

**GUIDELINE FOR THE DEVELOPMENT
OF
TYPE III DRUG MASTER FILES (DMFs)**

The Society of the Plastics Industry, Inc.

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Preamble

This manual has been prepared for suppliers of packaging materials for drug products as a guide to the regulatory considerations and procedures to be taken into account when establishing a Type III Drug Master File (DMF). It should be recognized that this publication is limited to a brief discussion of new drug regulation and general principles on the preparation of DMFs. In specific cases, consultation with competent technical and legal advisors is well advised.

Disclaimer

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SPI does not endorse the proprietary products or processes of any manufacturer. Consult the product manufacturers for specific information. In all cases, the instructions of manufacturers and suppliers must be followed.

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I. Introduction

By necessity, and for the common good, the pharmaceutical industry is closely regulated. Suppliers to the pharmaceutical industry should be knowledgeable about the regulatory requirements to which the industry and their customers are subject. The main purpose of this manual is (1) to provide general information on the regulatory scheme applicable to packaging materials for new drugs, (2) to provide information on how to prepare a Drug Master File (DMF) for materials used in drug packaging applications, (3) to explain those regulatory considerations that limit the ability of drug manufacturers to change suppliers of their packaging materials and of packaging manufacturers to alter the materials or manufacturing processes used in the production of their products, and (4) to provide practical advice on maintaining, transferring, and closing DMFs.

An exhaustive discussion of the finer points of drug regulation is beyond the scope of this manual; however, an understanding of the basics of the regulatory process is essential to placing the respective roles of the supplier of plastics for drug packaging and its customer into perspective. In this regard, a little history is always helpful in understanding the present.

Until the late 1930s, direct regulatory considerations probably played little, if any, role in a drug manufacturer's selection process. Until 1938, "preclearance" requirements for drugs were minimal, and the Food and Drug Administration (FDA) typically did not move against a drug company unless the Agency could prove that the company was selling dangerous, adulterated, contaminated, or mislabeled products. This situation changed somewhat with the passage of the Federal Food, Drug, and Cosmetic Act (the Act) in 1938. When this law was passed, FDA premarket approval became a requirement for "new drugs." Nevertheless, between 1938 and 1962, relatively little attention was focused on drug packaging materials, *per se*.

The emphasis changed considerably with the Drug Amendments of 1962 and the promulgation of regulations by FDA pursuant to these amendments. The Drug Amendments of 1962, for the first time, gave FDA the responsibility of passing on the efficacy, as well as the safety, of every new drug. At the same time, new packaging materials were coming to the fore. The regulations in this area now clearly indicate that, when FDA evaluates a drug, it must be convinced that the package for the specific drug will be satisfactory for preserving the purity, stability, and efficacy of the drug.¹

¹ While FDA has jurisdiction over the regulation of packaging materials that are used to store and ship drugs from the pharmaceutical manufacturer, it is the states that have jurisdiction over the regulation of transfer bottles and other containers that are filled with drugs dispensed at a pharmacy.

II. FDA Product Jurisdiction and Review

A. Definition of a “New Drug”

To fully understand the premarket approval requirements applicable to “new drugs,” one must start with the definition of this term. Under Section 201(p) of the Act, a “new drug” is defined as follows:

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized among [qualified] experts . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a “new drug” if at any time prior to [1938] it was subject to the Food and Drugs Act of 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of use; or

(2) Any drug . . . the composition of which is such that [the] drug as a result of investigations to determine its safety and effectiveness for use under [the intended] conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under [those] conditions.

Federal Food, Drug and Cosmetic Act § 201(p).

The term “old drug,” though not a defined term in the Act, is sometimes used as a shorthand description of any drug that is not a “new drug.” In essence, the term “old drug” is sometimes used to describe a drug for which FDA does not require approval prior to commercial marketing for the intended use as prescribed in its labeling, *e.g.*, an over-the-counter preparation covered by an applicable monograph, or one that was “cleared” prior to the passage of the 1938 law. Because “old drugs” do not require premarket approval, FDA does not review the packaging materials for such drugs and, therefore, FDA does not review DMFs for old drugs.

