As of 11/21/03, Section V of this document titled "Bundling Multiple Devices in a Single Application" has been superseded by a new guidance document titled: Bundling Multiple Devices or Multiple Indications in a Single Submission

# Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**

**Center for Devices and Radiological Health (CDRH)**
**Center for Biologics Evaluation and Research (CBER)**

# Preface

## Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to Docket No. 03D-0062. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance, contact Joanne R. Less, Ph.D. (CDRH) at (301) 594-1190 or by email at jrl@cdrh.fda.gov or Robert Yetter, Ph.D. (CBER) at (301) 827-0373 or by email at yetter@cber.fda.gov. In addition, contacts for the specific topics addressed in the guidance are provided in Section VII.

## Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/mdufma/guidance/1201.pdf , or to receive this document via your fax machine, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system. At the second voice prompt, press 1 to order a document. Enter the document number 1201 followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

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# Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA

***This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.***

## I. Introduction

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA), P.L. 107-250, amends the Federal Food, Drug, and Cosmetic Act (the act) to provide the Food and Drug Administration (FDA) new responsibilities, resources, and challenges. One particularly significant provision of MDUFMA is that which permits FDA to collect user fees for certain premarket reviews (i.e., premarket approval applications, premarket reports, supplements, premarket notifications, biologics license applications, and efficacy supplements as discussed in more detail below), including those applications received on or after October 1, 2002. On February 20, 2003, enabling appropriations were enacted, thus allowing the agency to immediately begin to collect fees for medical device applications.

FDA recently established a public docket to obtain input on the implementation of MDUFMA. (Docket number 02N-0534) The agency established this docket in order to provide an opportunity for all interested persons to provide information and share views on the various provisions of MDUFMA. However, FDA is implementing this Level 1 document upon issuance because it is essential for the agency to provide immediate guidance to help the industry determine the appropriate fees for their applications. FDA intends to review all comments it receives and issue a new guidance for public comment. In the meantime and until a new final guidance is issued, this document will be in effect. The agency is committed to obtaining input on the implementation of MDUFMA and encourages its stakeholders to participate in the process by commenting on this guidance and other MDUFMA provisions.

## II. PMA Supplement Definitions

In accordance with MDUFMA, the following types of premarket approval applications (PMAs) are subject to a review fee:

- Original PMAs
- Premarket reports (PMRs)
- Product development protocols (PDPs)
- Panel-track supplements
- 180-day supplements
- Real-time supplements

For fiscal year 2003, an applicant who submits an original PMA/PMR/PDP or panel-track supplement will be charged a fee of $154, 000. The review fee for a 180-day supplement is $33,110, and the fee for a real-time supplement is $11,088.[1]

Note that there are no fees associated with the following types of applications, so they are not discussed in this document:

- 30-day notices
- 135-day supplements
- Special PMA Supplements-Changes Being Affected
- Express PMA supplements
- PMA annual reports[2]

Because the review fees vary for the three types of PMA supplements identified above, the agency is providing this information to assist the industry in determining the appropriate type of supplement and associated fee that should be submitted for a change to an approved Class III device.

In making a decision as to whether to supplement an original PMA or submit a new original PMA for a particular change to an approved device, the applicant should determine whether the preclinical and clinical data submitted in support of the original PMA are still pertinent to demonstrate safety and effectiveness (S&E) of the modified device. In general, if completely new pre-clinical and clinical data are needed for assuring S&E of the modified device, the sponsor should submit a new original PMA because we are, in essence, dealing with a new device. If, however, the sponsor can rely on the original pre-clinical testing and only new

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[1] Small businesses may qualify for a waiver of the fee for their first PMA and for lower rates for subsequent PMAs, PMRs and supplements. Detailed procedures for determining if an applicant qualifies for a small business waiver is available on the FDA website at http://www.fda.gov/cdrh/mdufma/guidance/1204.pdf.

[2] In addition, it should be noted that there are no fees associated with investigational device exemptions applications (IDEs) or humanitarian device exemption applications (HDEs).

clinical data are required to demonstrate S&E for the modification, then a supplement may be submitted for the change. Similarly, if the sponsor can rely on the clinical data from the original application and only new pre-clinical testing is required to support S&E of the change, a supplement may be submitted.

As stipulated under 21 CFR 814.39(a), "a PMA supplement is required, but is not limited to, the following types of changes if they affect the safety or effectiveness of the device:

- New indications for use for the device.
- Labeling changes.
- The use of a different facility or establishment to manufacture, process, or package the device.
- Changes in the sterilization procedures.
- Changes in packaging.
- Changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device.
- Extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA."

