As of 11/21/03, Section V of this document titled "Bundling Multiple Devices in a Single Application" has been superseded by a new guidance document titled: Bundling Multiple Devices or Multiple Indications in a Single Submission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

Document Issued on: February 25, 2003

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:** - A new indication for use; - A change in device design or performance that could significantly affect clinical outcome.	**At most, confirmatory clinical data to support a significant change involving:** - The principle of operation; - The control mechanism; - The device design or performance - The labeling (e.g., removing a contraindication); or - New testing requirements or acceptance criteria.	**No clinical data or inspection needed for minor changes to:** - The device design; or - The labeling (not including contraindications); - The sterilization and packaging. **The following should also be true:** - There is an accepted test method, FDA-recognized standard, or guidance, and - 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:** - A new indication for use; - A significant change in design; or - A significant change in performance.
Cost (Fiscal Year 2003)	$154, 000	$33,110	$11,088	$154,000

Guidance for Industry and FDA Staff

Bundling Multiple Devices or Multiple Indications in a Single Submission

This guidance document supersedes Section V, "Bundling Multiple Devices in a Single Application," of the February 2003 guidance entitled, "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," which was issued in final for immediate implementation with an opportunity for public comment on the guidance after issuance. The agency received and reviewed comments on that guidance. FDA also invites comments on this document. Please submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register. FDA will review any comments we receive and revise the guidance when appropriate.

For questions regarding this document contact Robert Gatling at 301-594-1190, ext. 140, or by email to RRG@CDRH.FDA.GOV. For devices reviewed by the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), contact Sousan Altaie at 301-594-3084, ext. 145, or by email to SSA@CDRH.FDA.GOV. For devices reviewed by CBER, contact Sheryl Kochman at 301-827-6123, or by email to Kochman@CBER.FDA.GOV.

Document Issued on November 26, 2003

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061 (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to "Bundling Multiple Devices or Multiple Indications in a Single Submission," which is the exact title of this guidance document. FDA will review any comments we receive and revise the guidance document when appropriate.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/mdufma/guidance/1215.pdf or http://www.fda.gov/cber/mdufma/mdufma.htm, 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 (**1215**) followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

Contains Nonbinding Recommendations

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Guidance for Industry and FDA Staff

Bundling Multiple Devices or Multiple Indications in a Single Submission

This guidance represents the Food and Drug Administration's (FDA'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 FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

A. Background

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA), P.L. 107-250, amended the Federal Food, Drug, and Cosmetic Act (the act) by authorizing FDA to collect user fees for certain premarket submissions received on or after October 1, 2002. A letter from the Secretary of Health and Human Services to Congress that accompanies the user fee legislation sets forth performance goals and policy and procedural provisions. One of these provisions is entitled, "Bundling Policy," and states that FDA will consider, in consultation with its stakeholders, when bundling multiple devices in a single submission may be appropriate.

Prior to MDUFMA, submitting separate applications for devices that could have been bundled in a single submission, or bundling of devices that should have been submitted in separate applications, was primarily an administrative issue related to the efficiency of the review process. Under MDUFMA, bundling within a single premarket submission takes on additional importance because of the fees that are now associated with premarket submissions as well as the performance goals that the agency has committed to meet. This guidance is intended to assist industry and FDA staff in understanding when bundling may be appropriate. This guidance will be used by both the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) when reviewing bundled premarket submissions.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

B. Consultation with Stakeholders

As discussed above, FDA has committed to considering the issue of bundling in consultation with its stakeholders. In developing this guidance, the Agency has considered comments on bundling that were submitted to the Public Docket on MDUFMA Implementation, Docket No. 02N-0534. FDA also received comments on the topic before and after issuing the guidance entitled, "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."[1] In that guidance, FDA asked for comments on bundling in general as well as specific comments on the concepts presented in the document.

