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September 18, 2006

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

Re: Docket No. 2006D–0063; Guidance for Industry and Food and Drug Administration Staff; the Review and Inspection of Premarket Approval Application Manufacturing Information and Operations

Dear Sir or Madam:

AdvaMed provides this submission in response to the Food and Drug Administration's (FDA's) request for comments on its draft guidance titled "**Guidance for Industry and Food and Drug Administration Staff; the Review and Inspection of Premarket Approval Application Manufacturing Information and Operations**."

AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's more than 1,300 members and subsidiaries manufacture nearly 90 percent of the $75 billion of health care technology products purchased annually in the United States, and more than 50 percent of the $175 billion purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. More than 70 percent of our members have less than $30 million in domestic sales annually. Among our member companies are companies that manufacture innovative medical devices which are classified by FDA as Class III and are therefore subject to inspection of their manufacturing operations as part of Premarket approval applications.

GENERAL COMMENTS

We support FDA's efforts to provide industry and FDA staff with guidance in the important area of inspection of manufacturing information and operations conducted as part of a Premarket approval application. We have found, however, several instances where vague terms such as "timely response," "significantly different," and "extended response time," tend to obfuscate the process rather than to provide useful guidance. In a similar vein, the flow charts in Attachment A are difficult to understand. Furthermore, FDA should clarify the

statement on page 9 of the guidance, "…manufacturing process should be in operation by the time the inspection is conducted," to include pilot manufacturing operations and surrogate product manufacturing.

SPECIFIC COMMENTS

A. Review Process in Brief

Page 6 section C states "…the applicant submits six copies[9] of the PMA or PMA supplement to the CDRH Document Mail Center…" The footnote (9) refers the reader to 21 CFR 814.20(b)(2). While Original PMAs do require six copies, PMA supplements require only three as per 21 CFR 814.39(c).
Recommendation: "… the applicant submits six copies of the PMA[9] or three copies of the PMA supplement[10] to the CDRH Document Mail Center…" Footnote (9) remains unchanged; footnote (10) references 21 CFR 814.39(c).

B. FDA Review Process

Page 7 point 1 "…establishes a due date for the OC, or OIVD review of the manufacturing information…" should be amended to read "…establishes a due date **(see Table 1)** for the OC, or OIVD review of the manufacturing information…"

Page 7 point 2 "The coversheet and the PMA are delivered…" To maintain consistency, the term "**transmittal**" should be used in place of the term "coversheet."

Page 7 point 2 Note: "The review and processing by DBM will be addressed in separate MDUFMA guidance." The guidance has been published for comment and should be cited. "The review and processing by DBM **is addressed** in a separate MDUFMA guidance, "Draft Guidance for Industry and Food and Drug Administration Staff; the Review and Inspection of Premarket Approval Applications Under the Bioresearch Monitoring Program."

Page 7 point 4 "A provisional inspection assignment for a foreign facility is transmitted from OC/FOB to ORO/DFI/OIG…" should read "…from OC/FOB to ORO/DFI/**IOG**…"

C. Completion of the review of the manufacturing sector

Page 8 section B point 1 states: "If OC or OIVD determines that the PMA's manufacturing section is significantly deficient, the applicant should expect to receive a deficiency letter…"
Recommendation: FDA should provide clear guidance as to what constitutes a "significantly deficient" section as the applicant would expect a deficiency letter. To simply state "If OC or OIVD determines…" offers little in the way of guidance. The purpose of guidance is to make the applicant aware of FDA's current thinking on a particular topic, as may be contained in informal policies or other means.

"The OC or OIVD reviewer should communicate in real-time with the applicant to clarify the number and type of deficiencies in a deficiency letter." The paragraph continues, "If there are only a few minor deficiencies, these will likely be handled solely by phone."
Recommendation: "Real-time communication of minor deficiencies may be handled by phone, e-mail, or fax, for example."

The paragraph continues, "An extended response time to a deficiency letter or to a phone call for more information … may significantly delay the completion of the initial review.
Recommendation: "An extended response time by the applicant to a deficiency letter or to a real-time communication (e.g., phone call) request for more information … may significantly delay the completion of the initial review."

D. Manufacturing process

On page 9 section B point 3 states: "The manufacturing process should be in operation by the time the inspection is conducted."
Recommendation: FDA should clarify that once all process validations have been completed, pilot operations or manufacturing of surrogate product may serve as an acceptable substitute for full manufacturing process operations.