In new section 737 of the act, which was added by MDUFMA, three types of PMA supplements are defined: panel-track, 180-day, and real-time. Below, we are providing our current interpretation of these terms to assist manufacturers in determining the appropriate fees for their submissions.

## A. Panel-Track Supplement[3]

In section 737(4)(B) of the act, "panel-track supplement" is defined as:

> "a supplement to an approved premarket application or premarket report under section 515 that requests a significant change in design or performance of the device, or a new indication for use of the device, and for which clinical data are generally necessary to provide a reasonable assurance of safety and effectiveness."

[3] Although a supplement may be designated as a panel-track supplement, FDA does not always bring these supplements before an advisory panel. If a supplement meets the definition of a panel-track supplement and the change is a first of a kind (i.e., raises new types of safety and effectiveness issues as compared to the original PMA device), FDA will take the application to panel. Subsequent "me-too" devices with the same change will also be designated as panel-track supplements; however, the agency will not take them to panel unless a particular application presents an issue that can be best addressed through panel review. ("Me-too" devices are considered those in which the device technology is the same, the indication is identical and the labeling contains no less stringent warnings and precautions than the original "panel-track" device that went to panel.) The fee for a panel-track supplement is the same, regardless of whether the agency takes the application to panel.

The term "panel-track supplement" is not defined in the PMA regulation. The regulation does describe, however, the types of supplements that require the agency to publish a new summary of safety and effectiveness (SSED). Under 21 CFR 814.39(c), the supplements that trigger the requirement for a new SSED are those:

> " submitted for new indications for use of the device, significant changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device, or when otherwise required by FDA."

Although this section of the regulation provides FDA with discretion as to the type of supplement that should be submitted, the agency has traditionally used this part of the PMA regulation to define when a panel-track supplement is necessary. Therefore, while the agency continues to receive and review stakeholder comments on this issue, applicants should submit a panel-track supplement and pay the associated fee for:

- a new indication for use (i.e., patient population/disease state); or
- a change in device design or performance that could significantly affect clinical outcome.

**For the types of changes listed above, a new clinical trial is generally necessary to demonstrate reasonable assurance of safety and effectiveness.**

For example, an excimer laser system approved for the indication of myopic photorefractive keratectomy (PRK) for the reduction or elimination of myopia will require submission of a panel-track supplement to expand the indication to include laser assisted in-situ keratomileusis (LASIK) treatments for the reduction or elimination of myopia. Similarly, a ventricular assist device (VAD) approved for bridge to transplant will require a submission of a panel-track supplement to expand the indication to include destination therapy. In both cases, a new clinical trial will be needed to demonstrate reasonable assurance of safety and effectiveness for the new indication.

## B. 180-Day Supplement

According to section 737(4)(C) of the act, "180-day supplement" is defined as:

> "a supplement to an approved premarket application or premarket report under section 515 that is not a panel-track supplement and requests a significant change in components, materials, design, specification, software, color additive, and labeling."

FDA believes the above definition closely captures current review practice for this type of supplement, which is set forth in more detail below. Therefore, while the agency continues to receive and review stakeholder comments on this issue, applicants should submit a 180-day supplement and pay the associated fee for a significant change involving:

- the principle of operation;
- the control mechanism;

- the device design or performance;
- the labeling (e.g., removal of a contraindication); or
- new testing requirements or acceptance criteria.

**For the types of changes listed above, clinical data for the original device must still be applicable to the modified device in order for the change to be submitted as a 180-day supplement. That is, demonstration of reasonable assurance of safety and effectiveness for the modified device either does not require a new clinical trial to be conducted or requires only limited clinical data.**

For example, consider an approved transurethral thermoablation system that is indicated to relieve symptoms associated with benign prostatic hyperplasia (BPH). The device was originally approved for a standard 60 minute treatment. The applicant later submits a supplement for a design change to include the option of a 28.5 minute treatment. The supplement included labeling changes, software documentation, and verification/validation data. Clinical data from a confirmatory trial demonstrating that the shortened treatment procedure would result in a safe and effective treatment for BPH (that is, comparable to the standard treatment procedure) was also included. In this case, because the supportive clinical data was confirmatory in nature, the changes made to the device were reviewed as a 180-day supplement.

## C. Real-Time Supplement

According to section 737(4)(D) of the act, "real-time supplement" is defined as:

> "a supplement to an approved premarket application or premarket report under section 515 that requests a minor change to the device, such as a minor change to the design of the device, software, manufacturing, sterilization, or labeling, and for which the applicant has requested and the agency has granted a meeting or similar forum to jointly review and determine the status of the supplement."