Most of the comments supported the concept of bundling, and some stakeholders provided examples of when bundling should be considered appropriate. FDA included many of these examples in this document. One stakeholder expressed concern that the practice of bundling was not well known and asked that the agency clearly identify "criteria" for both industry and FDA staff. The agency has attempted to be as specific as possible in defining when bundling should be appropriate. Because not all situations can be anticipated, there may be bundling issues that are not addressed in this guidance. Finally, one commentor was concerned that the misuse of bundling could lead to higher user fees in subsequent years. FDA believes that the concepts and examples of when bundling should be appropriate that are provided in this document will help to alleviate that concern.

The agency recognizes that bundling is a complicated topic and continues to invite comments. In addition, the agency intends to include "bundling" as a topic for discussion at future stakeholder meetings.

C. The Least Burdensome Approach

We believe we should consider the least burdensome approach in all areas of medical device regulation. This guidance reflects our careful review of the relevant scientific and legal requirements and what we believe is the least burdensome way for you to comply with those requirements. However, if you believe that an alternative approach would be less burdensome, please contact us so we can consider your point of view. You may send your written comments to the contact person listed in the preface to this guidance or to the CDRH or CBER Ombudsman. Comprehensive information on CDRH's Ombudsman, including ways to contact him, can be found on the Internet at

[1] This guidance can be found on the following websites: http://www.fda.gov/cdrh/mdufma/guidance or http://www.fda.gov/cber/gdlns/mdufmauserfee.pdf.

http://www.fda.gov/cdrh/resolvingdisputes/ombudsman.html. CBER's Ombudsman can be reached at (301) 827-0379.

II. Frequently Asked Questions on Bundling of Multiple Devices or Multiple Indications in a Single Submission

A. Overview of Bundling

1. What is "bundling"?

Bundling refers to the inclusion of multiple devices or multiple indications for use for a device in a single premarket submission, including products subject to the device and biologics license application (BLA) authorities, for purposes of review and user fee payment. In CBER, the term may also include the designation of separate submissions as one premarket submission for review and user fee payment. Multiple devices may include different models within a generic type of device[2] or devices that are of differing generic types.

Under current review practices, CDRH and CBER have accepted submissions in which multiple devices or indications for use were bundled when the devices or indications presented issues that could be addressed during one review.[3] An applicant is not required to bundle multiple devices or indications, but may choose to do so when appropriate. Each device or indication in a bundled submission must satisfy the applicable statutory and regulatory premarket requirements.

Prior to MDUFMA, bundling was primarily an administrative issue. The Agency's primary consideration in determining what devices, or indications for use, could be bundled in one premarket submission was the Agency's ability to conduct efficient reviews and render timely decisions. The

[2] Generic type of device is defined in 21 CFR § 860.3(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."

[3] The classification letter for a bundled submission generally will identify the classification regulation for the device with the highest regulatory class within the bundle (e.g., if the submission bundles a Class I device and a Class II device, the letter will refer to the Class II classification). This letter does not impose any additional regulatory requirements on devices within the bundle beyond those associated with their individual classification. Unless devices within the bundle are subject to their own classification regulations, they are subject to the regulatory requirements applicable to the device with which they are intended to be used.

total review time for an application in which multiple devices presenting disparate scientific and regulatory issues were bundled was determined by the device that took the longest time to review.

2. What effect does MDUFMA have on bundling?

Under MDUFMA, bundling within a single premarket submission takes on additional importance because of the fees[4] that are now associated with certain submissions as well as the performance goals that the agency has committed to meet.[5] According to the new law, there is one user fee per submission. In addition, as specified in the Secretary's letter to Congress, the agency has committed to improving its premarket review times by meeting both cycle and decision goals for 510(k)s and PMAs. Thus, if devices or indications for use are bundled when they should have been submitted in separate applications, the user fee revenues for that year will be affected and subsequent fees for all regulatory submissions may require adjustment. Premarket review times may also suffer if devices or indications are bundled inappropriately.

Appropriate bundling, however, will help ensure that user fees revenues are not adversely affected and that the agency meets its cycle and decision goals. The agency is providing this guidance to help its own staff and industry determine when it may be appropriate to bundle multiple devices or indications for use in a single submission.

