow acceptable potency range and ensure control over product

	development a change of the relative potency of representative product lots is common and almost inevitable when the biosimilar manufacturing process needs to be changed in the course of development in order resolve differences observed in the comparative analytical assessment (see Lines 905 and 906). Therefore, we propose to clarify that for products with variable potency, reference standards can be assigned by a stated potency, which may deviate from 100 %. We believe that this is an important addition which enables appropriate assignment of subsequent reference standards. By applying similar criteria of stringency as prescribed for the assignment of 100% potency (e.g. the 95 % CI is included in a sufficiently narrow interval), this proposal is also suitable to control for drift	drift. For example, a sponsor should consider the use of a pre-determined two-sided confidence interval (CI) of the mean of the replicates, where the mean relative potency and the 95% CI are included within a sufficiently narrow range (e.g., 90-110%). **In case of a potency difference of a subsequent reference standard, an assigned stated potency that may deviate from 100%. Accurate assignment with high precision is important to control for drift, for example the 95 % CI is included in a sufficiently narrow acceptable range."**
Lines 590-591	As described above, differences in potency between subsequent reference standard is reality in many cases. Sponsors need to account them appropriately, e.g. by the assignment of a stated potency for subsequent reference standards. In addition, the term "correction factor" may lead to misunderstandings as it is not defined and may have different meanings.	"A sponsor generally should ~~not use a correction factor~~ **use adequate measures (e.g. appropriate assignment of a stated potency)** to account for any differences in, for example, potency or biological activity between reference standards."
Lines 637-640	To evaluate the stability profiles in a comparative manner not all storage conditions might be required (e.g. accelerated and stress). The sponsor should be able to choose the most sensitive condition to evaluate stability and to detect potential differences.	"As part of an appropriate physicochemical and functional comparison of the stability profile of the proposed product with that of the reference product, accelerated and/**or** stress stability studies, as well as forced degradation studies, should be used to establish degradation profiles and to provide a direct stability comparison of the

		proposed product with the reference product."

VI. Comparative analytical assessment		
Line Numbers	**Comment and Rationale**	**Proposed Change**
Lines 747-749	The Agency should consider striking the phrase "as a scientific matter" since we believe that this requirement represents a regulatory policy and not a scientific matter. In cases where U.S. and non-U.S.-licensed product are made by the same process and employ the same control strategy, they provide a single data population with respect to quality attributes. Therefore, we believe that pooling of data should be allowed in cases where it is possible to provide a level of evidence confirming that the manufacturer of the reference product is using the same manufacturing process for the U.S. reference product and the non-U.S. comparator product. Specifically, we propose addition of examples by which sponsors could justify the pooling of data obtained with U.S. and non-U.S. licensed material.	**~~"As a scientific matter,~~** **C**ombining data from the reference product and non-U.S.-licensed comparator product to determine the acceptance criteria or to perform the comparative analytical assessment to the proposed product would **~~not~~** be acceptable **in certain situations** to support a demonstration that the proposed product is biosimilar to the reference product, **when the sponsor can provide evidence that U.S. and non-U.S.-licensed product are made by the same process, representing a single data population with respect to quality attributes**. **Such evidence can be gained, e.g. by** **a. Multivariate data analysis showing that the U.S. reference and the non-U.S. comparator represent the same population.** **b. Confirmation by analysis of product related substances (e.g. quality and quantity of low-level variants and impurities) and process related impurities (e.g. host-cell proteins) that U.S. and non-U.S. material are indistinguishable** **c. Public information confirming that reference product manufacturer is using the same manufacturing process for U.S. and non-U.S.-licensed products."**

Lines 750-752	Acceptance of non-U.S. licensed comparator product in l situations as described in the draft guidance facilitates reference product sourcing and greater sample size of reference product. The goal is to achieve a better estimation of the true population of the reference product, not to get a broader similarity acceptance range. We therefore propose to delete this sentence.	Delete sentence: ~~**"For example, combining data from the reference product and non-U.S.-licensed products may result in a larger range and broader similarity acceptance criteria than would be obtained by relying solely on data from reference product lots**~~."
Lines 771 ff.	We appreciate the section on Risk Assessment. We also noted two paragraphs in other sections of this guidance, which provide further considerations on risk assessment. For clarity purposes, we therefore propose to move these paragraphs into this section.	We propose to move the following two paragraphs into this section "Risk Ranking": Move paragraph of Lines 831-833 into section B.1, following line 790. Move paragraph of Lines 850-859 into section B.1, following line 790
Lines 787-790	We propose this edit to maintain consistency with lines 831-833. We fully agree with the statement in lines 831-833 that attributes that are known to be of high risk should be prioritized over attributes with unknown but potentially high risk (i.e., attributes with a high-risk ranking due to higher uncertainty). However, the example of lines 787-790 state that higher uncertainty should **always** result in higher risk ranking. The latter is, in our opinion, true for potentially low risk attributes only. Therefore, we propose to limit this example here to potentially low risk attributes to maintain consistency with lines 831-833.	"The degree of uncertainty surrounding a certain quality attribute: For example, when there is limited understanding of the relationship between the degree of change in ~~**an**~~ **a potentially low risk** attribute and the resulting clinical impact, FDA recommends that that attribute be ranked as having higher risk because of the uncertainty raised."
Lines 817-819	We interpret these lines that biosimilar and reference product should be similar in both population	"The objective of the comparative analytical assessment is to **compare** ~~**verify that**~~ each