B. New Drug Manufacturer Responsibilities

As indicated above, all new drugs are subject to FDA pre-market approval; it is the responsibility of the new drug’s manufacturer to demonstrate the safety and effectiveness of its particular product to FDA. The regulations relating to the approval of new drugs require that the application (*e.g.*, the New Drug Application (NDA)) include a description of the manufacturing procedures and in-process controls for the new drug product including all its components, as well as complete details about the drug’s

composition. The application also must include information relating to the packaging of the drug.²

The NDA process is significant to manufacturers of packaging materials because a package may, at least under some circumstances, affect the safety and efficacy of the drug. Accordingly, in preparing an NDA, the drug manufacturer must include adequate data to demonstrate that the package for the particular drug of interest will not in any way affect the safety or efficacy of the drug. In addition, the drug company is restricted to the use of the packaging material that was described and evaluated in the NDA for the specific drug product, unless the drug company provides FDA with information on a new packaging material either through submission of a Supplemental New Drug Application (SNDA) or as part of the drug company's Annual Report to FDA, depending upon the nature of the change. The notification requirements applicable to specific types of changes to packaging materials are discussed in Section IV of this manual.

C. Role of Drug Master Files

Submission to FDA of all information required for an NDA is the responsibility of the drug manufacturer; however, in many cases, information on materials used in the production or packaging of the drug product, such as the formulation of a packaging material, is considered by the supplier to be confidential trade secret information. Consequently, the Drug Master File (DMF) system was developed to permit suppliers to make this information on their products directly available to FDA for its review of drug company applications that involve the use of the supplier's material. SPI's Food Packaging Materials Committee (since renamed the Food, Drug, and Cosmetics

² FDA provides useful guidance for the submission of DMFs on its website, available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFiles/DMFs/default.htm> (last updated 5/11/2012). As noted on this website, FDA also has published an older guidance document addressing in general terms all types of DMFs. See FDA's "Guideline for Drug Master Files," (September 1989). While this guidance also can be useful, some of the information provided therein has been superseded by the information provided on FDA's website, which is routinely updated.

Additional FDA guidance on the supporting information expected on the packaging of a drug product in the Chemistry, Manufacturing, Controls section of a regulatory filing is described in the May 1999 FDA Guidance for Industry: "Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation" (Container Closure Guidance). This is the most comprehensive FDA guidance available for container closure systems for drug products. It details the information that should be submitted to FDA to support the primary container closure system used for specific dosage forms of drugs and biologics. This information includes a description of each component of the container closure system, its respective material(s) of construction, and relevant functional information. Generally, the Container Closure Guidance suggests including more detailed information in a DMF than has been requested traditionally.

Also of relevance, FDA has issued a Manual of Policies and Procedures (MAPP 5015.5) covering reviewer responsibilities for review of Type III DMFs; FDA provides a link to this manual on its DMF website. This manual provides background information on the information typically provided in a Type III DMF and details how a reviewer should determine whether the information provided in a Type III DMF and the application it supports satisfies the requirements for assessing the safety of certain packaging systems for drug substances and drug products.

Packaging Materials Committee) was instrumental in negotiating with FDA to establish this system.

There are now four types of DMFs (type I DMFs were recommended for drug manufacturers outside the United States to provide FDA with information on their manufacturing site, facilities, operating procedures, and personnel, but this category has been abolished³):

(1) Type II DMFs are used to provide FDA with information on drug substances, drug substance intermediates and materials used in their preparation, or drug products;

(2) Type III DMFs are established to provide FDA with information on drug packaging materials;

(3) Type IV DMFs are used to provide FDA with information on excipients, colors, flavors, essences, or materials used in their preparation; and

(4) Type V DMFs are used to provide FDA with reference information of the type that does not fit within one of the above-listed categories. Type V DMFs for the following information may be filed without requesting prior clearance from FDA:⁴

(a) Manufacturing Site, Facilities, Operating Procedures, and Personnel for sterile manufacturing plants; and

(b) Contract Facilities for the manufacture of biotech products.

This manual addresses Type III DMFs for drug packaging materials.

III. DMF Basics

A. Supplying Information for a Type III DMF

Although the DMF procedure is completely voluntary, companies that choose to use this process must comply with certain requirements with respect to the content and maintenance of the file. Type III DMFs must contain the following administrative information:

(1) The name and address of the DMF holder's corporate headquarters;

³ See 65 Fed. Reg. 1776 (Jan. 12, 2000).

