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AdvaMed
Advanced Medical Technology Association

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Dockets Management Branch (HFA –305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20857

Re: Docket No. 01D-0262—Draft Guidance for FDA Reviewers: Premarket Notification Submissions for Automated Testing Instruments Used in Blood Establishments

Dear Sir or Madam:

These comments are submitted by the Advanced Medical Technology Association (AdvaMed), in response to the Food and Drug Administration's (FDA's) draft document titled "Draft Guidance for FDA Reviewers: Premarket Notification Submissions for Automated Testing Instruments Used in Blood Establishments" (ATI guidance document) dated August 3, 2001. AdvaMed is a Washington D.C. based trade association and the largest medical technology association in the world. AdvaMed represents more than 800 manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's members manufacture more than 90 percent of the $58 billion of health care technology products purchased annually in the United States, and more than 50 percent of the 137 billion purchased annually in the world.

GENERAL COMMENTS

The information that CBER has proposed requiring during the review of 510(k) submissions goes beyond the legal responsibility that CBER has in regards to review of 510(k) submissions. This information clearly exceeds the legal requirement of reviewing data for the purpose of arriving at a determination of substantial equivalence between a proposed medical device and a device that is already legally marketed. The information listed in this guidance document is focused on requiring a medical device manufacturer to prove that a medical device is safe and effective instead of substantially equivalent. This is

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contrary to the purpose of a 510(k) as well as the intended purpose of the guidance document created.

By requiring the level of information proposed in the ATI guidance document, it appears that CBER is attempting to modify the regulations for medical devices as they apply to medical devices used in blood bank establishments via promulgation of a guidance document rather than following the legal requirements for modifying federal regulations. CBER appears to be applying the requirements of a BLA or PMA to a medical device simply because of the operation and location of the device without any legal justification.

The guidance document serves as an example of CBER's failure to apply FDAMA's Least Burdensome provisions to medical devices within the division's area of review. If the ATI guidance document is implemented, the review process for these devices will take a dramatic step backwards in terms of review time, as well as alignment with the device review policies implemented within CDRH. In addition, CBER, by implementing requirements for data that clearly exceed not only the Least Burdensome provision of FDAMA, also fails to align with the initiatives that CDRH has undertaken to implement the Least Burdensome provisions in terms of the Interagency Collaboration portion of the FDAMA (section 414(c)).

If the manufacturer has followed the requirements for labeling and design controls, they will have all the requested data on file in support of the instrument. Requiring a company to submit data that is not necessary to a substantial equivalence determination is clearly burdensome.

SPECIFIC COMMENTS

Section A

1. This part states that the information should include the software version number. The software version information is not a part of the information required in 21 CFR part 807.87(a) and should not be required if it is not normally referred to in the actual name of the device. Software versions are revised from time to time due to "bug" corrections that do not exceed the threshold of a subsequent 510(k) submission and as such, may not remain the same as the version number cited in the premarket notification, while still meeting the legal obligations of the premarket notification regulations. When a significant change is made in such a device, the FDA will be part of the process. Tracking of software versions for non-submission criteria should not be part of the CBER process.

   This would be a valid request if clarified to indicate that the requirement is to list the version of the software in use at the time the supporting data was generated. As stated, it is left open to interpretation by CBER reviewers. The software version would be incorporated in the labeling accompanying the instrument (User Manual

and Guides) and would have to be updated when the software version changed as described with significant changes.

Section E

2. Item 3-Only instrument reagents necessary to operate and maintain the device should be included in the instrument premarket notification. Assay kits used on the instrument are regulated independently of the instrument and a list of the assay kits is not necessary to establish substantial equivalence. This requirement infers that a new premarket notification is required when additional assays are introduced on the instrument. Most often, instrument changes are not necessary for the additional assays to the menu.

   While reagents are regulated independently from the instruments/software, the requirement should be to provide data for the specific assay reagents utilized to produce the equivalency data in submission. All subsequent assays added to the system, that fit the same intended use, should be added without FDA notification as long as the assay is approved and does not change the indications for use of the instrument.

Section F

3. Item 2- Inclusion of the software version and/or release numbers is not a requirement of 21 CFR807.92 (a)(3). See comment 1.

Section G

4. The requirement for including a 510(k) statement or summary is codified in 21 CFR part 807.87(h) instead of 21 CFR part 807.92(b)(2).

Section J

5. Item 1-The information required in item 1 is the same information as required in Part E item 4 i.e., information sufficient to describe the devices operating characteristics, etc. This separate requirement for the same information in different format is a duplicitous requirement that is contrary to the Least Burdensome provisions of FDAMA.

6. Item 2-The requirement for a listing of all of the functions that are controlled by software represents an overly burdensome requirement when the fact that the topic of the submission is for an AUTOMATED SYSTEM. This full and detailed list exceeds the requirement that the agency's review focus on the information directly **relevant** to supporting the substantial equivalence (the determinant in a 510(k) submission) of the medical device.

