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AdvaMed

Advanced Medical Technology Association

February 25, 2004

Thinh Nguyen
Premarket Approval Section
FDA/CDRH/ODE (Room 230T)
9200 Corporate Blvd. (HFZ-450)
Rockville, MD 20850

Re: FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment

Dear Thinh:

AdvaMed is pleased to provide comments on FDA's guidance document, ***FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment***. AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's more than 1,100 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. Nearly 70 percent of our members have fewer than \$30 million in sales annually.

The following comments are supplemental to comments previously submitted to FDA in a letter dated October 16, 2003. A copy of the October 16 letter is attached.

General Comments:

Although we commend the agency for memorializing its practices for stopping and starting the review clock for the review of premarket applications (PMA), we do not believe that FDA has consistently understood the agreement reached during the industry/FDA negotiations on performance goals in 2002. The AdvaMed comments in the October 16 letter on the clock stopping procedures related to the "Approvable, Pending GMP" letter illustrates this point. In that letter, we point out that the use of the Approvable Letter, pending GMP inspection was to be used, not for the purposes of stopping the review clock once CDRH's Office of Device Evaluation completed its review of the application, but for situations in which the sponsor requested a delay of the inspection. The agreement was that FDA would schedule the pre-

approval inspection during the review period and would not wait until the review was complete and thus delay the issuance of an **“Approval”** letter.

Another example of where the agency has not completely understood the agreement reached during the negotiations is the case for issuance of a “Not Approvable” Letter. A “Not Approvable” letter is issued in those rare cases when a sponsor’s application has deficiencies which have not been addressed, even after responses to repeated major deficiency letters. A “Not Approvable” letter, however, was not intended to provide another mechanism to be routinely used by FDA to stop the review clock for purposes of meeting its performance goals.

Throughout the document, FDA references a minor deficiency and defines it as a clarification of previously submitted information. We believe that the definition for minor deficiency should be expanded to include any questions that can be answered real-time by phone, fax, or email. Criteria should be established for major deficiencies and everything else by definition should be a minor deficiency. Minor deficiencies should be resolved real-time and should not be allowed to accumulate such that FDA could designate them as a major deficiency by the numbers alone. Minor deficiencies are used throughout review to quickly resolve questions that arise and FDA should define methods by which it seeks to resolve them on a real time basis.

In this guidance document, FDA sets non-binding criteria for measuring the performance review clock per MDUFMA performance goals. Such criteria should be clear and binding and therefore should be regulation rather than in a guidance document. Therefore AdvaMed recommends that FDA establish these criteria through notice and comment rulemaking.

Specific Comments:

III.A. Approval Order

3: Effect on the Review Clock

The footnote mentions that the review clock stops for an “Approvable, pending GMP” letter. However, the description of the effect on the review clock should indicate that if an “Approvable” letter preceded the “Approval” order, then the reported FDA review time for the PMA is the cumulative FDA day for all 180 day review cycles including the potential 30 day cycle after an “Approvable” letter.

III.B. Approvable Letter

2: FDA’s Criteria for Issuing the Approvable Letter

FDA presents two criteria for issuance of an “Approvable” letter with an “and/or”. This creates a potential for issuance of two “Approvable” letters as final actions. This provides the opportunity for the agency to issue an “Approvable” letter prematurely in order to stop the review clock and meet the performance goal. To avoid this potential, AdvaMed recommends that FDA delete the “or” between 2.a. and 2.b to ensure that the “Approvable” letter will be issued for either condition.

III.C. Major Deficiency

2: FDA's Criteria for Issuance of a Major Deficiency Letter

AdvaMed recommends that FDA better define the criteria for issuance of a "Major Deficiency" letter. For example, in sub item (c), it states that the lack of scientific justification for test data is a rationale for a major deficiency. If this is a systematic problem, a "Major Deficiency" letter may be appropriate, but in limited situations this could be addressed as a minor deficiency. In sub item (e), it states that any "other substantive deficiencies" may be grounds for issuance of a "Major Deficiency" letter. The term "substantive" needs to be better defined to avoid the situation where a list of minor issues could be considered to be substantive, if not resolved one for one.

III.C. Major Deficiency Letter

4: Effect on MDFUMA Goals

In the last paragraph, FDA states that it intends to allow only one extension (180 days maximum); then a new PMA and fee would be required. The legal basis for this is not clear and it clearly poses a financial burden if FDA establishes significant new requirements. There may be legitimate reasons when it is appropriate and necessary for a sponsor to request another extension. AdvaMed believes that FDA should not arbitrarily limit such opportunities. A similar situation arises in III.D.5.

III.D. Not Approvable Letter

1. Definitions

Once a "Not Approvable" letter is issued, three potential pathways are listed. If the PMA is withdrawn, it is indeed a final action for performance goal purposes. However, if the sponsor addresses the identified deficiencies or seeks administrative review and is successful, this should not be considered a final action for performance goal measurement. FDA needs to be very clear on this in this document. AdvaMed is concerned that FDA will use "Not Approvable" letters as alternatives for "Major Deficiency" letters. This issue arises again with PMA-Supplements where FDA issues a "Not Approvable" letter instead of "Major Deficiency" letters.