⁴ FDA discourages the use of Type V DMFs for miscellaneous information. If a company wishes to submit information in a DMF that does not fall within one of the above two categories and is not covered by Types II through IV, the company must first request permission from FDA by sending a request to dmfquestion@cder.fda.gov explaining the necessity for filing the information in a Type V DMF.

- (2) The manufacturing/processing facility address;
- (3) The name, title, and contact details (including mailing address, telephone number, fax number, and email address) of the contact for FDA correspondence;
- (4) The name and contact details (including mailing address, telephone number, fax number, and email address) of the agent, if applicable;
- (5) The companies authorized to refer to the DMF in conjunction with the review of New Drug Applications or other FDA drug approval processes;
- (6) A Statement of Commitment (an original, signed statement by the holder of the DMF certifying that the DMF is current and that the holder will comply with the statements made in it); and
- (7) A Statement of Environmental Compliance (an original, signed statement that the manufacturing facility will be operated in substantial compliance with applicable environmental laws).

In addition, a Type III DMF must contain confidential information regarding the product(s) of interest. There are no strict requirements regarding the confidential information required for a Type III DMF; however, one hard and fast rule is that the DMF must contain some confidential information. The confidentiality of information provided to FDA in a DMF is discussed further in Section B, below.

The confidential portions of a Type III DMF typically include information on the generic formulation of the packaging materials. Information that may or may not be considered confidential typically includes testing methods used to determine compliance with specifications for the finished packaging and, in some cases, toxicology data or data to show compliance with United States Pharmacopeia (USP) tests, which may be included if available.⁵ The information contained in the DMF also may include references to any clearances for the raw materials under FDA's Food Additive Regulations (21 C.F.R. Parts 170-199).

As discussed in more detail later in this document, a DMF holder needs to balance FDA's preference for detail in reviewing New Drug Applications (NDAs) and the burden of notice to FDA and to customers when changes are made. In preparing the initial DMF

⁵ FDA's 1999 Container Closure Guidance suggests that drug company applicants provide more detail on packaging than is indicated in the more general 1989 Guideline for Drug Master Files. In point of fact, the information on packaging required by an FDA drug reviewer in any particular case will vary with the nature of the drug product, the nature of the packaging material, and the experience and predilections of the reviewer. In establishing a DMF, a packaging supplier should work closely with its customers and consult available FDA guidance, including the information provided on FDA's DMF website, available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFiles/DMFs/default.htm>, and FDA's 1989 and 1999 guidelines and Manual of Policies and Procedures (MAPP) 5015.5 (links to these guidance documents are provided on FDA's DMF website).

submission, companies should, wherever possible, avoid including an excess amount of information that is not relevant to FDA's evaluation of the safety and efficacy of the drug packaged using the product of interest. Thus, for example, it would be appropriate to include in the initial DMF submission for a drug packaging material only general information on the identity of the material, its specifications, and the tests used by the manufacturer to determine compliance with these specifications. This would include referring to materials by generic chemical identity rather than specific trade name, and reporting product specifications as ranges rather than as particular values. Maintaining this level of generality avoids the need to amend the DMF if the manufacturer replaces a component with a chemically identical material from a different supplier. If FDA requires more information than is initially supplied, such information can be added to the file as it is requested. It should be noted, however, that an FDA request for more information may delay the completion of the review of a customer's application.

There will be cases in which no satisfactory chemical definition or other specification for a component can be provided by a packaging material supplier without reference to another supplier. This might occur because of the inability to obtain such a definition from the component supplier or because the finished chemical composition is so complex or amorphous that only a description of the manufacturing process will provide adequate characterization of the product for FDA purposes. In such cases, the package or overall packaging material supplier should at least attempt to indicate a number of alternative sources of supply. This could mean that a number of component suppliers will have to submit their own master files for cross-referencing purposes. Often such files are already established or may be established quite readily. If the differences between materials from different suppliers are too significant, FDA could require a drug company to conduct separate tests to assure the suitability of each formula variation, though this is rare. In this situation, the packaging supplier probably will be forced by the drug company to eliminate from the DMF those variations that have triggered the need for additional data. Accordingly, there is a trade off between maintaining maximum flexibility to make changes without creating excessive testing requirements for the drug company.

