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March 20, 2017

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

**Reference:** FDA Draft Guidance for Industry Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA  
Docket [FDA-2016-D-4412-0001]

Dear Sir/Madam:

PDA appreciates FDA provision of guidance for sponsors that seek approval of a proposed generic combination product that includes both a drug constituent part and a delivery device constituent part as to what differences in the user interface will be acceptable for acceptance as an ANDA.

Specifically, PDA agrees with the following FDA assertions in the draft guidance:

- FDA's recognition that a user interface that has certain differences from the user interface approved for the reference listed drug (RLD) *can be accepted if [the differences] are adequately analyzed, scientifically justified, and do not preclude approval in an ANDA.*
- FDA's acknowledgement that the critical criteria for approval as an ANDA *is that the sponsor is able to establish that the generic combination product can be substituted for the RLD without additional physician intervention and/or retraining prior to use.*
- FDA's identification of the potential for situations when the RLD is *approved as a vial or PFS where another presentation, [such as an autoinjector] may meet the critical criteria above, and that discussion would be accepted.*
- FDA's assertion that the *comparative analyses of any differences identified in the threshold analyses be risk based and that for many products with minor difference in design intended for use by HCPs that the threshold risk assessment may be all that is needed* (i.e. no user studies are required)

PDA agrees that in some cases **Human Factors studies** may be required to establish that the generic combination product can be substituted for the RLD to users of the current RLD (without additional physician intervention and/or retraining prior to use) without resulting in a level of critical task errors that would represent an unacceptable risk. However, PDA disagrees that the proposed **Comparative** Human Factors studies are reasonable, appropriate and address all use scenarios (i.e. when naïve users are provided the proposed generic). Please see the specific comments and proposals in the attachment.



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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. Our comments were prepared by a committee of experts with experience in combination product manufacturing and development including members of the Combination Products Interest Groups representing the PDA Board of Directors and PDA Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson  
President, PDA

CC: Richard Levy, PDA; Denyse Baker, PDA

**Food and Drug Administration Draft Guidance**

FDA Comparative Analyses and Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA  
March 20, 2017

**General Comments**

Comment and Rationale	Proposed change (if applicable)	Critical Comment Y/N
<p>Several times the guidance suggests that if the threshold analyses determine that a design difference may not be minor, 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.</p> <p>This approach may promote duplication of existing designs even in cases where innovation in a generic combination product could enhance patient experience and product usability.”</p>	<p>PDA suggests this be refocused to state:</p> <p>If the threshold analyses determine that a design difference may not be minor, potential applicants should first consider whether the design and usability attributes of the device have been compared to, and determined to be superior to, the RLD based on sound Human Factors principles and formative HF studies. If so, the sponsor is encouraged to discuss these differences with the FDA to establish if these Human Factors studies are sufficient to establish that the proposed generic product can be safely substituted with current users of the RLD device without training.</p>	Y
<p>This guidance focuses on essentially one use case – that where the users of the current RLD are switched to the generic product. However, there are two other use cases that are also likely once the generic is launched.</p> <ul style="list-style-type: none"> <li>• There will be naïve users who are first introduced to the product through the generic product without having been prescribed or having used the RLD.</li> <li>• There will be users of the generic product who, due to preference, availability or other factors, may be switched to (or back to) the RLD at some point in their therapy.</li> </ul> <p>The criteria by which the FDA states it will determine whether the generic Combination Product with more than minor differences can be accepted as an ANDA is if it demonstrates non-inferiority of critical task use error rate as compared to the RLD. This unfairly biases the testing against the Generic Combination Product.</p> <ul style="list-style-type: none"> <li>• First, the criteria by which the RLD would have been</li> </ul>	<p>PDA suggests that standard Human Factors studies, consistent with those described in the CDRH final HF guidance, be performed for two proposed use cases:</p> <ul style="list-style-type: none"> <li>• Current users of the RLD who are provided the generic combination product without training</li> <li>• Naïve users (potential patients who could be prescribed the RLD but who are not on the therapy or are on a different therapy that is not the RLD) who are provided training on the generic combination product that is consistent with the current level of training provided for the RLD</li> </ul> <p>In addition, PDA suggests that the results of these studies be assessed to establish that the risk of use error on critical tasks with the generic combination product is acceptable. This can include comparisons to the RLD where the design of, or use of the generic combination product eliminates the potential for errors that are possible on the</p>	Y

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**March 20, 2017**

<p>approved is that which is contained in the existing CDRH guidance that this guidance eschews – which is a risk based assessment from a study with 15 users per group (which may have included training) that there are no preventable use errors that could cause harm. The criteria for establishing that the level of use-related risk is not increased with the generic combination product must be similar in nature.</p> <p>Comparing the use errors with the RLD for users who have been trained and have experience with the RLD to the errors with the generic combination product on the FIRST use is not a fair comparison. Users of the generic combination product will need to go through the same learning curve as those who received, were trained on and use the RLD. The testing proposed by FDA does not identify or capture that the same errors may have happened during the first use(s) of the RLD. If those risks were acceptable to support approval of the RLD, they should also be acceptable to support approval of the generic combination product.</p> <p>Human Factors evaluations are qualitative, observational exercise that identifies potential use errors and risks to the patient or user that must be either mitigated or accepted. The proposal to implement Comparative HF studies with a non-inferiority success criterion based on a quantification of use errors on critical tasks does not recognize that all use errors on critical tasks are not equal or comparable.</p> <ul style="list-style-type: none"><li>• Human Factors studies are designed to identify the root causes of all use errors on critical tasks to determine the adequacy of the user interface to support users to use the product safely and correctly. As such, one use error may not be due to the same root cause as another, and the severity of the consequential potential harm could vary based on the root cause; and therefore, these use errors are not comparable. Also, all critical tasks are not equal – a use error during</li></ul>	RLD..	
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**March 20, 2017**

<p>“pressing and holding” an auto-injector against the skin for the required time (or inhaling from a DPI for the right amount of time) may not present an equal risk to not activating the injection (or inhalation) at all.</p> <p>Human Factors studies also must address instances where an error does not occur, but there is confusion or hesitation, or where the user makes an error but identifies and self-corrects the error without consequence. Ignoring these elements, and only focusing on failures, will not present a true picture of the relative safety, effectiveness or usability of the devices.</p> <p>Human Factors assessments are risk based, where the FDA proposal is quantitative – based on number of use errors on critical tasks. There are many devices where the use errors on critical tasks would be significantly less than 10%. Products where users fail to execute a critical task 1 out of every 10 times would be unlikely to be considered an acceptable product. Establishing statistically significant non-inferiority to products with low use error rates (&lt; 1/100) on critical tasks would require significantly larger studies than provided in Appendix A. This amount of testing could be substantially reduced through the use of risk-based assessment of any identified use errors on critical tasks as provided in the PDA proposal.</p>	
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