November 21st, 2017

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

Re: Docket No. FDA-2017-D-5525: Statistical Approaches to Evaluate Analytical Similarity

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance on Statistical Approaches to Evaluate Analytical Similarity.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO commends FDA on this Draft Guidance which provides important advice on the evaluation of analytical similarity for Sponsors of biological products licensed under section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). In finalizing the Draft Guidance, and in assisting sponsors on the evaluation of analytical similarity, we strongly urge the agency to consider our comments and to implement the suggested changes.

1. **General Comments**

   - The approaches outlined in this Draft Guidance are complex and warrant product-specific discussion with the Agency very early in development to discuss lot selection, risk ranking of attributes, and initiate analytical similarity plan and statistical analysis plan discussions. We support the Agency's view in lines 170-172, that Sponsors should develop an analytical similarity assessment plan and discuss this approach with the Agency as early in the development program as feasible.

   - Due to the stepwise process of biosimilar development, early discussions between FDA and sponsors will help to avoid misinterpretations of expectations (lines 170-172). However, follow up discussions may be needed as more information is gained throughout development.

2. **Challenges and Limitations to Applying Statistical Analyses in the Evaluation of Analytical Similarity Data**

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- BIO is supportive of the Draft Guidance's acknowledgement that there are many challenges and limitations to applying statistical analyses in the evaluation of analytical similarity data (lines 78-86; 94-95; 263-265; 378-382; 403-404). However, there are other challenges that are not directly acknowledged or addressed in the Draft Guidance. For example, another risk to the biosimilar developers' ability to design the statistical analyses is the absence of control over the reference product, whose quality attribute levels may fluctuate or change at any time during or even after the proposed biosimilar product's development.

- The approach recommended by FDA for statistical analysis of analytical similarity can be a useful tool in supporting interpretation of data when applied appropriately. However, the interpretation should be considered complementary to the overall analytical similarity assessment and not used as a decision tool.

3. **Analytical Similarity vs. Analytical Similarity Assessment Plan**

- Throughout the Draft Guidance the term analytical similarity assessment plan is used both to describe the application of analytical procedures for demonstration of biosimilarity and to encompass the statistical assessment similarity plan. This may contribute to a lack of clarity for the reader as they may infer this to relate to the totality of analytical data collected to assess whether the proposed product is highly similar to the reference product rather than the evaluation of these data. For clarity, these two concepts should be clearly distinguished. FDA should consider other terminology – perhaps *analytical similarity data evaluation plan* or *statistical assessment plan* to encompass the risk ranking, method determination, and statistical analysis plan. Use of the term analytical similarity assessment plan could mislead readers as to the scope of this Draft Guidance.

4. Quality Attributes

- The Draft Guidance should make a clear distinction when referring to "Quality Attributes", between structural/physicochemical attributes and functional attributes (e.g., lines 211-212: "Determination of the statistical methods to be used for evaluating each ~~quality~~ *physical/chemical* and functional attribute based on the risk ranking and on other factors")

- Keeping the concepts of structural/physicochemical attributes separate from that of functional attributes will help maintain a link between the Product Quality Attribute Assessment (PQAA) performed as a component of the Quality by Design (QbD) development process.

- This distinction among attributes would also afford companies that do not include functional attributes in their risk assessment to not have to perform separate risk assessments for the similarity exercise. Rather they could utilize their PQAA and assess functional attributes as an additional component to complete the similarity analysis.

5. Challenges of Developing a Pre-Specified Statistical Analysis Plan

- The Draft Guidance states (lines 315 – 318) that the statistical analysis plan should be pre-specified to the fullest extent possible and notes preliminary data to get an initial estimate of variability of the reference product's attribute.

- Reference product changes over the duration of shelf-life will not be known to the biosimilar manufacturer at early stages of biosimilar product development. An accurate estimation of the variability of the reference product's attributes may not become apparent until many years after initial lots are sampled.

- Thus, developing a pre-specified statistical analysis plan based on initial reference product lots may be irrelevant or even contradictory as the reference product is sampled and tested throughout the development program of the proposed biosimilar product; changes observed, which conflict with early estimates of variability, should be accounted for and the plan adjusted accordingly.