3. What are the general bundling principles applicants should follow?

The general principles are:

- Bundling is appropriate for devices that present scientific and regulatory issues that can most efficiently be addressed during **one review**. In determining whether it can review a bundled submission during the course of one review, FDA may consider whether: (i) the supporting data are similar; (ii) primarily one review division/group will be involved; and (iii) the devices or indications for use are similar.

- FDA should not "cull out" a device or an indication for use from a premarket submission for the purpose of collecting additional user fees.

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

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[4] For fiscal year 2004, see http://www.fda.gov/OHRMS/DOCKETS/98fr/03-19655.htm or http://www.fda.gov/OHRMS/DOCKETS/98fr/03-19655.pdf.

[5] The performance goals can be found at: www.fda.gov/cdrh/mdufma/pgoals.html or http://www.fda.gov/cber/gdlns/mdufmauserfee.pdf.

B. Bundling of Specific Types of Devices or Indications for Use

4. Can I bundle multiple devices within a generic device type in a single 510(k) or PMA submission?

You generally may bundle multiple devices within the same generic device type for both 510(k)s and PMAs. You should consider whether the devices have similar indications, rely on similar data, and/or whether primarily one review division/group will review the devices. If the devices have these characteristics in common, bundling is typically appropriate.

Examples include:

- Bundling of catheters or single lumen hypodermic needles with various dimensions and configurations in a single 510(k) submission.
- Bundling of soft contact lenses of various materials and lens designs in a single 510(k) submission when the lens designs and indications for use of each lens material are generally the same. (This example may also illustrate the bundling of "changes" discussed following question 10 below.)
- Bundling of class I (or II) spinal implants made of multiple metallic alloys (stainless steel and titanium versions) into one 510(k) submission, if the indications for use are generally the same for the two materials.
- Bundling of several sizes of aortic heart valves in a single PMA submission.

5. Can I bundle differing generic device types in a single 510(k) submission?

In some cases, you may bundle differing generic device types in a single 510(k) submission. In determining whether bundling differing generic device types in a single 510(k) is appropriate, you should consider the general principles outlined above and also whether the bundled devices are used together during a therapeutic or diagnostic procedure. You generally may bundle the devices if one device is an accessory to another. Examples of differing generic device types that may be bundled include a device with its ancillary components or peripherals, and devices generally included in convenience kits and device systems.

6. Can I bundle differing generic device types in a single PMA submission?

Generally, you should not bundle differing generic device types in a single PMA submission because of the substantially different pre-clinical and clinical data needed to support each of the devices.

7. Can I bundle multiple indications for use for a device in one 510(k)?

In many cases, you may bundle multiple related indications for use in a single 510(k) submission. An example is a spinal implant system intended for both anterior and posterior spinal fixation for fracture, scoliosis, tumor, and grade 3 and 4 spondylolisthesis.

If one of the indications for use is new (i.e., a use that has not been cleared), the applicant should consider submitting a separate 510(k) for the new use because it will likely include clinical data and the review may take longer than the review for the other indications for use. Additionally, devices with different indications for use in multiple medical specialties, which would require reviews by different divisions, should have separate submissions.

8. Can I bundle multiple indications for use for a device in one PMA?

You generally should not bundle multiple indications for use in one PMA because each indication is usually supported by a clinical study that requires significant review resources. Bundling multiple indications in one PMA might be appropriate, however, if much of the data needed to support approval of the indications would be the same (e.g., the same clinical data). For example, CDRH has permitted bundling of multiple indications for use in a single PMA for cardiac ablation catheters when all the indications were supported by the same clinical data.[6]

9. Can I bundle a 510(k) device with a PMA device in a single submission?

You generally should not bundle PMA and 510(k) devices in a PMA. There are some exceptions, however, for devices that are used together in a single procedure or that are part of a system. In those instances, bundling the PMA and 510(k) devices in a single PMA submission might be appropriate. For instance, if a Class II special surgical instrument is used to implant a Class III device subject to premarket approval, such as a pacing lead, it may be appropriate to bundle both devices in a PMA. Additionally, a digital mammography system is frequently bundled with its printer. If a 510(k) device and a PMA device are bundled in a single submission, the PMA user fee and review timeframe will apply.

