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FDA-2016-D-4412

VIA ELECTRONIC SUBMISSION

March 20, 2017

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

Re: Docket No. FDA-2016-D-4412: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry" ("Draft Guidance"). Overall, the CPC believes that the Draft Guidance is a positive step forward in clarifying the approval pathway for generic/biosimilar drug-device combination products. However, as detailed below, the CPC has significant concerns surrounding the Draft Guidance. We hope that FDA will consider our comments as it finalizes its guidance, and works toward providing a balanced and sustainable pathway to market for generic/biosimilar combination products that both protects patient safety and allows for innovation that can improve user experiences.

While the CPC agrees with many of the recommendations in the Draft Guidance, we strongly recommend that FDA revise the document to:

1. Improve alignment between the Draft Guidance and existing human factors ("HF") guidance provided by FDA and by recognized U.S. and international standards;
2. Focus comparative analyses on risk, not use error rates;

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad and unique perspective to these issues.

3. In accordance with item 1, describe HF studies as qualitative research (to assess the adequacy of the product user interface) rather than quantitative research (to assess the capabilities of the users);
4. Promote innovation and improvements to the design of products to enhance safety and effectiveness; and
5. Provide more information regarding topics not sufficiently addressed in the Draft Guidance.

We have also included additional, specific comments in Appendix A.

I. Improve Alignment between the Draft Guidance and Existing HF Guidance Provided by FDA and by Recognized U.S. and International Standards

To enable a consistent HF engineering approach, the CPC strongly recommends that FDA align the Draft Guidance with previous FDA HF guidance documents[2] and FDA-recognized consensus standards.[3] Previous FDA HF guidance offers input on the "appropriate human factors and usability engineering processes to maximize the likelihood that new medical devices will be safe and effective for the intended users, uses and use environments."[4] Specifically, these guidance documents describe a risk-based approach for analyzing a product's user interface, identifying the critical tasks, and conducting HF evaluations to assess potential use errors on the critical tasks that could impact safe and effective use. In addition, FDA-recognized consensus and internationally harmonized standards provide guidance on managing use-related risks for medical devices and implementing a rigorous HF engineering process.

One specific area where FDA can improve alignment between these documents and standards and the Draft Guidance is in its use of terminology. For example, FDA introduces in the Draft Guidance the term "external critical design attributes," which it defines as "features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product" (lines 168-170). We find this term problematic because some design attributes are not "external," but they impact device use nonetheless. For instance, spring force, which is an internal design attribute, impacts the injection time of an autoinjector. The use steps associated with the injection are considered critical tasks in the administration of the drug.

To improve consistency and avoid confusion, we recommend that the Draft Guidance instead use the term "primary operating functions," which is defined in IEC 62366:2015 as a "function that involves user interaction that is related to the safety of the medical device." Using

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[2] FDA, CDRH, *Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and FDA Staff* (2016) ("HF/Usability Engineering Guidance"); FDA, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff* (2016) ("Combination Product HF Draft Guidance").

[3] See e.g., AAMI/ANSI HE75:2009, *Human factors engineering – Design of medical devices*; IEC 62366-1:2015, *Medical devices – Part 1: Application of usability engineering to medical devices*; ISO 14971:2007, *Medical devices — Application of risk management to medical devices*.

[4] HF/Usability Engineering Guidance at 1.

this term in the Draft Guidance, rather than FDA's proposed term, can serve FDA's purpose while facilitating sponsors' ability to comply with international standards as well as FDA's expectations.

II. Focus Comparative Analyses on Risk, Not Use Error Rates

The Draft Guidance provides two categories for external critical design attributes: "minor" and "other (non-minor)" (lines 232-268). The only difference between the two categories is whether the difference in user interface would affect a primary operating function. The problem with this approach is that it would lead to the definition of "other differences" being too broad (lines 250-254).