- The statistical analysis plan should be pre-specified to the fullest extent possible, however, as the reference product variability is outside the control of the biosimilar developer, circumstances may arise which require the original estimate of reference product variability to be adjusted.

6. Tiered Approach

- In general, we agree with the Draft Guidance regarding the utilization of different categories based on levels of clinical criticality.

- In some cases, however, the use of Tier 1 equivalence testing may not be appropriate (or possible). BIO requests that the Agency clarify the guidance by noting that in such cases, the sponsor should approach the Agency to discuss alternative approaches. In addition, it is concerning that equivalence testing statistics could extend the statistical recommendation for Tier 1 quality attributes to future manufacturing process changes proposed for biological drugs (e.g., necessitate the need for head-to-head analytical and functional comparisons of biological drugs). We request clarification from the Agency that this guidance does not apply post-approval.

- Some scientific concerns with the approach for Tier 1 may include:

    - The requested equivalence testing for Tier 1 attributes, if approached as a pass/fail criteria, may pose the risk of restricting biosimilar approvals for reasons associated with reference product variability.

    - BIO respectfully requests that FDA hold a stakeholder workshop to work with sponsors to identify scientifically appropriate ways with which to deal with changes in reference product attributes over time and how statistical methods may be used appropriately in this context.

- The Draft Guidance lacks description of possible justifications which would allow biosimilar approval in cases of failed Tier 1 equivalence results. The Draft Guidance should expand possible justifications to overrule a failed equivalence test in cases where the mean of the reference product changes over time. This would ensure alignment with existing guidance (ICH Q6B, ICH Q5E, ICH Q7, ICH Q8, ICH Q11). A possible suggestion in this regard may include justification by scientific understanding of the impact of the range of Tier 1 quality attribute(s) to safety and efficacy.

BIO appreciates this opportunity to submit comments on the Draft Guidance on Statistical Approaches to Evaluate Analytical Similarity. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
General	The Draft Guidance references both, *similarity* and *comparability* without making a clear distinction.	FDA should clarify its use of similarity and comparability. We also request the Agency clarify whether the principles and concepts outlined in the Draft Guidance on *Comparability Protocols for Human Drugs and Biologics* and ICH Q5E *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* would apply in those instances where comparability is referenced in the document.
General	Throughout the document, use of the term *analytical similarity assessment plan* may contribute to lack of clarity as the reader may infer this to relate to the totality of analytical day data collected to assess whether the proposed product is highly similar to the reference product rather than the evaluation of these data. Use of the term analytical similarity assessment plan could mislead readers as to the scope of this Draft Guidance.	FDA should consider other terminology – perhaps *analytical similarity data evaluation plan* or *statistical assessment plan* to encompass the risk ranking, method determination, and statistical analysis plan.
Line 34	Companies need the flexibility to employ other statistical approaches that are not included in the draft guidance. We would like FDA to state explicitly that alternative scientifically-defensible statistical approaches, not specified in the draft guidance, may be used.	Add language to the effect that: "Alternative scientifically-defensible statistical approaches, not specified in the draft guidance, may be used."
II. BACKGROUND AND SCOPE		

SECTION	ISSUE	PROPOSED CHANGE
Lines 76-77	The Draft Guidance states: "Conducting appropriate statistical analyses in the evaluation of analytical similarity can provide a high degree of confidence in the results and reduce the potential for bias." The application of inferential statistical methods should be considered in the context of supportive information, to assist or facilitate comparative evaluation of quality attributes. The use of orthogonal, comprehensive characterization techniques should represent the primary comparative data source for quality attribute comparison.	Conducting appropriate statistical analysis can assist the comparative evaluation of quality attribute data generated using comprehensive orthogonal analytical procedures. "Conducting appropriate statistical analyses in the evaluation of analytical similarity can provide a ~~high~~ higher ~~-~~degree of confidence in the results and reduce the potential for bias."
Lines 77-86	Challenges are acknowledged to exist in the application of statistical analysis but the three points stated do not include one of the most substantial risks to the biosimilar developer, namely the absence of control over the reference product, whose quality attribute levels may change at any time during the proposed biosimilar development process. The fact that the reference product quality attributes levels can change at any time means that the dataset used as the gold standard for comparison is completely outside the control of the biosimilar developer.	Include a fourth challenge, the potential for the reference product ranges to change at any time during the development of the potential biosimilar product which could impact the viable application of statistical analysis as a supportive comparison tool.
Lines 78-79	The Draft Guidance states: "First, there may be a limited number of reference product lots, and those obtained may be the result of biased sampling" Biased sampling may be of concern regardless of the number of product lots. Biosimilar manufacturers do not have control over the reference product lots they are able to obtain. As such, there is limited ability to address this challenge.	"First, there may be a limited number of reference product lots, ~~and~~ or those obtained may be the result of biased sampling"