10. Can I bundle changes that affect multiple devices of the same or differing generic types?

You may submit one application when a change affects multiple devices of the same or differing generic types if the impact of the change on each of the devices can be efficiently assessed during

[6] Please refer to the guidance entitled, "Cardiac Ablation Catheters Generic Arrhythmia Indications for Use; Guidance for Industry," which may be found on CDRH's website at: http://www.fda.gov/cdrh/ode/guidance/1382.html.

one review. You should consider the complexity of device design, technological characteristics, and the modifications/changes being made to the existing devices.

Examples of when bundling might be appropriate for changes affecting multiple devices of the *same* generic type include:

- Bundling a change from one polyethelene (material) in various hip acetabular cups to another highly crosslinked polyethelene (material) in a single 510(k) submission.

- Bundling when a contact lens manufacturer proposes the addition of a color additive to a line of its contact lenses (i.e., lenses of differing materials and/or configurations), where the color additive has been listed or certified for that use.

- Bundling a change to a pacemaker programmer where the programmer is used for several types of pacemakers. Even though the change would affect several PMAs, only one PMA submission need be made.

Examples of when bundling might be appropriate for changes affecting multiple devices of *differing* generic types include:

- Bundling in a single 510(k) submission a change that involves the addition of a heparin coating to various cardiopulmonary bypass devices, such as an arterial line blood filter and pump tubing.

- Bundling in a single PMA submission changes that involve a manufacturing facility or a manufacturing process where the same equipment and closely related processes are used for all the devices in the submission. For example, if a manufacturer makes a material for two products using the same equipment and closely related processes, one PMA supplement may be submitted in support of the process change affecting both products.

- Bundling in a single PMA submission changes in sterilization (e.g., a change from ethylene oxide sterilization to radiation sterilization or a change in sterilization release method), where the scientific evidence provided is valid for all devices referenced.

- Bundling certain labeling changes in either a 510(k) or PMA submission. For example, a labeling change to multiple devices of differing generic types may be bundled in a single 510(k) or PMA submission when the labeling change involves a change to the packaging of the devices, such as new instructions for opening the package.

A change that affects multiple devices that are reviewed by different divisions may be appropriate for bundling if the change can be reviewed during one review. For example, a software change to a

stimulator that has gastric and neural indications could be bundled even though the original PMAs were reviewed by different divisions.

Finally, there are some instances when you may bundle a change that affects a device that has both a 510(k) and a PMA indication. For example, it may be appropriate to bundle a software change to a lithotripter that has a 510(k) indication (kidney stones) and a PMA indication (tennis elbow) if the change can be assessed during one review.

11. Can I bundle reprocessed single-use devices (SUDs) in a single submission?

MDUFMA amended the act to provide new regulatory requirements for reprocessed SUDs (MDUFMA § 302). One of these requirements is the submission of validation data in 510(k)s for certain reprocessed SUDs. The validation data submitted must demonstrate that these SUDs will remain substantially equivalent to their predicate devices after the maximum number of times the device is reprocessed as intended by the person submitting the premarket notification (MDUFMA § 302(b), the act § 510(o)). The validation data to be submitted include cleaning, sterilization, and functional performance data.

Although some aspects of the validation process may be common to various reprocessed SUDs (e.g., SUDs of the same generic type), the designs of these SUDs may be unique (e.g., different original equipment manufacturers (OEMs)). If the SUDs are within the same generic type and have the same OEM, the validation data may apply equally to each of the SUDs, and a single 510(k) would likely be appropriate. If the SUDs were produced by different OEMs, however, the reprocessor should explain how the submitted data apply to all the devices in the submission and only bundle those SUDs that can be reviewed together.

