Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA

DRAFT GUIDANCE

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For questions regarding this draft document contact the Office of Combination Products, Office of Special Medical Programs in the Office of the Commissioner, Dr. Patricia Love, 301-796-8933 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products
Office of Special Medical Programs
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Draft — Not for Implementation

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U.S. Department of Health and Human Services
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Office of the Commissioner

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Guidance for Industry and FDA Staff:[1] Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA (Draft)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

This document provides guidance to industry and FDA staff on the underlying principles to determine the type of marketing submission that may be required for postapproval changes to a combination product, as defined in 21 CFR 3.2(e), that is approved under one marketing application, i.e., a biologics license application (BLA), a new drug application (NDA), or a device premarket approval application (PMA).

This guidance supplements existing guidance documents developed by the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Office of Combination Products (OCP).

This guidance does not address changes to combination products that are not approved under a BLA, NDA or PMA (e.g., those cleared solely under a device premarket notification submission[2] or those marketed under an over-the-counter drug monograph[3]). Nor does this guidance address changes to combination products that were approved under more than one marketing application. Further, while this guidance does address the type of submission to provide when making a change to a constituent part of a combination product approved under one marketing application, it does not address the scientific or technical content to provide in any such submission.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory

[1] This guidance has been prepared by the Office of Combination Products (OCP) in the Office of Special Medical Programs, Office of the Commissioner, in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.
[2] Device premarket notification submissions are also referred to as 510(k) submissions.
[3] See 21 CFR Part 330.

requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

As defined in 21 CFR 3.2(e), a combination product is a product comprised of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.[4] Under Section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a combination product is assigned to a center (CBER, CDER, or CDRH) with primary jurisdiction (the lead center) for premarket review and postmarket regulation. The lead center assignment is based on a determination of the primary mode of action (PMOA) of the combination product or other defined regulatory criteria when the PMOA cannot be determined with reasonable certainty.[5] Regardless of center assignment, in most instances FDA may regulate the entire combination product under one type of marketing application (e.g., one BLA, NDA, or PMA).[6] This one application would include all necessary information to support the approval of the combination product as a whole, including each of its constituent parts (drug, device, and/or biological product).[7]

For a combination product that is approved under one application, there may be uncertainty on the part of the application holder in determining the appropriate regulatory pathway for submitting a postmarket submission for a change to a constituent part or to the combination product as a whole.[8] The FD&C Act,[9] the Public Health Service Act (PHS Act),[10] and FDA's associated regulations[11] contain provisions describing when a

[4] *Combination product* includes: (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed; e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect. 21 CFR 3.2(e).

[5] 21 CFR 3.2(m) and 3.4(a), (b). See also Final Rule for *Definition of Primary Mode of Action of a Combination Product*, published August 25, 2005, 70 Fed. Reg. 49848, accessible at http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.pdf.

[6] In some instances FDA may require two or more marketing applications for a combination product. 21 CFR 3.4(c). Further, as appropriate, FDA may accept two marketing applications upon request by the applicant(s).

[7] See Section 503(g)(2) of the FD&C Act.

[8] For purposes of this document, changes to the combination product are assumed to not affect the primary mode of action, the lead center assignment or the underlying type of marketing application for the combination product.

[9] Sections 505, 506A, and 515(d) of the FD&C Act.

[10] Section 351 of the PHS Act.

postmarket submission is required for a change to an approved, stand-alone[12] drug, device, or biological product or its manufacturing process.[13] As a general matter, these provisions set forth similar criteria for determining when a postapproval submission is required; e.g., a prior approval submission is generally required for a product change that could affect safety or effectiveness.[14] These provisions do not, however, expressly address the criteria for when, how, and what type of submission to submit for a change to a constituent part of an approved combination product. The intent of this guidance document is to provide clarity in the postapproval change requirements and consistency in the type of postmarket submission to provide for a change to a combination product approved under one application (BLA, NDA, or PMA), regardless of which agency center has lead jurisdiction for the combination product.