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Lines 84-86	Problems with Formal Statistical Tests do not only happen in the context of limited lots. There are statistical methods that could be adapted or developed to adjust for the risk of "concluding incorrectly that . . . truly highly similar products are not highly similar."	Consider in line 84 a modification to "indiscriminately subjecting all of these attributes" to reflect that there are approaches that can be included in a formal testing strategy to address the concern. Consider adding after the end of line 86: "Alternate justified statistical comparisons that focus on estimations of the magnitudes of the similarities and the differences could be considered by the sponsor and specified in the statistical analysis plan. Bayesian or multivariate approaches could be taken, for example."
Lines 88-89	The Draft Guidance states: "To address these challenges, the Agency recommends using a risk-based approach in the analytical similarity assessment of quality attributes." However, it is not clear how a risk-based approach in the analytical similarity assessment of quality attributes addresses the challenges outlined in Lines 77-86; this is particularly true of the first challenges raised relating to limitations relating to lot availability and selection. Risk ranking, and tier analyses will not resolve these challenges.	FDA should clarify how a risk-based approach in the analytical similarity assessment of quality attributes addresses the challenges outlined in Lines 77-86. Further, consider adding text that recommends that these challenges may need to be further discussed with the Agency to achieve full resolution.
Lines 92-94	The discussion provides no guidance on how a ranking approach would be determined acceptable to both the Agency and the Sponsor.	Consider adding text in this section, which recommends that sponsors are encouraged to discuss ranking and rationale to gain agreement with the agency as early as possible. We recognize that this recommendation is currently included in the draft guidance in Lines 326-330.
Lines 93-94	"…these attributes/assays are evaluated according to one of three tiers of statistical approaches based on a consideration of risk ranking as well as other factors."	Clarification proposed: "…these attributes/assays are evaluated according to one of three tiers ~~of statistical~~

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	Evaluation of attributes in Tier 3 is not necessarily through statistics. See text in line 259, "an approach that uses visual comparisons (Tier 3)".	~~approaches~~ based on a consideration of risk ranking as well as other factors."
III. REFERENCE AND BIOSIMILAR PRODUCTS		
General	It is suggested that the scope of the Draft Guidance be limited to statistical approaches to evaluate analytical similarity and that the Quality Considerations guidance be updated to include information pertaining to lot selection, and analytical similarity. Content of Section III. should be limited to content necessary to facilitate the statistical analysis and would be better placed under Section IV. A. in order to ensure it is clear that any discussion of reference product and biosimilar lots is specifically related to the statistical approaches to evaluate the analytical similarity data.	Content should be limited to content necessary to facilitate the statistical analysis. The organization of the content could be improved for better reading. Section III relating to lot selection is part of the analytical similarity assessment plan. Therefore, it should be relocated to Section IV-A.
Lines 110-111	The Draft Guidance states that the analytical similarity plan is developed "based on information obtained about these [structural/physicochemical and functional] attributes during development of the proposed biosimilar…" This suggests that the analytical similarity plan is developed a posteriori. However, Lines 316-316 state "…to minimize bias and the chance of erroneous conclusions, the statistical analysis plan should be pre-specified to the fullest extent possible." This seems contradictory.	The statistical analysis plan should be pre-specified to the fullest extent possible, however, as the reference product variability is outside the control of the biosimilar developer, circumstances may arise which require the original estimate of reference product variability to be adjusted based on data.