In addition, reprocessors generally should not bundle differing generic device types in one submission because different data requirements will typically apply. For example, a reprocessor should not bundle catheters and compression limb sleeves in a single 510(k).

For additional information on MDUFMA's validation data requirements for reprocessed SUDs requiring 510(k) clearance, please refer to the guidance entitled, "Medical Device User Fee and Modernization Act of 2002, Validation Data in Premarket Notification Submissions [510(k)s] for Reprocessed Single-Use Medical Devices."[7]

MDUFMA also requires the submission of validation data for reprocessed SUDs subject to premarket approval requirements. The data must demonstrate that the reasonable assurance of the safety and effectiveness of the reprocessed SUD will remain after the maximum number of times the device is reprocessed as intended by the person making the premarket submission (MDUFMA §

[7] This guidance may be found on CDRH's website at: http://www.fda.gov/cdrh/ode/guidance/1216.html.

302(c)(2)), the act § 515(c)(2)). The validation data and other data required to support the premarket submission, in this case, a "premarket report," requires significant review. Thus, it may be inappropriate to bundle reprocessed SUDs across multiple OEMs because the design, etc., of each of the SUDs may be unique and require significant review resources. If, however, multiple individual submissions would contain substantially the same pre-clinical and clinical information, then it may be appropriate to submit a single premarket report for these reprocessed SUDs across multiple OEMs. The reprocessor may contact the relevant review division to discuss whether bundling in a specific situation might be appropriate.

C. In Vitro Diagnostic Devices

12. Are there specific considerations for in vitro diagnostic devices?

Yes. For in vitro diagnostic devices, FDA recommends that you consider the points below. If, after reading this guidance, you are still unsure as to whether it is appropriate to bundle, we encourage you to discuss the issue with the responsible review division.

Multiple Analytes

You generally may bundle in a single submission multiple analytes (e.g., recognized test panels or profiles) or instruments when the same analytical and clinical data can be used for all the analytes/instruments referenced. (Recognized test panels or profiles can be found through the Centers for Medicare and Medicaid Services (CMS) reimbursement national coverage book and include profiles such as lipid profiles and liver function tests.) You should not bundle multiple analytes, or across test panels or profiles, if they present disparate scientific and clinical issues. Bundling of multiple analytes is routinely done, and is generally recognized and utilized, in premarket submissions.

For example, although antimicrobial susceptibility testing (AST) systems should include only one drug, you may bundle gram-negative and gram-positive uses, as well as different methods for reading the results (e.g., semi-automated, fully automated, or inoculation (direct, growth, other)).

Two other examples of panels that could be bundled into one submission include:

(1) TORCH (Toxoplasma, Rubella, CMV, and Herpes) panel

(2) Drugs of abuse (cocaine, THC, opiates, methamphetamine, and amphetamine) panel

For any type of premarket submission, assayed controls and/or calibrators may be bundled with an assay. Also, controls or calibrators used for multiple assays (and/or multiple platforms) may be bundled to cover their use in all of the assays.

Multiple Reagents

You may bundle multiple reagents that are intended to be used together to obtain a profile (e.g., to obtain a donor or patient blood group phenotype, or a cardiac panel (tryponin, CK MB, and myoglobin)) into a single submission. Whereas a single reagent could be submitted as a single submission, there are situations where multiple reagents have many commonalities, and the additional information to support each of the reagents is minor and does not require substantial review resources. These multiple reagents may be bundled. Reagents generally should not be bundled if the reagents require separate preclinical data, clinical data, or downstream processing information that would preclude efficient review of the submission. Although CBER accepts separate submissions for individual reagents, CBER would consider the applicant's designation of these separate submissions meeting the above criteria as a bundle for purposes of review and user fee payment.

Multiple Intended Uses

You generally should not bundle multiple intended uses of a single test system (or indications for use such as professional and over-the-counter (OTC) use), because it is unlikely that such multiple uses would be supported by the same studies.