	mean and population standard deviation for each quality attribute. We find this requirement overly strict, because of two reasons: 1. For low risk quality attributes, any such differences that may exist can be clinically irrelevant. 2. For the high risk quality attributes, we believe that a low population standard deviation is generally desirable for robust manufacturing. Therefore, a smaller population standard deviation of the biosimilar compared to the reference product should be acceptable.	attribute, as observed in the proposed biosimilar and the reference product. **~~, has a similar population mean and similar population standard deviation.~~**"
Lines 831-833	This paragraph provides helpful guidance for risk ranking of quality attributes. Therefore we propose to move this paragraph into section B. 1 Risk assessment following line 790.	We propose to move paragraph of Lines 831-833 into section B.1, following line 790.
Lines 835-837	The advice to target the center of the reference product distribution helps to guide successful biosimilar development. However, the center typically may change over time in the course of development when new reference product lots become available for analysis. In the end, the entire range of the reference product, as regulated by the Agency, defines acceptable quality. We propose to add this clarification as it helps to maintain consistent regulatory requirements for biosimilars and reference products. This also eliminates the risk of unintentional bias in market competition (see also our general comment No 3).	"In general, the Agency recommends that sponsors develop the manufacturing process to target the centers of distribution of the quality attributes of the reference product as closely as possible. **For the final biosimilar evaluation, the entire range of the reference product distribution reflects acceptable quality."**
Lines 837-839	The QR actually accepts smaller standard deviation of the biosimilar candidate than the reference product. This is also scientifically acceptable and desirable for high process robustness.	"Therefore, the QR, which assumes that the population mean **~~and standard deviation~~** are similar, is an appropriate approach to demonstrate that the proposed

		product is highly similar to the reference product."
Lines 845-846	The requirement that a bias towards one side of the reference product distribution raise concerns and may require appropriate justification, poses a risk that manufacture of biosimilars companies are held to stricter requirements than those that are applied to reference products . Depending on the degree by which this potential requirement is applied by the Agency, this may, in the worst case, lead to an unintentional bias in market competition between companies that may ultimately limit patient access to biologic medicines. Two avoid this risk we propose to add two examples how to justify a biased distribution: 1. A bias of the biosimilar product to one side of the reference products distribution should be acceptable, if the control strategy of the biosimilar ensures containment within the entire range of the reference product. 2. Bias is of no concern when sufficient product knowledge is available to exclude a clinically meaningful difference.	"If such a distribution is observed, appropriate justification may be needed, as a scientific matter, to support the comparative analytical assessment of the products **(e.g. control strategy ensures containment within the reference product range; sufficient product knowledge is available to exclude a clinically meaningful impact)**."
Lines 847-848	We have observed situations where the distribution of a given quality attribute of the reference product is stable over time, but then undergoes a significant shift from the prior mean of distribution.	"In cases where an attribute in the reference product is not normally distributed **or when the mean of distribution shifts significantly over time**, sponsors should consult with the Agency."
Lines 850-859	This paragraph provides helpful guidance for risk ranking of quality attributes. Therefore, we propose to move this paragraph into section B. 1. Risk assessment following line 790. Line 851 - 853 state that the abundance may alter the risk. It should be therefore part of the risk assessment section in order to avoid inconsistencies within the guidance.	We propose to move paragraph of Lines 850-859 into section B.1, following line 790.

We appreciate the opportunity to provide comments as FDA continues to implement a key policy issue related to use of biological drugs. If there are questions about our comments please do not hesitate to contact us.

Sincerely,

Bieber Florian

Digitally signed by Bieber Florian
DN: dc=com, dc=novartis, ou=people, ou=GX, serialNumber=1843760, cn=Bieber Florian
Reason: I am approving this document
Date: 2019.07.19 13:36:46 +02'00'

Rizzo Jessica

Digitally signed by Rizzo Jessica
DN: dc=com, dc=novartis, ou=people, ou=GD, serialNumber=1754730, cn=Rizzo Jessica
Date: 2019.07.19 07:32:25 -04'00'

Florian Bieber, MD
Global Head of Biopharmaceutical Development
Sandoz Inc.

and

Jessica Rizzo
Regulatory Policy & Intelligence Manager
Novartis Pharmaceuticals Corporation