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Line 128	The Draft Guidance sates: "Lots with remaining expiry spanning the reference product shelf life should be selected." The availability of reference product and the assigned expiry is outside the control of the biosimilar developer, and therefore requiring the reference product lots to span the shelf life may not always achievable.	"Lots with remaining expiry (at time of purchase), and lots ideally spanning the reference product shelf life should be selected."
Lines 132-133	"Sponsors should account for all of the reference product lots available to them." Clarification proposed. The current text gives the impression that all reference product lots available on the market during the development window are to be listed.	"Sponsors should account for all of the reference product lots ~~available to them~~ acquired during biosimilar product development."
IV. GENERAL PRINCIPLES FOR EVALUATING ANALYTICAL SIMILARITY		
A. Analytical Similarity Assessment Plan		
Lines 172-173	"The final analytical similarity report, which should include the analytical similarity assessment plan, should be included when a 351(k) biologics license application is submitted." Submission of internal reports, which may contain references to documents which are not part of the submission, should not be necessary.	"~~The final analytical similarity report, which should include~~ A detailed description of the analytical similarity ~~assessment~~ plan~~,~~ and results should be included when a 351(k) biologics license application is submitted."
Lines 190-192	With regards to pre-specifying which test results to select for analytical similarity assessment, it is unclear if this refers to defining the reportable value.	Request for clarification.

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Lines 207-209	The text should refer to ' structural/physicochemical and functional attributes rather than simply quality attributes. This is consistent with other references in the guidance (see Lines 21, 73, 91).	"Development of ~~the risk~~ a ranking structure for the assays/attributes that will be used to assess ~~of~~ the reference product's ~~quality~~ structural/physicochemical and functional based on the potential impact on the clinical performance categories (i.e., the product's activity as well as pharmacokinetic/pharmacodynamic (PK/PD), safety, and immunogenicity profiles)"
207-209, 226-231, 237-238	The guidance mentions PK/PD at several points but does not provide clarity about what PK/PD parameters are of importance or clarity about how to determine which PK/PD parameters are high risk and which may not be. At Lines 226-231, it seems that the guidance is describing an *In vitro In vivo* Correlation (IVIVC)-type assessment for establishing analytic similarity but clarity is not provided.	The guidance should clarify if an IVIVC-type assessment is expected and reference, with appropriate qualifications, the IVIVC guidance for small molecules, or provide either specifics about the PK/PD parameters of importance or how a sponsor is to risk-rank PK/PD parameters.
Lines 211-212	The text should refer to 'structural/physicochemical and functional attributes rather than simply quality attributes	Recommended change: "Determination of the statistical methods to be used for evaluating each ~~quality~~ structural/physicochemical and functional attribute based on the risk ranking and on other factors"
Lines 204-216	The draft guidance recommends that the analytical similarity assessment plan be developed in four listed stages. Analytical method variability is discussed later in the document.	For clarity, please preface that the analytical methods performance characterization and validation data should be conducted at the start of the analytical similarity assessment plan. It would be useful to provide guidance on the particular parameters to highlight from the method performance characterization or validation data which should be highlighted in the overall similarity plan.

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1. Development of Risk Ranking of Attributes		
Lines 244-246	"The scoring criteria used in the risk assessment should be clearly defined and justified in the analytical similarity assessment plan, and the risk ranking for each attribute should be justified with appropriate citations to the literature and data provided." It is agreed that the justification for the risk ranking should be provided. However, use of the term "scoring" criteria could be interpreted as establishment of numerical values which may not be necessary to fully convey the justification of the risk ranking.	~~"The~~ A justification of the proposed ~~scoring criteria used in the risk assessment should be clearly defined and justified in the analytical similarity assessment plan, and the~~ risk ranking for each structural/physicochemical and functional attribute should be provided ~~justified~~ with appropriate citations to the literature and data provided."
2. Determination of the Statistical Methods to be Used		
Line 255-257	The text should refer to 'physical/chemical attributes and biological functions' rather than simply quality attributes	Recommended change: "Equivalence testing (Tier 1) is typically recommended for ~~quality~~ structural/physicochemical and functional attributes with the highest risk ranking and should generally include assay(s) that evaluate clinically relevant mechanism(s) of action of the product for each indication for which approval is sought."
Lines 259-260	The Draft Guidance states: "…an approach that uses visual comparisons (Tier 3) is recommended for quality attributes with the lowest risk ranking."	"…an approach that uses visual comparisons (Tier 3) is recommended for quality attributes with the lowest risk ranking or those not amenable to statistical analysis."
Line 276	The Draft Guidance states: "The justification should also include consideration of how the level of the attribute changes over time."	"The justification should also include consideration of how the level of the attribute changes over ~~time~~ shelf life."

