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Parenteral Drug Association

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

Reference: FDA Draft Guidance Considerations in Demonstrating Interchangeability With a Reference Product: Draft Guidance for Industry
Docket [FDA-2017-D-0154]

Dear Sir/Madam:

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. This response addresses aspects of the draft related to delivery, design, and human factors considerations and was prepared by the members of the Combination Products Interest Group on behalf of the Regulatory and Quality Advisory Board and Board of Directors. PDA appreciates the opportunity to respond to the draft guidance.

It is PDA's recommendation that the goals for any Human Factors studies performed on a biosimilar claiming interchangeability are essentially the same as for those already in international standards, published literature and established FDA guidance documents. It is important to note that the latest revision of the IEC 62366-1 standard specifically eliminated the setting of usability goals and acceptance of statistical measures as evidence of success and now provides the more widely accepted assessment of the overall risk of critical task use errors through investigation, root cause determination and mitigation, or justification/acceptance of the risk.

Method of Comparison

PDA recommends an approach where the "equivalence" in risk between the interchangeable biologic and reference biologic is established through a Human Factors study performed with current users of the reference biologic, who are switched without training to the proposed interchangeable biologic. The criteria for acceptance will be based on a thorough investigation, root cause determination and justification/acceptance of the risk of critical use errors. This is the same criteria which will have been assessed and used to approve the use risk of the combo product with the reference biologic, only more stringent, as the reference biologic use assessment would have been conducted with users who had completed training.
In PDA's opinion, this draft guidance introduces an untried and unproven method of comparing Human Factors information from two different products. Although the suggested approach of comparing the equivalence or non-inferiority of two products is well established for clinical results or analytical data, this has never been applied to the types of qualitative, observational and investigational information generated from a Human Factors usability test. In contrast to the reliance on a statistical comparison of the non-inferiority of the rate of critical use errors with the

interchangeable biosimilar to the reference biologic, the balance of the guidance stresses the importance of the risk of use error as the primary criteria for acceptability of the interchangeable biosimilar.

Use of Existing Standards
PDA recommends that this guidance recognize and incorporate the extensive amount of information available in international standards, published literature, as well as established and widely accepted FDA guidance documents[i, ii]. These references provide methods that are extremely effective at determining and assessing the risks of the use of medical products. In addition, these methods can be used in a manner that would address the stated goal of determining the risk of the interchangeability of a new product (interchangeable biosimilar) to a population trained and experienced with an established product (reference biologic).

There are numerous areas in the guidance that conflict with this approach. These include, but are not limited to:

- Use of non-inferiority of critical task failures as the success criterial for the proposed Human Factors studies instead of direct determination of the risk of critical task failures in the use of the interchangeable biosimilar by a user population trained and experienced with an established reference biologic.

- Characterizing Human Factors studies as quantitative assessments of critical task error which can be compared, rather than the universally accepted idea that HF Studies are observational, qualitative studies that are used to assess risks, not failure rates.

- Requiring extensive studies with significant numbers of patients to establish critical task failure rates, where failures on the same task may be due to different root causes, rendering them different and not comparable. Sample size requirements should leverage established guidance and standard Human Factors studies designed specifically to assess use risk. PDA recommends that this new guidance recognize and state that the samples sizes and method of evaluation of risk established in the current FDA guidance[2] (which are considered adequate for the initial approval of the reference biologic) are adequate for establishing the use risk for biosimilar products in the use context proposed.

Product Enhancements
As drafted, this new guidance does not encourage innovation and improvements to the design of the product to enhance its safety and effectiveness. Lack of implementation of state of the art designs that result in more usable products will likely lead to stagnation to the detriment of the patient. Medical devices are predicated on continuous improvement in design to improve the product and enhance safety. This applies to drug delivery devices as much as to therapeutic devices. PDA recommends this guidance encourage and simplify the process for approval of biosimilars that can be interchanged, while ensuring that users not subjected to unacceptable use risk.