Using a prefilled syringe ("PFS") as an example, "remove syringe needle cover" is identified as a critical task per the Combination Product HF Draft Guidance. Therefore, under the Draft Guidance, the needle cover itself would be considered an "external critical design attribute." By extension, any design differences in the needle cover, even the color, would then be considered an "other (non-minor)" difference and may require a comparative HF study. This results in a mischaracterization of risk and ultimately an undue burden on the generic or biosimilar product manufacturer.

Instead of assessing differences in a binary fashion (impact or no impact), we recommend that the Draft Guidance utilize a tiered approach based on a risk assessment of the proposed generic/biosimilar product. For example, AAMI ANSI ISO 14971 provides an example of qualitative severity levels (catastrophic, critical, serious, minor, and negligible), as well as the definitions for each. We recommend that the impact of differences in the user interface be assessed in a similar fashion, i.e., based on the risk analysis of the proposed generic/biosimilar product.

We understand FDA's concern about the potential for the proposed generic/biosimilar product to introduce use errors that could result in serious harm. And we agree that the best method for determining the adequacy of the proposed new product is to perform a side-by-side analysis of the product and the reference listed drug ("RLD"), as the Draft Guidance suggests. However, we ask that FDA include the following in the threshold analysis to provide additional clarity and specificity:

- Differential task analysis – What are the tasks (and sub-tasks) for using each device that differ between the proposed new product and the RLD? This analysis should be sufficiently granular such that differences in user interface, such as differences in primary operating functions, are detected. For example, differences in the specific action(s) a user would take to activate an autoinjector should be listed individually (e.g., push on skin and press activation button), and not lost under a general "Activation/Dose Delivery" task.

- Use error analysis – What use errors could the user make while performing these tasks with the proposed generic/biosimilar? What use errors could the user make that are a direct result of the differences between the new product and the RLD, e.g., due to negative transfer of learning from the RLD to the new product?

- Severity analysis – What could be the consequences of each of the use errors that the user could make with the proposed generic/biosimilar? The results would be used to identify the critical tasks of use (i.e., those tasks that if performed incorrectly or not at all could result in serious harm).

The results of the analyses listed above would enable identification of the criticality of the differences between the new product and the RLD, which would determine whether HF testing would be needed to assess those differences. If testing is necessary, the HF testing should then focus on those tasks for which the use-related risks are different from those of the RLD, and on which use errors associated with the differences in product design could result in serious harm. Such testing could either be conducted separately from or in conjunction with the standard HF validation testing proposed for a new product.

We recommend that this testing not include user testing of the RLD as assessment of the RLD has already been carried out through the previously described differential task analysis, and post-market safety reporting could be problematic, as described in the next section. The goal of the HF testing is to ensure that the intended users of the proposed generic/biosimilar product can use the product safely and effectively, even if some of the design elements differ from those of the RLD.

III. Describe HF Studies as Qualitative Research (to Assess the Adequacy of the Product User Interface) Rather than Quantitative Research (to Assess the Capabilities of the Users)

The CPC has concerns regarding the non-inferiority ("NI") inter-device comparative study design approach described in Appendix A of the Draft Guidance, and proposes a different approach. HF validation studies are designed (as explained in IEC 62366-1:2015 and FDA's HF/Usability Engineering Guidance) as studies where understanding the root cause of a participant's use error is as important as the fact that it occurred. Percentages of successful use and use error rates are less important than detecting use errors that could result in serious harm, regardless of how infrequently they occur, or even if they occur only once in the study. The number of use errors that occur when using a device does not provide evidence, either positive or negative, about the safety or effectiveness of that device unless the potential consequences of those errors are also analyzed.

In its 2015 update of IEC 62366 (now designated as IEC 62366-1), the international committee that wrote the standard removed the acceptance criteria that were included in the first (2007) edition specifically for this reason. For the same reason, the phrase "pattern of use error" was removed from the draft version of the HF/Usability Engineering Guidance when it was finalized in 2016. Requiring a NI approach, based on principles used in placebo-controlled clinical trials of medicinal products, and in this case comparing use error rates, is not appropriate for assessments of user interactions with a user interface, especially where (multiple) different types of use errors could result in different severities of harm.