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Lines 286-288	"For example, compendial assays, qualitative assays, or limit assays might be excluded from evaluation with Tier 1 and, in some cases, Tier 2 methods." Reference to compendial assays is considered too broad as some assays may be used to measure critical attributes such as protein concentration.	Recommended change: "For example, ~~compendial assays,~~ qualitative assays, or limit assays might be excluded from evaluation with Tier 1 and, in some cases, Tier 2 methods"
3. Development of the Statistical Analysis Plan		
Lines 307-308	"For each attribute, a determination of the largest acceptable difference between the proposed biosimilar and reference product that is considered to not have clinical impact;" It is unclear why an *a priori* determination of the largest acceptable difference between the proposed biosimilar and reference product that is considered to not have clinical impact is recommended for each attribute beyond the determination of the tiering classification and associated justification of the statistical plan. An evaluation of the potential clinical impact of differences is needed only for attributes where a difference is found between the biosimilar and the reference product as an outcome of the analytical assessment. When differences are identified between the biosimilar and reference product, an assessment should be provided on the potential clinical impact of the difference.	Recommended change: ~~"For each attribute, a determination of the largest acceptable difference between the proposed biosimilar and reference product that is considered to not have clinical impact;"~~
Lines 315 - 318	The Draft Guidance states that the statistical analysis plan should be pre-specified to the fullest extent possible, on an estimate of reference product	The statistical analysis plan should be pre-specified to the fullest extent possible, however, as the reference product variability is outside the control of the biosimilar developer,

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	variability. An estimation of the variability of the reference product may not become apparent until many years after initial lots were sampled. Thus, making a plan pre-specified on initial lots may be irrelevant or even contradictory as the reference product is sampled and tested throughout the clinical program of the potential biosimilar product and changes observed, which conflict with early estimates of variability, should be accounted for.	circumstances in which more data may become available that may require the original estimate of reference product variability to be adjusted.
Lines 317-318	The draft guidance notes "it may be necessary to first collect preliminary data (e.g., to get an initial estimate of the variability of the reference product's attribute or to select an assay at the outset before finalizing the statistical analysis plan)."	It would be useful to provide guidance on the particular parameters to highlight from the method performance characterization or validation data which should be taken into account in the design of the statistical analysis plan.
B. Statistical Methods for Evaluation		
Lines 378-85	It should be clearer that other ways can be justified by the sponsor to determine the appropriate margin of equivalence.	
Lines 420-421, 429-430	The Draft Guidance notes that the lots used for testing should, if possible, be the same for all Tiers. There are limitations to this suggestion. Specifically: • Not all analytical methods used in the final similarity assessment are necessarily available at the beginning of the biosimilar development. Analytical methods may be revised, replaced, or added. • Some of the more difficult characterization methods may not be ready as early as other	Suggest deletion.