We are summarizing below our current review practices for determining whether a "real-time supplement" is appropriate for a relatively minor change of the type listed above (i.e., design, software, manufacturing, sterilization or labeling). While the agency continues to receive and review stakeholder comments on this issue, applicants should submit a real-time supplement and pay the associated fee for minor changes to:

- the device design, excluding those listed above under 180-day supplements;
- the labeling (i.e., instructions for use, warnings, or precautions, but not contraindications); or
- the sterilization and packaging.

For the changes listed above, the following should also be true:

- there is an accepted test method, FDA-recognized standard, or guidance document to address the safety and effectiveness of the change;

- clinical data are not required to demonstrate S&E of the change;
- an inspection of the manufacturing facility is not required; and
- FDA and the applicant have agreed that the review can be achieved in a real-time setting.

**For the types of changes listed above, the review can be performed in a real-time setting because an extensive multidisciplinary review is not required.**

Examples of changes that were reviewed in real-time supplements include: 1) minor design modifications (e.g., new lengths, diameters, and curve types) for cardiac ablation catheters and 2) a change in the storage temperature and expiration dating for an injectable gel.

Manufacturing process changes that can be adequately assessed through Quality Systems requirements alone should continue to be submitted as 30-day notices. If the notice is not adequate, FDA will inform the applicant that a 135-day supplement is needed and, in accordance with 21 CFR 814.39(f), describe what further information is required for the change.[4] Other minor manufacturing changes involving a modification to the device should be submitted as real-time supplements.

Table 1 of the Appendix summarizes all of the above information regarding panel-track, 180-day, and real-time supplements.

For instructions on the submission of the above fees, see the Federal Register notice [Publication pending]

# III. Modular PMAs

Section 209 of MDUFMA amended section 515(c) of the act to create a modular review program for PMAs. New section 738(a)(1)(C) provides that applicants submitting portions of applications under this new program must pay the fee upon submission of the first portion of such application. Accordingly, fees for modular applications are assessed as follows:

- For modular PMAs for which at least one module was submitted before October 1, 2002, no fee is due for any subsequent module.

- For modular PMAs for which the first module was submitted on or after October 1, 2002, the full fee for an original PMA is due when the first module is submitted.

For instructions on the submission of the above fees, see the Federal Register notice [Publication pending]

[4] For guidance on 30-day notices and 135-day supplements, see the guidance entitled, "30-Day Notices and 135-Day PMA Supplements for Manufacturing Method and Process Changes" on CDRH's website at: www.fda.gov/cdrh/modact/daypmasp.html

# IV. Biologics License Applications and Supplements

In accordance with MDUFMA, device applications subject to section 351 of the Public Health Service Act (PHS Act), Biologics License Applications (BLAs) and BLA Efficacy Supplements (BLSs), are subject to a review fee. For fiscal year 2003, an applicant who submits an original BLA or a BLA Efficacy Supplement will be charged a fee of $154,000.

A BLA is submitted when an applicant wishes to pursue licensure for a biological product. When a licensed applicant wishes to make a change to a licensed biological product, s/he must submit a supplement in accordance with 21 CFR 601.12. This section of the regulation describes changes requiring submission and approval of a supplement prior to distribution of product (Prior Approval Supplements [PAS]), changes requiring submission of a supplement at least 30 days prior to distribution of product (Changes Being Effected [CBE-30 & CBE]), and changes to be described in an annual report (AR). Efficacy Supplements are a subset of PASs and are defined below. Note that there are no fees associated with the following types of submissions, so they are not discussed in this document:

- CBEs
- CBE-30s
- ARs
- PASs that do not meet the definition of an efficacy supplement

According to section 737(4)(E) of the act, "efficacy supplement" is defined as:

> "a supplement to an approved premarket application (i.e., BLA) under section 351 of the Public Health Service Act that requires substantive clinical data."

User fees will be assessed for original applications and efficacy supplements containing the following types of clinical data that are required to form the primary basis for approval:

- study reports or literature reports that are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials.

For purposes of assessing user fees, "clinical data" do not include data used solely to modify the labeling to add a restriction that would improve the safe use of the product (e.g., to add a limitation or warning to the labeling). In addition, supplements to BLAs based solely on equivalence studies (in-house testing with limited external testing) are not considered to contain clinical data for purposes of assessing user fees.

For the types of changes listed below, substantive clinical data are generally necessary to demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Therefore, while the agency continues to receive and review stakeholder comments on this issue, applicants should submit an efficacy supplement and pay the associated fee for:

- a new indication for use (e.g., patient population/disease state);
- a significant change in design; or
- a significant change in performance.