There may be cases, however, when you could bundle different intended uses. For example, you may not bundle assays intended for the detection of *Neisseria menigitidis*, and *Neisseria gonorrhoea*, but you may bundle *N. gonorrhoea* and *Chlamydia trachomatis* if the same clinical trial using the same specimen type and same population are used.

Sample Matrix

Bundling when similar matrices (e.g., serum and plasma) are used generally should be appropriate. You should not bundle dissimilar sample matrices (e.g., hair and/or saliva with serum and/or plasma), because the information for review would be expected to be substantially different. For example, a *Helicobacter pylori* assay indicated for use with serum, plasma, and/or finger-stick capillary blood may be bundled. However, a *H. pylori* breath test or a saliva test may not be bundled with a *H. pylori* assay using plasma or serum.

Replacement Reagent

The replacement reagent 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.

Process for Multiple Markers that Require a PMA

For a PMA submission where one analyte (e.g., hepatitis B virus) may have multiple markers (e.g., HBsAg, anti-HBc, HBe, anti-HBs, anti-HBcIgM, anti-HBe), the first marker may be submitted as an original PMA. After the original PMA is approved, the other markers may then be submitted as individual 180-day PMA supplements to the original PMA. All data should be generated from the same clinical trial. In the past, all the different markers were reviewed as original PMAs. While this is not a true bundling issue, this issue has been raised numerous times in bundling discussions with industry and is therefore being included in this guidance. The same logic for hepatitis B above may also apply to the processing of other assays such as prostate-specific antigen (PSA). For example, rather than submitting Total PSA, Free PSA, and Complexed PSA assays as separate original PMAs, it may be appropriate to submit one original PMA and two 180-day PMA supplements.

In Vitro Diagnostic Devices Regulated by CBER

As with devices reviewed by CDRH, some devices reviewed at CBER are marketed as 510(k) products, while others are marketed as PMA products. These products are subject to the procedures discussed in this document. Instruments used to test the blood supply are regulated as either 510(k) devices or PMA devices. Reagents and test kits used to test the blood supply are regulated as licensed biological products. When the reagents and instruments can be used together and significant portions of multiple individual submissions would contain the same information, you may bundle the submission for the different articles, even though one article is regulated under the device authorities and the other under the BLA authorities. The BLA user fee and review time would apply when making such a submission. Please identify the submissions to be bundled in the cover letter submitted with the applications.

In cases involving a BLA or efficacy supplement where one submission in a bundle is delaying approval of the others, CBER may discuss mechanisms for "de-linking" the problem submission so that the others can be finalized. The remaining portion of the bundle would be handled at a later date and the labeling would be revised to include the additional reagent. These cases primarily involve immunohematology reagents. For example, ABO/Rh blood grouping reagents that use the same clinical data set and the same labeling can be considered for bundling. If the ABO reagents are ready for approval, but the Anti-D reagent has a few issues remaining, CBER would consider allowing the applicant to revise the labeling to delete the references to Anti-D and approve only the ABO reagents. Upon subsequent approval of the Anti-D reagent, the labeling could be revised to include the references to Anti-D.

D. Bundling Procedures

13. How do I bundle multiple devices or indications for use in a single submission?

FDA recommends the following when:

- **Bundling in a 510(k) the same or differing generic device types or multiple indications for use for a single device**

  As is true for any 510(k), you must provide all the information required by 21 CFR § 807.87. Therefore, the submission should include the appropriate supporting information for each of the different devices or indications for use. You should also include an "Indications for Use" form for each device in the submission, if individual devices will have differing indications for use.

- **Bundling in one 510(k) a change that affects more than one previously cleared device**

  When submitting one 510(k) for a change that affects multiple devices, you should refer to the other previously cleared 510(k)s. Like all 510(k)s, the 510(k) must provide all the information required under 21 CFR § 807.87. You should also provide updated Indications for Use forms that address all the devices in the submission, if individual devices will have differing indications for use.