III. WHAT TYPE OF SUBMISSION TO PROVIDE WHEN MAKING A CHANGE TO AN APPROVED COMBINATION PRODUCT?

As stated above, a combination product is comprised of different constituent parts. These constituent parts retain their regulatory identity as a drug, device or biological product. Therefore, if a change is made to any constituent part of the combination product that would have required a postmarket submission to FDA if the constituent part were a stand-alone product, then a postmarket submission is required for the combination product. In addition, a postmarket submission would also be required for the combination product if a change to any of the constituent parts would otherwise trigger the requirements associated with the application type used for approval of the combination product. In cases where the regulatory identity of the constituent part differs from the approved application type for the combination product, and a change is made that would require a postmarket submission to FDA, the requirement for submitting information about the change to the agency is generally satisfied with one postmarket submission to the original application. The type of submission to provide for the change will depend on the type of application used to obtain approval of the combination product. For example, a change to the device constituent part of a combination product approved under an NDA should be reflected in the appropriate postmarket NDA submission and be submitted to that NDA. In some cases, it may be easier to first identify the type of submission typically associated with the constituent part before determining what type of submission is required to the original application that was used for approval of the combination product. To aid in this determination, tables are provided in this document to generally align the corresponding postmarket submissions for changes to a constituent part of a combination product approved under a BLA, NDA, or PMA.

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[11] 21 CFR 314.70, 601.12, and 814.39.

[12] For purposes of this document, the term "stand-alone" refers to an individual drug, device, or biological product that is not part of a combination product.

[13] The types of submissions describing a change to an approved product include, but are not limited to, a new original application, a prior approval supplement, a changes being effected supplement, and an annual or periodic report.

[14] For purposes of this document, the term change or modification is used interchangeably to apply to a postapproval or postmarket change to an approved application or approved product.

The following steps outline the process for determining which type of submission to provide for a postmarket change to a constituent part of a combination product approved under a BLA, NDA, or PMA.

1. Identify the type of premarket application used to obtain approval of the combination product (NDA, BLA, or PMA).

2. Identify the type of postapproval submission that ordinarily would have been submitted for the modification(s), if the constituent part(s) were marketed as a stand-alone product. For a device constituent part, apply the appropriate device criteria in determining what type of submission to FDA would ordinarily have been submitted because of a change to the device constituent part.[15] For a biological product or drug constituent part, apply the appropriate biological product and drug criteria, respectively.

3. If the original application type used for approval of the combination product (step 1 above) is the same as that customarily used for the constituent part being changed, then submit the postapproval submission identified in step 2. If not, then proceed to step 4.

4. Use the tables below as guidance in determining the appropriate postapproval change submission type for the combination product. The tables correlate the submission type typically used for the changed constituent part as identified in step 2 with the appropriate submission type for the combination product based on the original application under which the combination product was approved.

Table 1, page 6 identifies the types of NDA or BLA submissions to submit when making a change to a device constituent part of a combination product approved under an NDA or BLA. Column 1 identifies the type of PMA submission that would customarily be submitted for a change in the device constituent part if it were a stand-alone device approved under a PMA.[16] Column 2 identifies the types of NDA or BLA submissions to submit for the change in the device constituent part of the combination product.[17]

Table 2, page 7 identifies the types of PMA submissions to submit when making a change to a biological product/drug constituent part of a combination product approved under a PMA. Column 1 provides information on both BLA and NDA submissions. Specifically, it identifies the types of NDA submissions that would customarily be

[15] For example, if the stent material of a PMA-approved drug eluting stent is changed, determine whether such a change would require a real-time PMA supplement, a 180-day PMA supplement, a panel-track PMA supplement, or an original PMA.

[16] See sections 515 and 737 of the FD&C Act, 21 CFR 814.39, and FDA Guidance for *Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process* (2008), at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf).

[17] This document does not address combination products approved with an ANDA under Section 505(j) of the FD&C Act. For such products, applicants should consider whether a postmarket change to a device constituent part would be permissible under the ANDA.

submitted for a change if the drug constituent part were a stand-alone drug approved under an NDA.[18] It also identifies the types of BLA submissions that would customarily be submitted for a change to the biological product constituent part if it were a stand-alone biological product licensed under a BLA.[19] Column 2 identifies the types of PMA submissions to submit when the change is in the biological product/drug constituent part of a combination product approved under a PMA.