Need for "other" tests
PDA recommends this guidance clearly state that "other" (comparative in-vivo or in-vitro) tests would not be required if the device was used in the clinical studies to establish interchangeability of the drug. If the device was not used in clinical studies, PDA recommends "other" studies should be restricted to in-vitro comparison of the delivery characteristic of the device.

If the to-be-marketed device is used in the clinical studies to establish interchangeability (or biosimilarity) of the biologic to the reference biologic, there should be no need for additional data or information to support the presentation beyond what is described in the existing FDA guidance[iii, iv]. Even if the to-be-marketed device is not used in the clinical study, other data should be limited to an in-vitro comparison of key performance attributes that may have an impact on delivery of the drug, and in-vivo data need not be required.

Use Scenarios

As drafted, the proposed guidance does not address a significant number of situations and/or use scenarios that could have an impact on usability and critical use errors related to substitution of an alternative delivery device without training such as multiple delivery devices for the reference biologic (e.g. PFS and AI) or whether there are multiple biosimilars with different injectors. Many biologics are provided in multiple configurations. In addition, drug delivery device designs, as is the case for all medical devices, are predicated on continuous improvement. These factors will present additional use scenarios, each with the potential for critical task error, over and above comparing the interchangeable biosimilar to the reference biologic. PDA recommends the guidance should address these likely situations. In PDA's opinion, relying on large, HF studies comparing rates of failure will make it difficult, if not impossible, to determine and assess the risk of device interchangeability. PDA is concerned such large studies may result in a suppression of usability improvements which will adversely impact patient convenience, usability and compliance.

Rather than a side-by-side comparison of critical tasks or incidence of use errors for similar critical tasks, PDA recommends the use-related risk analysis, to determine whether a human factors validation study is needed for the proposed product, consider how the product would be used without training (if substituted at the pharmacy) or with prior experience/knowledge of the reference product (if interchanged).

Terminology

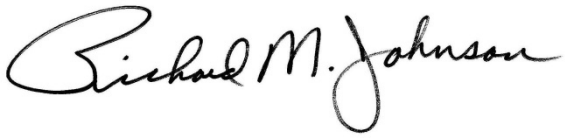
Several terms introduced in this guidance document are not aligned with those used in related guidance documents[v, vi]. New, undefined terms could be confusing and misinterpreted if they are similar to other terms already widely used in the industry. For example, the guidance suggests sponsors compare "external critical design attributes" between the proposed and reference products and defines these attributes as "those features that directly affect the performance of critical tasks" (702) and as "those features that end users rely on to perform [critical] tasks" (708). This incorrectly implies that external features alone affect performance of critical tasks (characteristics of the user and use environment also affect performance) and is not aligned with the risk-based determination of whether a critical task has been performed successfully, as described in previously published human factors guidance documents.

Other terms introduced in this guidance but not defined nor aligned with previously published human factors guidance documents and standards[vii, viii] are "comparative use human factors studies" (845) and "use error rate" (846). Both appear to borrow comparative analytical test methods from pharmaceutical development and apply them towards human factors and usability engineering (HF/UE) studies. However, data collected in HF/UE studies is subjective and empirical. In PDA members' experience, when a use error occurs, a root cause analysis followed by a risk-benefit analysis is conducted to determine the likelihood and severity of the harm due to that error. Use errors are typically not "counted" and cannot be statistically analyzed for a product or compared between products. Given the effort FDA has made to educate industry on the design and execution of human factors validation studies, introducing

new terminology and methodology at this point is likely to adversely impact understanding and effective performance of both HF studies and "comparative" HF studies

If there are any questions, please do not hesitate to contact me. (Johnson@pda.org)

Sincerely,



President and CEO, PDA

CC: Rich Levy, PDA; Denyse Baker, PDA

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[i] FDA Final Guidance or industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices.*
[ii] FDA Draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.
[iii] FDA Final Guidance or industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices.*
[iv] FDA Draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.
[v] FDA Final Guidance or industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices.*
[vi] FDA Draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.
[vii] FDA Final Guidance or industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices.*
[viii] FDA Draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.