The Draft Guidance states that the goal of HF studies in this circumstance is to ensure that the intended users can use the proposed generic or biosimilar product "without the

intervention of [a] health care provider and/or without additional training…" (lines 143-144). We believe that this goal can be achieved more meaningfully with a threshold analysis and a standalone HF study on the generic or biosimilar product, rather than a quantitative, statistically powered non-inferiority comparative use HF study on the proposed new product and the RLD.

The evidence needed to prove the safety of switching a patient to a generic or biosimilar product can and should be generated using standard HF engineering methods for these products without testing of the RLD. We believe that the most appropriate study design would be to test two user groups in the study of the proposed generic or biosimilar product: (1) users who are familiar with the RLD (and/or other similar RLDs), and (2) users who are naïve to the product category. Training would not be provided to those users familiar with the RLD. Training would only be provided for naïve patients as appropriate per the label if they were receiving the product for the first time. Both groups would be provided the instructions for use, but not required or asked to read them; and the results would show whether these users could use the proposed new device safely and effectively without intervention of a health care provider or additional training. We believe this study design directly addresses FDA's concerns regarding the risks associated with switching users from the RLD to a generic/biosimilar alternative.

Finally, with respect to the study design proposed in the Draft Guidance, we have concerns about the post-market safety reporting that would be required if the RLD is tested by the generic/biosimilar product applicant. Our concern is that the Draft Guidance does not explain FDA's expectations for reporting use-error complaints and/or malfunctions of the RLD that occur during such HF testing. Our proposal above, which precludes testing of the RLD in the HF validation study of the new product would avoid this concern, and is therefore our preferred approach.

IV. Promote Innovation and Improvements to the Design of Products to Enhance Safety and Effectiveness

The Draft Guidance repeatedly emphasizes minimizing differences in the user interface between the RLD and the proposed generic/biosimilar product. While this is understandable from the standpoint of minimizing differences for the lay user who may experience a substitution without additional physician intervention or additional training, it discourages improvements to the safety and effectiveness of the product via innovation and improvement of the design.

Accordingly, we believe that the Draft Guidance should more closely reflect the approach articulated in FDA's draft guidance entitled, "Considerations in Demonstrating Interchangeability with a Reference Product," which notes that "FDA generally encourages optimization of the design of the delivery device constituent part to enhance safety of the product" (FN 35). Applying a holistic risk-based approach to HF assessments allows the generic/biosimilar applicant to justify improvements that reduce the residual risks associated with use of the product. This approach would apply to the design of the labeling (especially the instructions for use). There is no benefit to the patient in replicating suboptimal instructions solely for the purpose of not being different. The approach would also apply to other items of labeling, such as training materials (e.g., videos, handouts, checklists, and training simulators).

V. Provide More Information Regarding Topics Not Sufficiently Addressed in the Draft Guidance

We also recommend that FDA provide additional guidance with respect to handling: (1) post-approval changes to the RLD product, and (2) RLDs with multiple presentations.

A. Post-Approval Changes to the RLD Product

The Draft Guidance focuses on a comparison of the generic to the RLD at the time of application. However, there will likely be design changes to the delivery device of the RLD over time. The Draft Guidance does not address how the generic applicant should handle such changes to the RLD in the future or how to handle situations where the user interface design of the generic and the RLD diverge over time. Additionally, this comparison may "lock in" one or both parties (the generic or RLD applicants) to the design at the time of application, instead of allowing continuous improvement and innovation over time to enhance patient safety and the user experience.

We ask that FDA revise the Draft Guidance to explain expectations on RLD and generic/biosimilar combination product manufacturers when there is a change in the RLD combination product (e.g., design change, software updates, etc.). The Draft Guidance does not specify the mechanism for notification of such change, or whether a new analysis would have to be conducted and submitted to FDA. We recommend that following approval, changes to the design of any individual product be handled independently under existing guidance.