To use these tables, first refer to relevant provisions in the FD&C Act, FDA regulations, and FDA guidance on the type of postmarket change being made to the constituent part to help you determine the type of submission ordinarily required for such a change. For a list of potentially applicable guidance documents, see Section VI of this document. You can then use the tables to identify the type of corresponding submission to provide for the combination product.

(Continue to next page)

[18] See FD&C Act Section 505, 21 CFR 314.70, and FDA Guidance for *Changes to an Approved NDA or ANDA* (2004), at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf). Also, see FDA Guidance for *Contents of a Complete Submission for the Evaluation of Proprietary Names* (2010), at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

[19] See 21 CFR 601.12 and FDA Guidance for *Changes to an Approved Application: Biological Products* (1997), at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM170166.pdf.

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Table 1: Type of NDA/BLA Submission for a Change in a Device Constituent Part of a Combination Product Approved under an NDA/BLA		
If the Device Constituent Part Were a Stand-Alone Device Approved under a PMA and the Change Would Have Required the Following Submission		**Then Submit Information on the Device Change Using This Type of NDA/BLA* Submission for the Combination Product**
PMA Original		**NDA/BLA Original**
PMA Panel-Track Supplement (New indication/population, without any other change to the constituent parts, supported by new clinical data and the original preclinical data)		**Prior Approval Supplement (Efficacy)**
PMA 180-day Supplement • Design • Manufacturing site change • Labeling change including nomenclature (And with a change from the next column)	Design change and labeling change supported by new preclinical and/or limited confirmatory clinical data	**Prior Approval Supplement (Efficacy)**
	Changes supported by limited confirmatory data (i.e., clinical bioequivalence or bioavailability data)	**Prior Approval Supplement (Manufacturing)** (With or without labeling changes)
	Manufacturing site change not requiring any clinical data	
	Significant labeling change that does not qualify for a Special PMA Supplement - Changes Being Effected, does not change the indication, and does not include a design change	**Prior Approval Supplement (Labeling)**
PMA Real-Time Supplement (Design or labeling change that does not require clinical data and for which the data provided fall within only one scientific discipline, e.g., electrical engineering, microbiology, or sterilization)		**Prior Approval Supplement (Manufacturing or Labeling)**
30-day Notice (Manufacturing process or method change only)		**30-day Changes Being Effected**
Special PMA Supplement - Changes Being Effected		**Changes Being Effected**
PMA Periodic Report		**Annual Report**
***Time lines and FDA-industry interactive procedures will be those of the NDA/BLA**		

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Table 2: Type of PMA Submission for a Change in a Biological Product/Drug Constituent Part of a Combination Product Approved under a PMA		
If the Biological Product/Drug Constituent Part Were a Stand-Alone Biological Product/Drug Approved under a BLA/NDA and the Change Would Have Required the Following Submission		**Then Submit Information on the Biological Product/Drug Change Using This Type of PMA* Submission for the Combination Product**
BLA Original; NDA Original (Section 505(b)(1) or (b)(2)) (New biological product, new drug, or new formulation with new clinical data and new preclinical data)		**PMA Original**
Prior Approval Supplement – Efficacy	New indication/population, without any other change to the constituent parts, supported by new clinical data and the original preclinical data	**Panel-Track Supplement**
	Same indication with manufacturing change in drug/biological product requiring clinical data	**180-day Supplement**
Prior Approval Supplement – Manufacturing	Drug/biological product manufacturing change requiring only bioequivalence or bioavailability clinical data	**180-day Supplement**
	Drug/biological product manufacturing and related labeling change that does not require any type of clinical or preclinical (animal) data	**180-day Supplement or Real-Time Supplement (depending on amount and complexity of data)**
Prior Approval Supplement – Labeling (When the labeling change does not rely on a clinical trial and is not related to a manufacturing change)		**180-day Supplement or Real-Time Supplement (depending on amount and complexity of data)**
30-day Changes Being Effected (Manufacturing process or method change only)		**PMA 30-day Notice**
Changes Being Effected (Manufacturing or Labeling)		**Special PMA Supplement - Changes Being Effected**
Annual Report		**PMA Periodic Report**
***Time lines and FDA-industry interactive procedures will be those of the PMA**		

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IV. ILLUSTRATIONS BY TYPE OF CHANGE BEING MADE

This section provides examples of some of the more significant changes that may be made to constituent parts of a combination product (i.e., changes that may require prior approval from FDA). The types of submissions that such changes may require, depending upon the submission type used to obtain approval of the combination product, are identified. These recommendations are based on relevant statutory and regulatory provisions as well as relevant CDER, CDRH, and CBER guidance documents (see Section VI of this document).