- **Bundling in one PMA multiple devices of the same generic device type or multiple indications for use for a single device**

  When bundling devices of the same generic type in a PMA, you should ensure that you provide all the information required by 21 CFR § 814.20 to support approval for each of the devices, including labeling that addresses all of the devices.

  As stated earlier in this guidance, bundling multiple indications for use in one PMA is generally not appropriate. If, however, much of the data needed to support approval of the devices would be the same (e.g., clinical data), you may submit one PMA for multiple indications. You should ensure that the supporting information and the labeling address all the indications.

- **Bundling in one PMA supplement a change that affects multiple PMAs**

  When bundling a change(s) that affects more than one PMA, you may submit all the required information to support approval of the modification, including any associated labeling changes that result from the modification, in one PMA supplement. In the cover letter for the supplement, you should identify the other affected PMA(s).

  If the affected PMAs are reviewed by different divisions, you may still be able to bundle the change(s) in one PMA supplement. In this situation, you should submit a complete copy of the supplement to each PMA, so that each division has its own copy. The same cover letter should be used for each copy and should clearly indicate that the same change(s) is being made to each of the affected PMA(s). The cover letter should identify all of the affected PMA(s).

- **Bundling a change that affects a device with 510(k) and PMA indications**

  When submitting a change to a device that affects both a previously cleared 510(k) and an approved PMA, you should submit a PMA supplement and reference the cleared 510(k). In this situation, the PMA review time and user fee would apply for the submission.

- **Bundling a 510(k) device and a PMA device in one PMA**

  As stated above, in general, a 510(k) device should not be bundled with a PMA device. If, however, you have devices that are used together in a procedure or that are part of a system, bundling may be appropriate. In such a case, the PMA should include all the information needed to support both approval and clearance of the devices when used as indicated. As above, the PMA review time and user fee would apply for the submission.

14. What will FDA do if devices or indications are bundled inappropriately?

If a submission includes a device or indication that should not be bundled because it presents disparate scientific/clinical or regulatory issues (from the other devices or indications in the submission), the agency will notify the applicant in writing and request that the applicant withdraw the device or indication from the bundled submission. Upon issuance of this letter, the application will be placed on hold. The applicant may resubmit the device or indication for use in a separate submission, withdraw the device or indication for use (the review of the rest of the submission will continue), withdraw the entire application, or appeal the decision. See related information in question 15.

15. How can I appeal an FDA determination that it is not appropriate to bundle a device or indication for use in a single application?

You should refer to 21 CFR § 10.75, which outlines the framework for internal review of decisions. Additionally, FDA intends to provide specific recommendations and procedures regarding appeals related to user fees in a future guidance document. While the appeal is under review, the submission will remain on hold (to ensure appropriate review of the submission and efficient use of resources).

16. Can I add more devices or indications for use to a submission once the review of that submission has begun?

FDA strongly recommends that bundling occur before the application is submitted to the agency.

17. Can I withdraw a device or indication for use from my premarket submission, for example, because the review of that device or indication for use is slowing down the review of the others?

Yes. Submitters may withdraw a device(s) (or indication for use) from a bundled submission for any reason. You may resubmit the device(s) or indication for use in a new application. Resubmission of a premarket submission for a withdrawn device or indication for use will require payment of the fee applicable to the type of submission.

18. How can I get information on the appropriateness of bundling certain devices or indications for use before submitting a marketing application?

The persons listed below can assist you with general bundling questions. For specific questions about bundling certain types of devices or indications for use, you should contact the branch chief in the appropriate review division.

Robert Gatling
Program Operations Staff
ODE, CDRH
301-594-1190, ext. 140 or by email to RRG@CDRH.FDA.GOV

Sousan Altaie
OIVD, CDRH
301-594-3084, ext. 145 or by email to SSA@CDRH.FDA.GOV

Sheryl Kochman
CBER 301-827-6123 or by email to KOCHMAN@CBER.FDA.GOV