7. Item 3-This item is too broad to provide any guidance on the actual information needed to fulfill the substantial equivalence determination. It also exceeds the information relevant to the determination of substantial equivalence and inappropriately addresses the limitations of the "test" (assay). Based on the interpretation of this section, a control material selected by the operator of the system would be considered a limitation of the medical device. These limitations are contained within the assay labeling and are part of the assay submission. Information on the materials required but not provided is already required in the labeling of the device. Section J.3 of the guidance is redundant as limitations are addressed in the Hazard Analysis and included in the instrument labeling described in Section E.4 of the guidance.

8. Item 5-This information is already required in the description of the operation of the instrument. It is also part of the design phase risk analysis and validation as required by the Quality System Regulations (QSR). Requiring this information in a 510(k) submission exceeds the information that is relevant to supporting the substantial equivalence of a medical device, which is the purpose of a 510(k) submission.

9. Item 6-The requirement for a matrix of cross-references to all functional requirements to the appropriate design specifications is an index of the entire design process. This represents information that, if required during the submission of a premarket notification, completely ignores the language and intent of the least burdensome regulation of FDAMA. Providing Design Control data to CBER also ignores Congressional intent of the Design Control addition to the Act and the subsequent regulations. A validation protocol and summary of results of the validation activities associated with the safety critical requirements (as submitted in the 510(k)) provide sufficient information to demonstrate the substantial equivalence as well as proper performance of the functional requirements.

Section K

10. Item 1-A summary of the design and development process is all that is needed to provide a process overview. Premarket controls, specifically Design Control, as required in 21 CFR part 820 (QSR), serves as an adequate method to establish and maintain Standard Operating Procedures (SOPs) and the use of related applicable industry standards. A description of the SOPs is not necessary to establish substantial equivalence. See comments in Section N.

11. Item 2-Providing a full description of all hardware components, their performance characteristics, and specifications is an overly burdensome requirement that exceeds the intended purpose of a 510(k) review for determination of substantial equivalence. Additionally, this contradicts the requirement that the Secretary "**shall** consider whether data required for approval of an application can be reduced through postmarket controls" (FDAMA section 205(C)). The QSR requirements of maintaining Device Master records (21 CFR part 820.181) is an adequate postmarket

control to fully define the hardware of a system. Additionally, hardware components (functional), as well as applicable specifications, are described in the product labeling and required in Section E.4. of the guidance.

12. Item 4-This requirement is unnecessary since calculations associated with either hazards or safety critical requirements are already required in Sections J.4 and J.5 of the guidance.

13. Item 5-Given the expected life of an automated instrument and the specific listing of required information presented in this section (as applicable), a sequential numbering process for every page printed over the life of the instrument can serve no useful purpose in demonstrating for reviewers the substantial equivalence of a device. In addition, this sequential number would serve no purpose for operators given the presentation of actual identifying information relevant to the printout being created.

14. Item 5-The requirement for a run valid/invalid determination to be generated on printed pages does not consider the method for printing. Prints that are not generated in a batch process (ie; generated as a data point is read or interpreted) cannot be assessed as valid until all appropriate pre and post operation controls and safeguards are performed. Also, the determination of the validity of test results is based on multiple factors that cannot be assessed until after operation is complete and the operator has reviewed the printouts and compared the results with the visual evaluation of the samples.

15. Item 5-Requiring all of the information on each page of a printout does not consider that the test method for some instruments is more of a modular process in that some pages contain the control information for the test run and some pages contain the actual test information for the samples. All of the pages together comprise the test run and each page, when considered independently from the total set of printouts for the run, is meaningless.

16. Item 6-The instrument is used in the manufacturing process of the blood facility that operates it. As such, modifications of the instrument and or test run methodology are a portion of the manufacturing process for the operating facility and outside the control of the instrument manufacturer. As such, the audit trail for tracking these changes should be considered as a portion of the manufacturing activity and appropriately documented in the operator's change control system. Given this system to control the changes to the instrument or test methodology, this requirement in a 510(k) submission violates the requirement that the Secretary "**shall** consider whether data required for approval of an application can be reduced through postmarket controls" (FDAMA section 205(C)). In addition, the process for tracking the changes to the instrument or methodology exceeds the information necessary to determine the substantial equivalence of a medical device.

17. Item 8 & 8 a-Inclusion of a detailed design specification and description of all the software components including the operating systems and databases exceeds the regulatory requirements of FDAMA section 205 (D) in that the Secretary "**shall only** request information that is necessary in making the determination of substantial equivalence" and that the Secretary "**shall** consider the least burdensome means of demonstrating substantial equivalence." The general description of the operating process of an automated medical device will include information related to the higher level software components, but the full listing of all components is neither least burdensome, nor necessary for substantial equivalence determinations.

18. Item 8 b-As written, this item requires the submission of the entire engineering schematic for the instrument to demonstrate the interfaces between the multiple printed circuit boards that make up an automated instrument. All of these interfaces are tested during the validation of the design of the instrument and are not necessary to demonstrate the substantial equivalence of a medical device. In addition, the requirement for this amount of detail exceeds the least burdensome provisions of the FDA Modernization Act.

