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January 15, 2016

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

Re: Docket No. FDA-2015-D-3390 for "Electronic Common Technical Document
Technical Conformance Guide."

Dear Sir/Madam:

PDA appreciates the opportunity to provide comments on the eCTD Technical Conformance Guide. 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 combination product manufacturing and quality. Our comments were prepared by a committee of experts representing our Combination Products Interest Group, Regulatory and Quality Advisory Board, and Board of Directors.

Technical conformance guides traditionally have been used to provide operational guidance on "how to submit" and have not provided substantive information on policy changes to the content of submissions. PDA believes this technical conformance guide has important new content expectations that will have a significant impact on industry, primarily those involved in combination product submissions. As such, PDA strongly believes that these expectations should have been issued in a Type 1 draft policy guidance and not as final. Publication in a final technical conformance guide, will not, and has not resulted in sufficient awareness among concerned parties. Thus, PDA believes FDA will not receive a full range of comments; which undermines the necessary public's input on these topics. PDA also believes this substantive content is more appropriate for a draft policy guidance and not for publication or inclusion in a technical conformance guide.

PDA has concerns about the recommended content and placement of combination product information as specified in this eCTD conformance guide. These new requirements will result in a document that is no longer a common document for drug delivery products in all the regions that accept the ICH CTD format. This puts FDA out of alignment with other ICH regions and impacts license holders as multiple versions of the quality module will need to be maintained for global products. To accommodate regional differences, the eCTD structure provides for the inclusion of a "regional" section that can contain information that is unique to, or necessarily differs from, the content required in one or more regions. PDA requests that FDA confine their divergent requirements to a regional section of the submission document, rather than in the "common" quality module section.





PDA strongly encourages FDA to withdraw the sections of the eCTD conformance guide related to Combination Products and Human Factors and re-issue these in a Type 1 draft guidance. In addition, PDA offers the following comments to these sections to be considered for the draft guidance.

PDA does not support the following proposals in Section 3.3.2 of the Technical Conformance Guide:

- Item 3: PDA does not view 3.2.P.7 as the appropriate location for all device information for all combination products for several reasons. First, there are many device constituent parts of combination products that are separate, finished devices that are either cross labeled or co-packaged with the drug consistent part. These are not considered “container closures”, thus placement of detailed device information in this section is not appropriate. A second concern, particularly for those device constituent parts that are integrated with the drug constituent part, is that placement in 3.2.P.7 is inconsistent with the agency’s statement in Section 3.2.2 of this Technical Compliance Guide: Page 9 states, “Generally, the combination drug and device product information (including an autoinjector or similar delivery) and related engineering and manufacturing information should be located in the same eCTD module that would provide similar information for the drug or biological product.” Product design and development information is provided in 3.2.P.2 for drug and biological products; thus this should also be the location of this information for the combination product, including the device constituents. Additionally, ICH M4Q (R1) recommendations in 3.2.P.7 state, “Suitability information should be located in 3.2P.2” and suitability is most often demonstrated in delivery device design and development activities. The eCTD structure must be flexible enough to support all of the scenarios.

- Item 5: Another key area of concern is the apparent requirement for sites to submit local GMP documentation in marketing authorization submissions. Please clarify it is not the Agency’s intent to collect additional documentation such as the SOPs from each site. The current wording in the technical conformance guide suggests the submission of GMP documents rather than a review of this information at the facility, as is done for traditional drug submissions. If a summary of the applicant’s quality systems related to 21 CFR Part 4 is requested, PDA views this information as regional and these US regional requirements should be included in the regional section (3.2.R).

Item 5 also suggests that the applicant should include an explicit description of the manufacturing, assembly, or testing processes with regards to the device constituent part taking place at each manufacturing facility provided on the Form FDA 356h, as an attachment to the form, and/or presumably in Section 3.2.P.3.1. PDA agrees that the name, address and brief description of the manufacturing steps and/or type of testing be provided for those facilities involved in commercial production (manufacturing and testing) of the Device Constituent Part be included in FDA Form 356h and, aligned with the M4Q requirements for other manufacturers listed in eCTD section 3.2.P.3.1. PDA does not support the listing or inclusion of information regarding facilities and service providers that provide components, or perform other non-production activities (e.g., design, verification and validation testing). If FDA would like additional information, including the implemented quality systems and responsibilities, these are unique regional requirements relative to the requirements of 21 CFR Part 4 and must be placed in the CTD regional section (3.2.R).

- Item 7 and on page 13: Another significant concern of PDA is the placement of Human Factors information in 5.3.5.4, Other Study Reports and Related Information. Human factors are design validation studies performed as part of design controls and are not clinical trials. Human factors studies do not involve active drug in an investigational manner, actual patient dosing (e.g. injection, inhalation), or the assessment of clinical effect. A human factors study evaluates the product under a simulated intended use rather than an actual intended use, and therefore is not a clinical study. It is an in-vitro assessment of usability of the of the combination product and is not a clinical assessment. Therefore, human factors information belongs in the Module 3 Quality section.

Industry is concerned that placement of human factors study reports in Module 5 will lead to inappropriate categorization of post-approval supplements that revise the product instructions for use and are supported by human factors studies, as clinical efficacy supplements instead of as manufacturing supplements. The impact of this categorization would be longer review timelines and substantial user fees. Furthermore, FDA guidance requires that Summative Human Factors studies for FDA review be performed in the United States, which makes this a regional requirement. Also, the review criteria applied by each region related to the usability of the product differs; as such, any detailed information should be placed in the regional section.

PDA supports the following proposals in Section 3.3.2 of the Technical Conformance Guide

- PDA supports the inclusion of a comprehensive Reviewer's Guide which provides the applicant the flexibility to place the device-related information in the eCTD in section 1.2 as specified in item 6.
- PDA supports the inclusion of technical/descriptive information related to functional secondary packaging components, e.g., identification and specification, in 3.2.P.7 – consistent with ICH M4Q (R1).

In addition to the comments above, PDA provides the following recommendations for the FDA to consider.

- PDA supports the inclusion of information related to the suitability of the delivery system (safety, materials of construction, performance) in section 3.2.P.2.4, particularly when the device is part of the container closure system. This is consistent with ICH M4Q (R1) recommendations. This would include or reference the location of design verification and design validation information. Where specific information is not consistent between regions, this information can be provided in a Master File in the USA, a technical file in other regions, and where appropriate included in the CTD regional section (3.2.R)
- PDA supports the inclusion of device-related information in Section 3.2.R. Although the ICH M4Q (R1) guidance titles this section as "EU Only", PDA members confirm that inclusion of device information in this section has been accepted globally, including by the FDA, for device-related information. PDA encourages FDA to provide applicants the opportunity to utilize this section. This is especially appropriate for cross-labeled and co-packaged finished devices, as these are typically not part of the container closure system. Additionally, applicants for devices which are part of the container closure system should be provided the flexibility to use this section for



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supportive performance documentation due to the regional differences in submission expectations (e.g., essential requirements vs. 510(k)/PMA analyses)

- PDA suggests that FDA consider the referencing Appendix II of the recent PDA Technical Report No. 73 (TR 73) Prefilled Syringe User Requirements for Biotechnology Applications which includes additional recommendations on content placement in the eCTD dossier format.

If you have further questions, please do not hesitate to contact me at Johnson@pda.org.

Sincerely,

A handwritten signature in black ink that reads "Richard M. Johnson". The signature is written in a cursive style with a large, prominent "R" and "J".

Richard Johnson, President and CEO, Parenteral Drug Association

Cc: Denyse Baker, PDA



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