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	methods making it difficult to test the exact same lots, particularly when the reference product expiry is short. • The lot selection for testing by individual method is often dictated by availability of the material (amount, expiry) and the final method. • It may not be possible to purchase sufficient quantities of a given lot of reference product to allow it to be tested in with the full array of physicochemical and functional assays. Further, all reference product lots available are expected to be representative of the originator's manufacturing process. Therefore, it is neither necessary nor practical to test the same set of reference product lots with all methods. It should be sufficient for the sponsor to provide justification of lot selection for a particular study as recommended in Lines 137-138.	
1. Tier 1 (Equivalence Test)		
General	There is lack of clarity in how to identify Tier 1 attributes	FDA should provide further clarity on which attributes should be assessed in order to determined biosimilarity, particularly clarifying how to identify Tier 1 attributes.
Lines 382-384	"With this limitation, FDA currently recommends use of an equivalence margin that is a function of the reference product's variability for the attribute being tested."	It should be noted that the true variability of attributes will not be known and rather estimation based on the assumption of a highly representative sample from a reference process which is under high degree of statistical control. This is a general fault of using a Tier 1 analysis for these attributes. For this reason, we would suggest that the

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		Agency conduct a workshop engaging stakeholders on this topic to come up with more generally applicable criteria based on scientific evidence.
Lines 403-408	"A limitation of the proposed approach to setting the equivalence margin is that σ_R is usually not known and must be estimated from the current reference product lots available to the sponsor. If one uses a t-test and does not consider the uncertainty in the estimate of the margin, the Type I error probability may be inflated. Alternative tests can be constructed to account for this additional uncertainty, but additional research is needed to better understand the operating characteristics of these tests (such as the small sample size performance of a Wald7 test based on large-sample approximations)." We note that the Agency acknowledges the limitations of the proposed approach. In order to account for the 'uncertainty in the estimate of the margin', a measure such as effect size could be used to address this issue. A confidence interval on the effect size can be calculated and compared to a pre-determined equivalence margin. We suggest the use of effect size $\frac{\mu_T - \mu_R}{\sigma_R}$ to avoid the issue of 'uncertainty in the estimate of the margin'. The equivalence margin, δ, would then be a fixed constant (e.g., 1.5).	If effect size is to be used, the equation in line 360 would become $-1.5 < \frac{\mu_T - \mu_R}{\sigma_R} < 1.5$

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Lines 403-408	The control of type I error is one of the major, but not the only, concerns of the current Tier 1 approach. For instance, the purpose of equivalence test here is to test the mean difference between the reference product and the biosimilar product. However, in reality, it is probably more important, and more clinically relevant, to ensure that the biosimilar product distribution falls within the reference product distribution. Please note that these two objectives are not completely aligned. Another limitation worth pointing out is the equivalence margin, which is not fully science-based. As shown in the draft guidance, the margin 1.5 $\hat{\sigma}_R$ is based on the assumption that the true mean difference is no more than σR /8, which may or may not be a clinically relevant difference. This approach seems arbitrary.	FDA should consider the limitations of the proposed approach. Per Lines 199-202, it should be considered appropriate for a sponsor to scientifically justify an alternative margin if there is knowledge that a difference in a particular quality attribute is not expected to have a clinical impact.
*2. **Tier 2 (Quality Range Approach)***		
Lines 412 - 414	The Draft Guidance defines similarity acceptance criteria for Tier 2 based on reference product results for all quality attributes in the same manner.	FDA is urged to consider allowing a one-sided range for attributes having a desired upper or lower limit only (i.e. HHMS and monomers).
3 Tier 3 (Visual Displays)		
Lines 430-433	The draft guidance mentions at a high level that in some cases a single lot of the proposed biosimilar and reference product may be used for the Tier 3 evaluation. Further clarity would be helpful.	Please provide examples of attributes that could be assessed using only a single lot of the proposed biosimilar and reference product.
4 Additional Considerations		

SECTION	ISSUE	PROPOSED CHANGE
Lines 454-455	"When the calculated equivalence margins or quality ranges are too wide or narrow, the Agency may adjust them to more appropriate levels." If there is a need to adjust the equivalence margins or quality ranges, this should be undertaken as a joint discussion and decision of the Agency and the Sponsor.	Request more clarification as to what is deemed "too wide or too narrow." Recommended change: "the Agency and sponsor should discuss the nature of the adjustments that will be undertaken, after which the sponsor will propose revisions and provide the rationale for the changes."
Lines 459-460	"For example, the Agency generally will consider the impact of an enhanced manufacturing control strategy when making this final assessment." This is unclear.	Additional clarification, perhaps in the form of examples, is requested.