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October 18, 2004

Division of Dockets Management [HFA-305]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

***Re: Docket Number 2004N-0267: Applications for Approval to Market a New Drug:
Complete Response Letter; Amendments to Unapproved Applications***

Dear Sir or Madam:

These comments are submitted on behalf of the Advanced Medical Technology Association (AdvaMed). 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.

FDA's proposed rule amending the regulations on new drug applications (NDAs) and abbreviated new drug applications (ANDAs) impacts our members as it also amends the Biologics Application (BLA) regulations to include a provision on issuance of complete response letters to applicants. The preamble to the proposed rule relies upon the Prescription Drug User Fee Act II (PDUFA) Goals Letter as the rationale for adding complete response letters to the regulations. Although not cited in the preamble, the Medical Device User Fee and Modernization Act (MDUFMA) Goals Letter contains similar language.

Our comments on revisions to the BLA regulations are the following:

- **Definition of complete response letter** – Section 600.3(jj) of the proposed rule defines a complete response as,

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“. . . a written communication to an applicant from FDA usually identifying all of the deficiencies in a biologics license application or supplement that must be satisfactorily addressed before it can be approved.”

Comment: The definition uses the term “usually”, which is contrary to the plain meaning of “complete response.” Any response that does not include all the deficiencies identified in an application is not a complete response. Use of vague language will undermine FDA’s efforts to ensure a consistent approach to informing a sponsor of needed changes to an application before it can be considered for approval.

The PDUFA performance goals for drugs and biologics, including licensed medical devices, do not include similarly vague language. Under the user fee performance goals, FDA made a commitment to “review and act on” a certain percentage of applications of various categories within specified timeframes. For the purposes of the goals, the term “review and act on” is defined in the MDUFMA Goals Letter (S11549) as being “understood to mean the issuance of a complete action letter after the complete review of a filed complete application.” It further states, “[t]he action letter, if it is not an approval, will set forth in detail the specific deficiencies and where appropriate the actions necessary to place the application in condition for approval.” Further, CBER’s SOPP “Complete Review and Issuance of Action Letters,” (version #3, Aug. 8, 2003), states “[t]he Complete Response letter will: [s]ummarize all of the deficiencies remaining and [w]here appropriate, describe actions necessary to place the application/supplement in a condition for approval.”

We recognize, however, that there may be circumstances under which it is reasonable for regulations to confer upon FDA the authority to postpone certain aspects of a “complete review.” These are appropriately described under CBER SOPP “Regulatory – License Applications Complete Review and Issuance of Action Letters,” SOPP 8405 (Version #3, August 8, 2003)¹ and are limited to testing of submitted product lots, pre-licensing inspections, and evaluation of final printed labeling.

Recommendations: Revise the definition of a complete response letter as follows:

“Complete response letter means a written communication to an applicant from FDA identifying all of the specific deficiencies in a biologics license application or supplement that must be satisfactorily addressed before it can be approved, **except when such communication is issued without conducting testing of submitted product lots, required inspections, or evaluation of final printed labeling. Where appropriate a complete response letter will describe the actions necessary to place the application in condition for approval.**

¹ SOPP 8405 states, “Approval Letter – Following completion of all aspects of the review process for both the product and establishment license application, including testing of submitted product lots, pre-licensing inspections and evaluation of final printed labeling or a suitable alternative, an approval letter and accompanying issuance of an appropriate license(s) will constitute the final action...” (page 2).

We also ask that CBER clarify in the preamble to the regulation that the exception, “evaluation of final printed labeling,” is not intended to include the communication of deficiencies pertaining to intended use or product claims. Early communication and resolution of such items are critical to an efficient submission review. Additionally, deficiencies related to intended use or product claims may require an applicant to conduct additional studies to resolve identified deficiencies.

- **Resubmission of the application or supplement** – Proposed section 601.3(b) outlines the actions the applicant must take after receiving a complete response letter, which includes,
 - (1) *Resubmission*. Resubmit the application or supplement, addressing all deficiencies identified in the complete response letter.

Comment: As currently stated this could be read to require resubmission of the original application or supplement, as opposed to resubmission of the response to the deficiencies identified in the complete response letter. Based on current practice and clarifying language proposed in section 314.110, it appears the intent of this provision is not to require resubmission of the original application or supplement.

Recommendation: We recommend adding similar clarifying language as proposed under section 314.110 describing resubmissions to section 601.3 (b).

(1) *Resubmission*. Resubmit the application or supplement, addressing all deficiencies identified in the complete response letter. **For purposes of this section, a resubmission means submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter.**

- **Failure to take action** – Section 601.3(c) states,
 - (c) *Failure to take action*. FDA may consider a biologics license applicant or supplement applicant's failure to either resubmit or withdraw the application or supplement within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application or supplement.

Comment: The preamble to the regulation states that section 601.3 is intended to incorporate current CBER policy.² However, this provision does not reflect current CBER policy and does not afford applicants the opportunity to notify FDA of their intent to amend an application in order to prevent FDA from considering it withdrawn. As written, the proposed rule does not address instances in which an applicant would need to conduct an additional study before the application can be resubmitted. In such cases, it may take more than a year to obtain suitable patient specimens for prospective studies or to design, conduct, analyze, and report certain studies.

² 69 Fed. Reg. 43358 (2004) (to be codified at 21 C.F.R. pt. 601) (proposed Jul. 20, 2004).

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Recommendation: We recommend the following modification to the provision:

(c) Failure to take action. FDA may consider a biologics license applicant or supplement applicant's failure to resubmit, **amend the application to request an extension of time to respond**, or withdraw the application or supplement within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application or supplement.

AdvaMed appreciates the opportunity to provide comments. Please contact me if you have any questions regarding our comments.

Respectfully submitted,



Carolyn D. Jones
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Technology and Regulatory Affairs