B. RLDs with Multiple Presentations

We also ask that FDA update the Draft Guidance to explain expectations when a RLD is approved for use with multiple presentations of delivery devices. For example, when a RLD is available in both a PFS and a prefilled autoinjector, there is a possibility that a physician might prescribe the RLD in an autoinjector, but the pharmacy chooses to dispense the generic in a PFS. In such a scenario, the comparative analyses would not be appropriate to assess interchangeability of the RLD and generic/biosimilar combination products.

Additionally, despite emphasizing that a generic/biosimilar product applicant should mimic the existing presentation, differences may very well occur due to life-cycle management activities by the RLD, such as significant design changes or the removal and/or addition of presentations (e.g., enhancements to a prefilled autoinjector that improve the usability of the product, or retiring a co-packaged presentation with a vial and empty syringe in favor of a PFS presentation).

The Draft Guidance states, "If a sponsor is proposing a presentation for which the RLD is not approved (e.g., seeking approval of a generic combination product as a pre-filled syringe in instances when the RLD was approved in a vial), FDA strongly encourages the sponsor to discuss the proposed presentation with FDA via controlled correspondence and/or pre-ANDA meeting package prior to product development or submission of an ANDA" (FN 13). As the applicant would be proposing a device with a new user interface, this product should follow the approaches set out in FDA's previous HF guidance documents (i.e., the HF/Usability

Engineering Guidance and the Combination Product HF Draft Guidance). We recommend that FDA reference these documents with respect to the approach to be taken in this situation.

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We appreciate the opportunity to provide input on the Draft Guidance and are happy to meet with the Agency to clarify or discuss any of our suggested revisions.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Appendix A: Additional Requested Revisions

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
37-39	"Applicants may consider modifying the design of the generic combination product to minimize differences from the RLD to avoid conducting comparative use human factors studies."	Replace "modifying the design of" with "designing." The sentence should read as follows: "Applicants may consider **designing** the generic combination product to minimize differences…"	Consistent with feedback in text above.
86	"…differences in device and labeling…"	Add "packaging" to the sentence so that it reads: "…differences in device, **packaging,** and labeling…"	For completeness, packaging should be included as it is part of the product user interface.
105-116	"For example, as applicable, a generic description of the entire delivery device constituent part should be provided in the CMC section of the ANDA…"	End this section after the sentence that ends in line 105, and provide a reference to appropriate guidance.	We recommend keeping the description in the Scope section succinct. This section, as currently written, provides more detail than necessary in describing what is needed for an ANDA CMC section. For example, the Draft Guidance refers to "comparative in-vitro performance testing," which is not described within the body of the document. We recommend streamlining this section to ensure clarity.
121-122	"This section discusses certain data and information that may be needed to support the design of the user interface of the proposed generic combination product…"	Replace "design of the user interface" with "assessment of the usability and use-safety." The sentence should read as follows: "This section discusses certain data and information that may be needed to support **assessment of the usability and use-safety** of the proposed generic combination product…"	Editorial changes to ensure clarity.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
134-136	"When developing a generic combination product for submission in an ANDA, it is important that applicants carefully consider the overall design of the user interface and should generally seek approval of a presentation approved for the RLD."	Add examples of preliminary analyses that should be performed as part of the design and development process of the generic combination product. The paragraph should read as follows: "When developing a generic combination product for submission in an ANDA, it is important that applicants carefully consider **performing preliminary analyses, such as heuristic analysis, identification of known use problems, etc.,** and should generally seek approval of a presentation approved for the RLD."	The Draft Guidance does not identify whether any preliminary analyses (e.g., heuristic analysis, identification of known use problems, etc.) are recommended, as identified in the HF/Usability Engineering Guidance. For example, new use-related problems may have come to light between approval of the RLD and development of the generic combination product. We ask that FDA reference the applicable preliminary analyses.
138-141	"FDA recognizes that a potential applicant of a proposed generic combination product may develop a user interface that has certain differences from the user interface approved for the RLD. FDA may accept such design differences if they are adequately analyzed, scientifically justified, and do not preclude approval in an ANDA."	Add risk assessment as part of the analysis, and a reference to residual risk related to usability. The paragraph should read as follows: "…FDA may accept such design differences if they are adequately analyzed, **justified according to risk assessment, and result in acceptable residual risk related to the usability and use-safety of the product. The differences** do not **necessarily** preclude approval in an ANDA."	A sponsor should follow a systematic risk assessment approach to analyze the difference(s) in user interface between the generic combination product and the RLD. FDA should identify risk assessment as part of the analysis. The acceptability of design differences from an HF perspective should be based on the acceptability of residual risks related to the usability and use-safety of the product.
194-196	"As a result, there is concern that patients or caregivers who encounter different user interfaces, such as differences in external critical design attributes,	Replace "differences in external critical design attributes" with "especially if they impact their ability to perform critical tasks," so that the paragraph reads:	The Draft Guidance defines "external critical design attribute" in the context of ability to perform critical tasks. We recommend highlighting the ability to perform critical tasks to