III. D. Not Approvable Letter

2. FDA's Criteria for Issuing a Not Approvable Letter for Original PMAs and Panel Track Supplements

AdvaMed recommends that the word "generally" be removed as it gives the agency latitude to not permit an applicant the opportunity to address the concerns in a "Major Deficiency" letter.

III.E. Denial Order

3. Effect on the Review Clock

FDA may issue a denial letter if the applicant requests so for administrative review purposes and the review clock stops. However, FDA does not state how it intends to handle the review clock when the administrative review is successful and the review of the PMA resumes. In this situation, AdvaMed recommends that the review clock should restart at the point at which it was stopped.

IV. Applicant's Actions

C. Minor Amendment

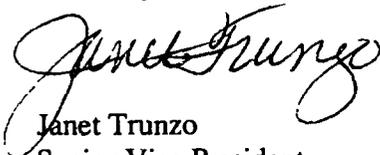
A minor amendment is defined as a response that is either unsolicited or at FDA's request. The latter is presumably a minor deficiency which is not clearly defined. AdvaMed recommends that FDA define the basis for submitting a minor amendment.

Table 1: Effects of FDA Action Letters on FDA Review Clock

Denial has no effect on the review clock since the application has been on hold since the "Not Approvable" letter was issued. This statement is not consistent with III.E.2.a (sponsor submit response to a not approvable letter) and suggests that the review of a response to a "Not Approvable" letter is off the review clock. This does not seem appropriate given the potential that the additional information could also change FDA's decision about the "Not Approvable" status. AdvaMed recommends that FDA clarify the calculation of the review clock for this scenario.

AdvaMed appreciates the opportunity to provide these comments and is available to discuss them further with the agency. Because we are in the second year of the user fee program, AdvaMed recommends that FDA address the concerns raised in this letter immediately.

Sincerely,



Janet Trunzo
Senior Vice President
Global Regulatory Affairs

Attachment (1)

cc: Joanne Less (FDA)
Dan Schultz (FDA)
Beverly Rothstein (FDA)

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October 16, 2003

Thinh Nguyen
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9200 Corporate Blvd. (HFZ-450)
Rockville, MD 20850

Re: Guidance for Industry and Staff: FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect of FDA Review Clock and Performance Assessment

Dear Thinh:

AdvaMed, the Advanced Medical Technology Association (AdvaMed), would like to provide the following comments on FDA's guidance document entitled FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect of FDA Review Clock and Performance Assessment. AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's more than 1,100 members 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.

Although we have significant concerns regarding the guidance document and plan to submit comprehensive comments identifying these concerns, we believe that there is one issue that requires immediate clarification--the "Approvable Letter, Pending GMP," (Section III. B.3). Because we are so concerned about the interpretation suggested in FDA's guidance document, we believe it is important to clarify the approach to this issue as agreed upon during our discussions with the agency regarding performance goals.

Issuance of an Approvable Letter, pending a GMP inspection

During the negotiation of performance goals, we agreed that the "Approval Letter, pending GMP" would only be issued in cases in which the manufacturer's facility was not ready for a GMP inspection. In fact, we discussed the need for FDA to conduct the GMP inspection

concurrently with the review and that FDA should not wait until the review is complete to schedule the inspection. Further, we agreed that under the PMA modular program, the GMP inspection could be scheduled upon receipt of the "Manufacturing Section" module. Both parties agreed that FDA needed to conduct these inspections in a timely manner to ensure that the reviews are complete within the time set by the performance goal. The agency expressed its concern that at times the sponsor's manufacturing facility is not ready for an inspection and delays in scheduling the inspection are due to the sponsor's request, not FDA. For those cases, we agreed that FDA would issue the "Approvable letter, pending GMP".

Effect on the Review Clock

The only way in which we would agree that the issuance of the "Approvable Letter, pending GMP" would actually stop the review clock would be of course, the case in which the sponsor's facility is not ready for the inspection and the delay in the inspection is due to the sponsor, not FDA. Otherwise, there would be no incentive for the agency to schedule the inspection in a timely manner in order to meet its performance goal commitment. Because this issue generated so much debate, it was agreed to add an additional goal to the Secretary's goals letter regarding the scheduling of GMP inspections. (Goal "P" of the Secretary's letter). The purpose of the goal was to ensure that the review clock would not be stopped waiting for the agency to decide when it could schedule the inspection. The review clock was to keep running in order to provide the incentive to FDA to schedule the inspection in a timely manner. In cases in which FDA had no control over scheduling the inspection, i.e., when the sponsor's facility was not ready, then FDA could issue the "Approval letter, pending GMP" and only then the review clock would be stopped.

AdvaMed is extremely disappointed that FDA has proposed this interpretation in the guidance document, an interpretation that is so contrary to the spirit, intent, and agreement reached during the negotiations last year. AdvaMed respectfully requests that FDA immediately modify the language in this guidance document to show its commitment to the agreements reached with industry on the user fee program and its associated performance goals.

Sincerely,



Janet Trunzo
Senior Vice President
Global Regulatory Affairs

cc: Linda Kahan (FDA)
Joanne Less (FDA)