OLYMPUS

June 11, 2003

Request for Comment--Docket No. 03D-0062: Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Medical Devices in a Single Application, and Fees for Combinations Products; Guidance for Industry and FDA

Dockets Management Branch (HFA-305)
Division of Management Systems and Policy
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To Whom It May Concern:

Enclosed, please find comments for the above referenced docket number from Olympus America Inc. for the proposed guidance document regarding assessing user fees authorized under MDUFMA.

The Olympus organization is a manufacturer of automated instruments used in blood establishments. Since 1988, Olympus has manufactured automated instruments used in blood establishments for ABO/Rh and infectious disease screening. Currently, more than 90% of North America's blood supply is tested on Olympus analyzer systems.

In addition to comments on the current guidance document, Olympus is presenting a revision suggestion to the user fee determination process that we feel would more appropriately assign user fees to licensed in vitro diagnostic medical devices. This suggestion is more in line with the FDA definitions of medical devices and in vitro diagnostic products as well as the current CBER handling of licensed IVDs and any future changes to those licensed products.

Respectfully submitted,

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03D-0062 C1

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Section IV. Biologics License Applications and Supplements--Comments

1. The general tone of this section of the guidance acts to consider all products, which require Biologics License Applications (BLAs) as products intended as drugs or for therapeutic uses. It does not appear to make any acknowledgement that there are products that must be licensed under section 351 of the PHS Act that are in fact in vitro diagnostic medical devices. A distinct and separate consideration and user fee determination criteria should be established for these licensed products. This consideration and user fee criteria should be a tiered program based on the PMA criteria rather than the current structure, which is similar to the Prescription Drug User Fee Act (PDUFA). This suggestion is based on the following points:

    a) In vitro diagnostic products that require licensing have historically been treated more closely to PMA medical device products, which is consistent with the definitions assigned by the FDA for Drugs, Biologics, and Medical Devices, in implementing regulations. Many IVD medical device products that require BLAs are clearly defined by the FDA as medical devices with biologic components, not drugs.
    b) Consideration and discussions that have occurred between FDA and stakeholders in the past year have suggested the possibility of moving all biological IVD product review into CDRH, which further strengthens the similarity between licensed IVD medical device products and PMA products.
    c) By the inherent nature of the in vitro diagnostic medical devices, clinical data is often-times critical in demonstrating substantial equivalence and safety and effectiveness for changes to the product. In the FDA Guidance "Deciding when to submit a 510(K) for a Change to and Existing Device" the FDA indicates in the explanatory text for section B.8.2 that in those situations where clinical samples are evaluated to show continued device performance conformity, a new 510(K) is not necessary. This FDA position should be consistently applied for **all** in vitro diagnostic medical devices despite the mechanism for premarket review/approval.

2. The definition of an efficacy supplement as one that requires "substantive clinical data" is overly broad and subjective when considering the application of this

definition and change review process to licensed in vitro diagnostic medical devices. These medical devices *almost always* require some level of clinical test data. Clearer guidance should be provided for IVD products that indicate what level the FDA considers as "substantive." Is the agency opinion that any clinical data used for demonstrating continued performance is "substantive" or only actual clinical trials?

3. The regulation text in 21 CFR part 601.12 outlines three types of changes (not related solely to labeling changes) to an approved BLA. These changes are:

   - 601.12 (b)—Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes)
   - 601.12 (c)—Changes being Effected Supplements (30 day prior notice and no prior notice)
   - 601.12(d)—Changes to be described in an Annual Report

   There is **NO** distinction made in the biologics regulations that apply to IVD medical devices between a Prior Approval Supplement (PAS) and a BLA Efficacy Supplement. In fact, a search of the FDA web pages for the term "efficacy supplement" clearly indicates that this term is **solely** used for combination Biologic/Drug products and **never** used when referring to a licensed Biologic/Device combination.

   Considering historical treatment by the FDA of the term "efficacy supplement" as referring to Biologic/Drug combinations, then the assumption could be made that all Biologic/Device combination changes (including in vitro diagnostic devices) would not be considered as efficacy supplements and would be considered as Prior Approval Supplements (PAS) that do not require a user fee.

4. If the current guidance concerning changes to licensed in vitro diagnostic medical devices remains as proposed, with any change to the original BLA requiring the full $154,000 user fee, this would have a significant impact on the diversity of manufacturers for many products. For example, there are only 2 major manufacturers of licensed IVD products blood grouping determinations. This situation is not healthy for the blood bank industry as it could have a significant impact on transfusion safety if a product quality or delivery problem were to occur.

5. The current guidance would also limit manufacturer diversity based on the fee charged versus the expected yearly revenues that would be generated by some products. For example, manufacturers typically submit anti-sera for blood

grouping determinations in sets. The first set would be anti-sera for A, B, AB and RH testing. Subsequent submissions would complete the product line (a market viability necessity) of blood grouping antisera (addition of anti-Jk^a and anti-Jk^b), have the same intended use (blood grouping determinations), require clinical data, and based on the guidance, require the full $154,000 review fee. The reagents (anti-Jk^a and anti-Jk^b), though necessary for laboratories to have a full panel of blood grouping reagents, are more similarly "orphan" products, in that they would not be expected to generate a yearly revenue the same as the user fee. Prior to user fees, if the manufacturing process was the same, this product review would be handled as a supplement to the original license as defined in 21 CFR 601.12(b).

Guidance Document Revision Suggestion for Licensed Biologic IVD Products

Changes to licensed biologic IVD products should require some level of device user fees based on the resources necessary for timely FDA review of the changes. However, as mentioned in item # 1 above, a distinct and separate consideration and user fee determination criteria should be established for these licensed biologic IVD products. This consideration and user fee criteria should be a tiered program based on the PMA criteria. Please consider the following situation; a manufacturer is modifying their licensed IVD product intended for use in blood grouping determinations to add anti-sera (manufactured in the same or similar processes) that will be used for more esoteric antigens (Jk^a or Jk^b). If the descriptions used in section II of this guidance were applied to this situation, this would be considered a 180-day Supplement and a more appropriate user fee would be required for the change. This would not be considered a Panel-Track Supplement because a new indication of use is not being requested, and the change to the design or performance does not significantly alter clinical outcome.

More important to the situation described and the revised user fee that would be identified, this is currently how this type of change is considered and managed by the CBER review branch.