1. Certain changes in the combination product device constituent part (e.g., those that result in a combination product new indication for use, new clinical effects, or in a modified analyte and indication/patient population for an *in vitro* diagnostic) customarily require new preclinical and clinical data to provide support for safety and effectiveness.[20] Generally, for any such changes that do not affect the primary mode of action, select the submission type to match the application type used to obtain approval of the combination product:

    a. PMA Original[21]
    b. NDA Original[22]
    c. BLA Original

2. Changes in the drug constituent part substance, drug constituent part production process, quality controls, equipment, or facilities that affect controlled release or drug particle size or have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug constituent part.[23] Such changes include those that may affect the sterility assurance of the drug constituent part, such as process changes for sterile drug substances and sterile packaging components.[24] Generally, for any such change, select the submission type to match the application type used to obtain approval of the combination product:

    a. NDA Prior Approval Supplement

[20] In some instances the change in the device constituent part may result in a new combination product.

[21] Ordinarily, changes to a device that require new preclinical and clinical data are submitted in an original PMA as explained in FDA guidance. FDA Guidance, *Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process* (2008) (see Section IV.A), at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf.

[22] For more information on the type of original NDA submissions, you may wish to refer to the FDA Draft Guidance, *Applications Covered by Section 505(b)(2)*, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf.

[23] 21 CFR 314.70(b).

[24] FDA Guidance, *Changes to an Approved NDA or ANDA* (2004) (see Section VII.B), at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf.

b. BLA Prior Approval Supplement
c. PMA 180-day Supplement

3. Modified chemical formulation of the device constituent part (not a chemical that would be considered a drug constituent part of the combination product), hardware or software modification of the device constituent part, or other design modification to the device constituent part (without also changing the indication or patient population) for which only new preclinical testing and/or limited confirmatory clinical data are necessary to demonstrate reasonable assurance of safety and effectiveness of the modified device constituent part.[25] Generally, for any such change, select the submission type to match the application type used to obtain approval for the combination product:

    a. PMA 180-day Supplement
    b. BLA Prior Approval Supplement
    c. NDA Prior Approval Supplement

4. Changes in the biological product constituent part, production process, quality controls, equipment, facilities, or responsible personnel that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product.[26] Generally, for any such change, select the submission type to match the application type used to obtain approval for the combination product:

    a. BLA Prior Approval Supplement
    b. NDA Prior Approval Supplement
    c. PMA 180-day Supplement

5. Changes in indication or in patient population (without any other change to the combination product itself or to any constituent part, except for relevant changes to the labeling) that require substantial clinical data to provide reasonable assurance of safety and effectiveness for the change but either no or very limited new preclinical testing. Generally, for any such change, select the submission type to match the application type used to obtain approval for the combination product:

    a. PMA Panel-Track[27]

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[25] See Section 737(4)(C) of the FD&C Act and 21 CFR 814.39(a)(6); see also FDA Guidance, *Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process* (2008) (see Section IV.C), at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf.

[26] 21 CFR 601.12(b).

[27] See Section 737(4)(B) of the FD&C Act and 21 CFR 814.39(a)(1); see also FDA Guidance, *Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process* (2008) (see Section IV.B), at

b. NDA Prior Approval Supplement
c. BLA Prior Approval Supplement

The preceding tables and illustrations provide correlations between NDA, BLA, and PMA submissions for a change to a single constituent part of a combination product approved under a single application. When changes are made to multiple constituent parts, the recommendations in Section III, above, still apply for each change. If the applicable submission requirements for each change do not match (e.g., one change requires a prior approval supplement and another requires a changes being effected supplement), then the type of submission should be that associated with the most significant change being submitted. For example, a manufacturer of a drug eluting stent approved under a PMA would like to modify the design of the stent and delete a test for the drug to comply with an official compendium that is consistent with FDA statutory and regulatory requirements. In isolation, the change in the design of the stent would generally require the submission of a PMA 180-day supplement, whereas the change in the test to comply with an official compendium for the drug would generally be submitted in an NDA Changes Being Effected-30 day supplement. In this case, when submitted together, the manufacturer should submit the PMA 180-day supplement for both changes.