19. A more realistic and useful subset of information would be of the greatest use for reviewers. The subset of interfaces between the instrument, and accessory components, and a host system (as applicable) would provide information useful in assisting the reviewer understand the configuration of the instrument

Section L

20. While there is no argument that performing an adequate Hazard Analysis is essential in the design and development process for any medical device, the requirement that this information be presented in the 510(k) submission for a medical device exceeds the information required in 21 CFR part 807 for the content of a 510(k) submission. In addition, the post market, and in fact, premarket control, of Design Control as required in 21 CFR part 820 (QSR) serves as an adequate method to reduce the amount of information required in premarket notifications pursuant to the requirements of FDAMA section 205 (C).

21. Item 3 c-When the standard operating procedures and national or international standards used in the design and development process are outlined and referenced in the previous section, the additional requirement for providing definitions of terms is a duplicitous requirement. If a manufacturer is conducting operations inline with applicable standards, the definitions used by that manufacturer would be the same as the definitions present in the applicable standard. [This requirement duplicates the previous section assuming SOPs and standards should be included in the premarket notification. It has been recommended that the procedures and standards should not be required (see comment 10) and therefore, definitions here are appropriate.]

22. Item 5-The presentation of the methods of controls used to eliminate or mitigate hazards in this section has been previously required in Part J item 5 of the guidance document.

23. Item 6-A full trace of the control methods to the design specifications, as well as the items of the design verification, validation, and testing, is an excessive matrix document that serves no purpose in the determination of substantial equivalence determinations, which are the legal focus of the premarket notification review. This information and linkage is present in the Design History File of a medical device. Additionally, it is reviewed during the Design Review process and the legal responsibility for creating and maintaining this information is a sufficient control pursuant to section 205 (C) of the FDA Modernization Act.

24. Example Hazard Analysis Table-See comment 20 concerning column heading "Trace".

Section M

25. The opening statement for this section is only correct in that the purpose of the validation information for safety critical requirements submitted during the premarket notification review is to substantiate the labeling claims for the instrument. (See comment 9. Only testing summaries associated with safety critical requirements is necessary to assess substantial equivalence).

    The opening statement in the guidance includes reference to substantiating kit/reagent compatibility. Reagent kits used on the instrument are regulated independently of the instrument and are not necessary to establish substantial equivalence. Reagent verification/validation testing is governed by the assay submission requirements. Additionally, the opening statement refers to Verification testing which is not supported by comments 27 & 28 following.

26. Items 1-3-The information required in these items is not part of the information needed to substantiate the labeling claims of the instrument. This Test Plan, Populated Decision Tables and Alpha testing in the developer's environment, is used to conduct and complete the design validation activities required in 21 CFR part 820.30. The Design Control requirements for this information is a sufficient control as indicated in section 205 (C) of FDAMA and requiring the inclusion of this data in a premarket notification violates that regulatory requirement as well as the least burdensome methods for demonstrating substantial equivalence.

27. Items 1-3-Presentation of this information does not satisfy the requirements for demonstrating substantial equivalence to a legally marketed device, as such it fails to comply with the legal requirements of the FDA Modernization Act. Also, information that is not directly necessary in the determination of substantial equivalence is not required in premarket notification submissions as specified in 21

CFR part 807. The information listed in items 4 and 5 of this section is the information critical to the demonstration of substantial equivalence and should comprise the extent of the validation information required in the premarket notification for medical devices.

28. Item 4-The term "Clinical Field Trials" should be replaced with "Design Validation". Clinical field trials are not necessary to substantiate labeling claims and determine substantial equivalence. Design Validation as defined in 21 CFR 820.30(g) provides the manufacturers the latitude to determine the appropriate testing.

29. Item 4-Providing all clinical trial data is an overly burdensome requirement. A more reasonable approach is to provide representative data.

30. Item 5-Providing all safety critical bugs is an overly burdensome requirement. Implementation of design changes is defined in 21 CFR 820.30(i). A more reasonable approach is to provide a listing of only those safety critical anomalies left open at the completion of the development process

Section N

31. The information regarding configuration management and change control that is required in this section fails to comply with the regulations for the content of a 510(k) submission as found in 21 CFR part 807. This information is not shown as a requirement of a 510(k) in the applicable federal regulations, thus CBER has no legal standing to list this information as a requirement of a 510(k) premarket notification in this guidance document. In addition, this information is irrelevant to the information that will be necessary to determine substantial equivalence pursuant to the requirements of FDAMA section 205 (D). Furthermore, the postmarket controls of Design Change (21 CFR part 820.30 (i)), Document Controls (21 CFR part 820.40), Device Master Records (21 CFR part 820.181), and Device History Records (21 CFR part 184) are more than sufficient postmarket controls that the Secretary **must** consider in the reduction of information required in premarket notification submissions (FDAMA section 205(C)).

AdvaMed appreciates the opportunity to provide comments on FDA's guidance document. Should you have any questions regarding our comments, please do not hesitate to contact us.

Respectfully Submitted,

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