For example, a change in an HIV test kit for blood donor screening to include an additional strain or a change in a Blood Grouping Reagent to include a different source of raw material (e.g., changing from one monoclonal to another) both require substantive clinical data to support the change. Therefore, these would be classified as efficacy supplements and would require payment of the associated user fee.

Table 1 of the Appendix includes a summary of the above information.

# V. Bundling Multiple Devices in a Single Application

In a letter from the Secretary of Health and Human Services to Congress that accompanies the user fee legislation, FDA agreed to consider when bundling multiple devices in a single application may be appropriate and to obtain input from its stakeholders on this issue. The agency intends to develop detailed guidance on this issue and to obtain input from its stakeholders during the development process. Until comments are received and such guidance can be developed, however, the agency is providing some guiding principles to help industry as they prepare their premarket submissions. The information provided below reflects current FDA policy towards bundling multiple devices in a single premarket submission.

Bundling refers to the inclusion of multiple devices, or multiple indications for use for one device, in a single premarket submission. For the purpose of this discussion, multiple devices may include different models within a generic type of device[5] or devices that are of different generic types. Current review practice within CDRH and CBER allows for bundling in many instances. The agency's primary consideration in determining what devices, or indications for use, should be bundled in one premarket submission has been the agency's ability to conduct efficient reviews and render timely decisions. The total review time for an application in which multiple devices presenting disparate scientific and regulatory issues are bundled is determined by the review time for the device with the slowest review. For this reason, review divisions have sometimes requested that submitters separate certain devices, or uses, to allow for the most efficient review. Until recently, submitting separate applications for devices that could have been bundled or bundling devices that should have been submitted in separate applications was primarily an administrative issue related to the efficiency of the review process. Under MDUFMA, however, proper bundling within a single premarket submission takes on additional importance because of the fees that are now associated with certain submissions.[6]

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[5] Generic type of device is defined in 21 CFR 860.4(i) as "a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness."

[6] For fiscal year 2003, the fee for a 510(k) is $2,187. Fees for PMAs (original and supplements) are listed in Section II of this document.

While FDA receives and reviews stakeholder comments on this issue and develops a detailed guidance on bundling, submitters should follow the general principles below:

1. Bundling is appropriate for devices that present scientific and regulatory issues that can most efficiently be addressed during the course of one agency review.

2. FDA will not "cull out" a device(s) from a premarket submission for the purpose of collecting additional user fees.

3. Industry should not inappropriately combine devices in a premarket submission for the purpose of avoiding user fees.

Specifically:

- Premarket submissions in which multiple devices within one generic device type are bundled would generally be appropriate. (For example, single lumen hypodermic needles with various dimensions and configurations could be bundled in a single 510(k)). Submitters may elect to withdraw a device(s) from a submission and resubmit in a separate application if the issues that are delaying a final decision affect only a subset of the bundled devices.

- Bundling devices of differing generic device types is appropriate when the devices are intended to be used together to fulfill a therapeutic or diagnostic purpose. Premarket submissions of this nature include convenience kits, device systems, and devices with accessories, ancillary components, or peripherals. (For example, a nuclear whole body scanner and nuclear scanning bed could be bundled)

- Submitters may, under certain circumstances, bundle multiple indications for use in a single 510(k). It should be noted, however, that in instances where multiple indications for use are associated with one device, a particular indication may present issues that are best addressed in a separate 510(k). For example, a multi-use device that has a new indication for use (i.e., a use that has not appeared in the labeling for a legally marketed predicate device) may be more efficiently reviewed in a separate 510(k). In addition, devices that have uses in multiple medical specialties and would, therefore, require reviews by different branches will generally require separate submissions.

- Bundling is generally not appropriate for multiple indications for use for a Class III device subject to premarket approval because each indication for such a device is usually supported by a clinical study that requires significant review resources. Nor is bundling of PMA and 510(k) devices in a single submission appropriate.

- One application may be submitted when a change affects devices of the same generic type or differing generic types if the impact of the change on each of the devices can be efficiently assessed during the course of one agency review. (For example, the

application of a heparin coating on various cardiopulmonary bypass devices, such as an arterial line blood filter, oxygenator, and pump tubing, could be bundled.)

**For bundling in vitro diagnostic devices:**

- Bundling for multiple analytes or instruments under the same classification panel or for recognized test panels or profiles or when each device can be efficiently assessed is generally appropriate.