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	may be at increased risk for a use-related error…"	"As a result, there is concern that patients or caregivers who encounter different user interfaces, **especially if they impact their ability to perform critical tasks**, may be at increased risk for a use-related error…"	ensure clarity.
205-206	"FDA recommends a side-by-side, line-by-line comparison of the full prescribing information, instructions for use…"	Remove prescribing information from the list or consider rewording to note aspects of the prescribing information that impact usability and use-safety.	Most of the prescribing information content is outside the scope of HF and the usability and use-safety of the product.
FN 18	"Prior to submitting an ANDA for a generic combination product, potential applicants are strongly encouraged to contact FDA via controlled correspondence and/or pre-ANDA meeting package to discuss the applicant's proposed product."	Move this footnote to the main body of the guidance. Clarify that the applicant could discuss its HF studies approach with FDA. "Prior to submitting an ANDA for a generic combination product, potential applicants are strongly encouraged to contact FDA via controlled correspondence and/or pre-ANDA meeting package to discuss the applicant's proposed product, **including the human factors approach**."	The Draft Guidance discusses data to be submitted as part of the ANDA, but it does not identify a formal process for communication with FDA on the approach to be taken. For example, in FDA's HF/Usability Engineering Guidance, manufacturers are encouraged to submit an HF testing protocol prior to conducting testing. FDA should apply a similar approach here. We acknowledge that footnote 18 does discuss meeting with FDA prior to ANDA submission, but we recommend formalizing this into a review of relevant documentation and move information on sponsor interaction with FDA to the main body of the document.
221-224	"*No design differences:* When no differences are identified between the user interface of the	The paragraph should be revised as follows: "***No differences in primary***	Sponsors routinely perform HF studies in part to fulfill the design validation requirement per 21 CFR §

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	proposed generic combination product and the user interface for the RLD, it is likely that certain information and/or data, such as data from comparative use human factors studies, will not be necessary to support approval of the ANDA."	***operating function or differences do not affect the ability of the user to perform the critical tasks****:* When no differences **in primary operating function** are identified between the user interface of the proposed generic combination product and the user interface for the RLD **(or the differences do not affect the ability of the user to perform the critical tasks)**, it is likely that certain information and/or data, such as data from comparative use human factors studies, will not be necessary to support approval of the ANDA. **In such instance, threshold analysis would be adequate in part to fulfill the design validation requirement (21 CFR § 820.30) for combination products**."	820.30. In the event threshold analyses reveal no design differences between the proposed generic combination product and the RLD, it would be important for the Agency to state that the results of the threshold analysis fulfills in part the design validation requirement, hence no additional HF validation is required on the generic combination product.
226-230	"If differences are identified between the design of the user interface of the proposed generic combination product and the user interface of its RLD, the sponsor should focus on whether the difference(s) involves an external critical design attribute that may potentially impact whether the proposed generic combination product can be substituted for the RLD…"	Clarify that risk analysis should be used to assess potential impact of the differences in the user interfaces. The paragraph should read as follows: "If differences are identified between the design of the user interface of the proposed generic combination product and the user interface of its RLD, the sponsor should focus on whether the difference(s) **may impact a critical task, hence the usability and use-safety of the product as it relates to that task. A risk analysis consistent with ISO**	The acceptability of the differences in the product user interfaces should come back to critical tasks, potential use errors, and an analysis of use-related risk.