E. Cancellation of inspection

On page 9 section B point 4 states: "OC/FOB plans to cancel the inspection assignment under the following circumstances: if the PMA is not filed; ODE or OIVD issues a major deficiency, not approvable, denial, or withdrawal letter; or, the applicant communicates to FDA that the manufacturing site is not ready for inspection." This section is unclear.
Recommendation: "OC/FOB plans to cancel the assigned or scheduled inspection under the following circumstances: If PMA is determined to be not fileable; ODE or OIVD issues a major deficiency letter, denial or withdrawal letter, or; the applicant communicates to the FDA that the manufacturing site is not ready for inspection."

Further, point 4 states: "The applicant should alert CDRH in advance of when the facility will be ready for inspection. OC/FOB will then reissue an inspection assignment."
Recommendation: FDA should clearly state that when an applicant is ready to reschedule an inspection, cancelled due to the applicant's manufacturing operation being unprepared, that the inspection will be completed within 45 days for domestic operations and 60 days for foreign operation, as stated in section C.

On a general note, the last paragraph on page 9 should be changed to "An additional 30 calendar days ***may*** be allotted for the field staff to write and forward a PMA application establishment inspection report to FOB for both domestic and foreign inspections."

F. After the establishment inspection report (EIR) is completed

Page 9 section D is difficult to follow. The differences between domestic and foreign inspection reports are not obvious. The process after an Approvable Letter is issued is

likewise not clearly stated. FDA should clarify under what circumstances an Approvable Letter may be issued. The handling of minor deficiencies and their impact on approval are unclear.

Recommendation: We recommend this section be re-organized in the following format:

1. When the inspection finds the manufacturing facility to be in compliance an *Approval Letter* is issued….

2. When the inspection identifies deviations at the manufacturing facility a *Deficiency Letter* is issued... An *Approvable Pending GMP Letter* is issued when….

3. When the inspection identifies minor deficiencies: Minor deficiencies are communicated to the facility during the inspection close out meeting….

4. When the applicant replies to correspondence from FDA: correspondences should be timely, complete, and thorough….

5. Foreign facility report: (include what is different from the domestic facility report).

In the fourth paragraph of this section, FDA states, "…PMA approval should be withheld…"
Recommendation: FDA should either state how long the PMA approval can be withheld or should use the standard expression "not approvable."

G. Factors that delay the review

Page 11 section F second bullet: Section B.1 on page 8 points out that the initial review may be "significantly delayed," but does not state at which point a deficiency letter is issued. This section uses similarly vague language by stating: "When a timely response is not received to real-time questions during the manufacturing section review, FDA may issue a manufacturing section deficiency letter and/or an approvable pending GMP letter."
Recommendation: "When a timely response is not received to real-time questions during the manufacturing section review and the milestone is exceeded (see Attachment A), FDA may issue a manufacturing section deficiency letter…"

Page 11 section F third bullet: "The manufacturing process should be in operation as soon as possible after PMA submission." It is not always possible for the manufacturing process to be in operation at the time of inspection. This should be handled on a case-by-case basis considering the unique circumstances.
Recommendation: As stated above, FDA should clarify that once all process validations have been completed, pilot operations or manufacturing of surrogate product may serve as an acceptable substitute for full manufacturing process operations.

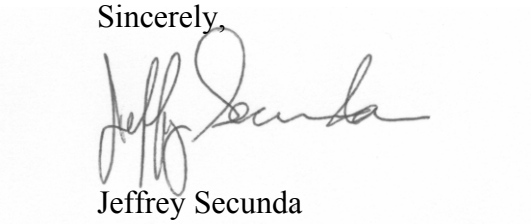
H. Attachment A Process Flow Charts

Both flow charts are very difficult to follow.

Recommendation: Add the header "Total FDA Calendar Days" to the column to the left of the flow chart. Add the header "FDA Assignment, Review or Inspection Days" to the right of the flow chart. Change the third milestone, "Issue PMA Domestic Assignment …" to "Issue PMA Domestic QS/GMP Inspection Assignment …" Change the fifth milestone: "Domestic Inspection Completed…" to "Domestic QS/GMP Inspection Completed." Change the sixth milestone: "Domestic Inspection Report Completed" to "Domestic EIR Inspection Report Completed." Change the seventh milestone: "OC Domestic Inspection Review Completed" to "OC Domestic EIR Inspection Review Completed." The Process Flow Chart for Foreign Inspections should be similarly adjusted.

AdvaMed offers these comments in an effort to make this guidance more understandable and therefore more useful to both FDA staff and Industry. The creation of Guidance is an invaluable tool in reducing the workload on both FDA staff and the Industry, by making clear the current thinking of FDA on important technical and regulatory matters.

Sincerely,



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