- Bundling for multiple reagents that would be used together to obtain a profile, e.g., to obtain a donor or patient blood group phenotype, is appropriate when significant portions of multiple, individual submissions would contain significant amounts of identical information, e.g., clinical trial data, downstream processing information, etc.

- Bundling when a novel sample matrix (e.g., hair) is used is generally not appropriate. Bundling when similar matrices (e.g., serum and plasma) are used is generally appropriate.

- Bundling between classification panels should not be done for a first of a kind analyte, a first of a kind instrument, or a first of a kind analyte/instrument combination, unless it is a well-recognized test panel or profile. (Recognized test panels or profiles can be found through the Centers for Medicare and Medicaid Services reimbursement national coverage book and includes profiles such as lipid profiles and liver function tests.)

- The reagent replacement policy entitled, "Data for Commercialization of Original Equipment Manufacturer, Secondary and Generic Reagents for Automatic Analyzers" (see www.fda.gov/cdrh/ode/odecl950.html) will continue to apply and those associated changes may be made without incurring a fee.

# VI. Fees for Combination Products

A combination product with a device component (i.e., a drug-device or biologic-device product) will be subject to the fee associated with the type of application required for the product's premarket approval, clearance, or licensure. For example, a biologic-device or a drug-device combination product regulated under a PMA will be subject to the PMA fee under MDUFMA, while a biologic-device or a drug-device combination product for which a 510(k) is required will be subject to the 510(k) fee under MDUFMA. A biologic-device product regulated under section 351 of the PHS Act will be subject to the BLA fee under MDUFMA, if the biological component meets the definition of a device. Other biologic-device combination products regulated under section 351 of the PHS Act, or drug-device combination products regulated under section 505(b) of the Federal Food, Drug, and Cosmetic Act, that are human drug applications as defined in section 735 of this act, will be subject to prescription drug user fees. Prescription drug user fees may include application and yearly product and establishment fees. Criteria for determining whether an applicant or submission qualifies for reduced or waived fees

under MDUFMA are provided at www.fda.gov/cdrh/mdufma/guidance/1204.pdf. Guidance documents for determining whether an applicant qualifies for reduced or waived prescription drug user fees are available at <http://www.fda.gov/cder/pdufa/>.

## VII. Questions?

Contact the personnel identified below for questions:

- For questions regarding PMA supplement definitions or modular PMAs, contact the CDRH PMA Staff at (301) 594-1186 or, for devices reviewed by CBER, contact Robert Yetter, Ph.D. at (301) 827-0373.

- For questions regarding BLAs and Efficacy Supplement Definitions, contact Robert Yetter at the number identified above.

- For questions related to bundling, contact Robert Gatling at (301) 594-1190. For questions regarding bundling of IVDs reviewed by CDRH, contact Steve Gutman, M.D. at (301) 594-3084 or, for IVDs reviewed by CBER, contact Robert Yetter at (301) 827-0373.

- For questions regarding combination products, contact the Office of Combination Products at (301) 827-3390.

# APPENDIX

PMA Supplement Definitions and BLA/BLS Definitions - Current Policy

| | Panel-Track Supplement | 180-Day Supplement | Real-time Supplement | Biologics License Application Efficacy Supplement (BLS-Efficacy) |
|---|---|---|---|---|
| **Statutory Definition** | "...significant change in design or performance of the device, or a new indication for use of the device, and for which clinical data are generally necessary..." | "...significant change in components, materials, design, specification, software, color additive, and labeling." | "... such as a minor change to the design of the device, software, manufacturing, sterilization, or labeling..." | "...a supplement to an approved premarket application under section 351 of the Public Health Service Act that requires substantive clinical data." |
| **Current Policy** | **New clinical trial to support:**<br>- A new indication for use;<br>- A change in device design or performance that could significantly affect clinical outcome. | **At most, confirmatory clinical data to support a significant change involving:**<br>- The principle of operation;<br>- The control mechanism;<br>- The device design or performance<br>- The labeling (e.g., removing a contraindication); or<br>- New testing requirements or acceptance criteria. | **No clinical data or inspection needed for minor changes to:**<br>- The device design; or<br>- The labeling (not including contraindications);<br>- The sterilization and packaging.<br>**The following should also be true:**<br>- There is an accepted test method, FDA-recognized standard, or guidance, and<br>- FDA and applicant have agreed that real time is appropriate | **Substantive clinical data to support the change and demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product:**<br>- A new indication for use;<br>- A significant change in design; or<br>- A significant change in performance. |
| **Cost (Fiscal Year 2003)** | $154, 000 | $33,110 | $11,088 | $154,000 |