FDA cautions that this document provides information only on the type of submission that should be made by the application holder when making a change to a constituent part of a combination product approved under a BLA, NDA, or PMA. It does not address the type and amount of information to include in each submission. Finally, FDA reminds industry that the recommendations in this guidance document do not affect other requirements that may apply to the application type used to obtain approval of a particular combination product.

V. HOW CAN I DISCUSS MY OPTIONS WITH FDA?

FDA recognizes that this guidance provides general recommendations and that the tables provided above are intended as useful tools, but may not provide the applicable correlation in all cases. There may be added complexity based on certain types of combination products. Further, FDA recognizes that it may not be possible to isolate the change of one constituent part from another constituent part (e.g., those meeting the definition in 21 CFR 3.2(e)(1) or if one constituent part activates or changes the other constituent part). FDA encourages applicants to anticipate the type of postapproval changes that they wish to make and to develop protocols to help establish comparability of the modifications in methodology or products to the original approved combination product. Further, FDA encourages industry to discuss with FDA the type of information that may be necessary to address the change to the constituent part, including whether and how this change may affect the other constituent part(s) and the combination product

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http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf.

as a whole; and any alternative approaches for submission types the applicant may propose.

To discuss possible postmarket changes to combination products, as well as the type of information and type of submission to provide to FDA, applicants should request a meeting with the intercenter review team. The meeting request should be sent to the lead center that approved the original application, with a cover letter requesting inclusion of representatives from the consulting center(s). OCP may attend such a meeting as well. The meeting request should include background material to support any proposed approach.

VI. WHERE CAN I OBTAIN ADDITIONAL INFORMATION?

OCP is available as a resource to industry and FDA review staff throughout the lifecycle (assignment, development, premarket review and postmarket regulation) of a combination product. OCP can be reached at (301) 427-1934 or by email at combination@fda.gov. In addition, OCP maintains an updated list of FDA guidance documents that industry may find helpful in the development of their products. The list is available at OCP's Internet Website at http://www.fda.gov/CombinationProducts/default.htm. Each center also maintains a webpage for guidance documents and information on the types of submissions addressed in this guidance document.

In considering possible changes to constituent parts and their potential to affect the safety and effectiveness of the approved combination product, the following FDA webpages may be useful. These webpages include information on requesting meetings with FDA:

- BLA Therapeutic Biologic Applications; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm

- NDA webpage; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm

- PMA webpage; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm

- BLA webpage; http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/default.htm

- Drug and Therapeutic Biologic Labeling website; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

- PDUFA reauthorization performance Goals and Procedures Fiscal Years 2012 through 2017; http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

- FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals, October 15, 2012; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089733.htm

In addition, the following FDA guidance documents, which focus on postmarket modifications to regulated articles, may help applicants in assessing which type of postapproval submission is typically required for various types of changes and may be helpful when applying Tables 1 and 2 of this document:

- *Changes to an Approved Application: Biological Products;* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM170166.pdf

- *Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process* (2008); http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf

- *Real-Time Premarket Approval Application (PMA) Supplements* (2006); http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089612.pdf

- *30-day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes (2011);* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf

- *Changes to an Approved NDA or ANDA* (2004)*;* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf

- *Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture* (2001)*;* http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076729.htm

- *Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products* (1996); http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm

- *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (1997); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM124805.pdf

- *Q10 Pharmaceutical Quality System* (2009); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073517.pdf

- *Q8, Q9, and Q10 Questions and Answers(R4)* (2010); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM210822.pdf

- *Cooperative Manufacturing Arrangements for Licensed Biologics* (2008); http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM069908.pdf

Finally, applicants may refer to the following FDA draft guidance documents for additional information. When finalized, these will provide FDA policy on these subjects.

- *CMC Postapproval Manufacturing Changes Reportable in Annual Reports; (Draft* 2010); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM217043.pdf

- *Annual Reports for Approved Premarket Approval Applications (PMA) (Draft* 2006); http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089398.pdf

- *Public Availability of Labeling Changes in "Changes Being Effected" Supplements (Draft* 2006); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075091.pdf