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		14971:2007, *Medical devices — Application of risk management to medical devices* and FDA guidance, *Applying Human Factors and Usability Engineering to Medical Devices*, is suggested."	
232-235	"FDA views a design difference as minor if the differences in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD does not affect an external critical design attribute."	As noted in the body of this document, we recommend coupling a differential task analysis along with a use error analysis and severity analysis to assess the criticality of use-related risks. This should be the basis to determine the impact of differences in primary operating functions and enables a level of granularity in the analysis with which to base the need for HF testing.	The use of primary operating functions and risk analyses to assess the impact of product differences is consistent with existing FDA HF guidance and recognized standards.
254-257	"In such cases, the potential applicant should first strongly consider modifying the design of the user interface (e.g., delivery device constituent part) to minimize differences from the RLD."	Allow flexibility for an applicant to modify the design, if warranted. The paragraph should read as follows: "In such cases, **as an option**, the potential applicant **may choose to modify** the design of the user interface (e.g., delivery device constituent part) to minimize differences from the RLD."	We believe FDA's goal to ensure safety and effectiveness of generic combination products can be achieved while maintaining FDA's stated mission to foster innovation. The current statement in the Draft Guidance can be misconstrued as a recommendation for new generic combination products to match older device designs, which may not have been tested according to current standards. This could reduce potential opportunities for industry to develop better delivery devices that are easier and safer to use for patients. Therefore, we

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			recommend the proposed revision to communicate that, as an option, generic manufacturers can consider modifying the design to minimize differences from the RLD. This approach is consistent with FDA's draft guidance, "Considerations in Demonstrating Interchangeability with a Reference Product" (footnote 35).
273-276	"If the threshold analyses determine that a design difference may not be minor, as described in section IV.B.1 of this guidance, potential applicants should first consider modifying the design of the user interface (e.g., delivery device constituent part) for the proposed generic combination product to minimize differences from the RLD."	"If the threshold analyses determine that a design difference may not be minor, as described in section IV.B.1 of this guidance, potential applicants **may, as an option**, **modify** the design of the user interface (e.g., delivery device constituent part) for the proposed generic combination product to minimize differences from the RLD."	See rationale in row directly above.
289-292	"The objective of the comparative use human factors studies described in this guidance is to demonstrate that the use error rate, associated with the change in an external critical design attribute for the proposed user interface, does not preclude approval of the proposed product in an ANDA."	Focus the comparative use HF studies on the residual risks of the generic product. The paragraph should read as follows: "The objective of the comparative use human factors studies described in this guidance is to demonstrate that the **residual risk related to use errors associated with the generic product** does not preclude approval of the proposed product in an ANDA."	FDA's HF guidance and recognized consensus standards recommend not calculating use error rates, but focusing on the root cause of observed errors and associated risks.

Line Reference	Draft Guidance Text	Proposed Revision/Comment	Rationale
400-429	Sample Size Considerations	The sample size described in this section does not align with FDA's HF/Usability Engineering Guidance, which states the following (p. 36): "Since the parameters needed to determine sample size cannot be estimated easily or cannot be at estimated at all prior to testing, a sample of 15 people to detect most of the problems in a user interface constitutes a practical minimum number of participants for human factors validation testing. This sample size theoretically provides the best possibility of detecting user interface design flaws while limiting the amount of resources required…"	Align text with previous FDA guidance. The described NI study design sample size would be overly burdensome for a generic/biosimilar applicant, especially considering the inability for such a study to fully address the question of interchangeability risks.