The DMF should be submitted, in duplicate, to FDA's Center for Drug Evaluation and Research.⁶ A typical cover letter for an original DMF submission is provided as Attachment B to this manual. Alternatively, an original DMF submission may be filed electronically, provided it is submitted in electronic Common Technical Document (eCTD) format. FDA provides guidance for submitting DMFs electronically on FDA's

⁶ As noted on FDA's DMF website, the applicable mailing address for original DMF filings, as well as all subsequent DMF documents, is:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

DMF website.⁷ A subsequent DMF submission in electronic format may not be submitted to a paper DMF; however, a DMF holder may convert an existing paper DMF to electronic format. There is no filing fee for a DMF submitted to FDA.

A typical cover letter for an original DMF submission is provided as Attachment B to this manual. There is no filing fee for a DMF submitted to FDA. Once received, FDA assigns a reference number to the DMF and notifies the DMF holder of this reference number. This reference number must then be included on all future correspondence with FDA regarding the DMF. Note that if a DMF is submitted electronically, the holder may request a preassigned DMF reference number from FDA.⁸ Pre-assignment of a DMF number can be useful because Letters of Authorization (a letter authorizing a drug customer to incorporate by reference information contained in a particular DMF), discussed further below, must include the DMF reference number. Because of this requirement, original, paper DMF submissions will not be able to include a Letter of Authorization. In contrast, when a DMF is submitted electronically under a preassigned DMF number, a Letter of Authorization may be submitted together with the original, electronic DMF submission.

FDA maintains an electronic inventory of DMFs, which may be accessed from FDA's website at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm>

The inventory includes the DMF number and type, original submission date, holder name, the subject of the DMF, and its current status (*i.e.*, Active (A), Inactive (I), or Pending Filing Review (P)). Because it will be publicly available on FDA's website, the subject matter designated for the DMF filing should be generic in nature and not include any information considered to be confidential.

B. DMF Confidentiality

In keeping with the purpose of a DMF, the information in the DMF is not disclosed to the drug company. When a drug manufacturer is authorized by the DMF holder to incorporate by reference information in a DMF, the Agency reviews the data in the DMF as a part of its review of the drug manufacturer's NDA or other drug submission. The confidential information in a DMF is afforded appropriate confidential treatment in accordance with the protective provisions of 21 C.F.R. § 314.430, which deals with the confidentiality of data in New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), and FDA's Public Information Regulations set forth

⁷ As noted elsewhere in this guidance, FDA's DMF website is available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm>.

⁸ The procedure for requesting a preassigned DMF number is described on FDA's website at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm>.

in 21 C.F.R. Part 20. It is important to note, however, that under the Freedom of Information Act (FOIA), information contained in drug-related submissions, including DMFs, is subject to public disclosure unless FDA considers the information to be confidential within the meaning of 21 C.F.R. § 20.61, “Trade secrets and commercial or financial information which is privileged or confidential.” Therefore, the identity of a particular material and any information in a DMF regarding its specifications and manufacturing should be marked “Confidential.” If, in the future, a DMF holder wishes to add information to the DMF that the company wishes to protect against disclosure, it should identify such information as confidential as well.

C. DMF Holder Responsibilities

Once a DMF has been established, the DMF holder may authorize its customers to incorporate by reference information in the DMF to assist in providing FDA with the information needed to fully evaluate the safety and efficacy of a packaged drug. DMFs must contain a complete and current list of each person or company authorized by the DMF holder to incorporate by reference information in the file.⁹ To permit a customer to make reference to the information in a DMF, the DMF holder must submit a “Letter of Authorization (LOA)” to FDA that includes the designated DMF number; a separate authorization letter must be submitted for each of the DMF holder’s customers. Further, a copy of the LOA should be forwarded to respective customers for inclusion in their drug submissions to FDA. A sample “Letter of Authorization” is provided as Attachment E to this manual. Note that LOAs may not be provided with the original DMF submission, except in cases where a DMF is filed in electronic format after receiving a preassigned DMF reference number from FDA, as mentioned above.

1. Amending a DMF

FDA’s regulations require DMF holders to report changes to their products or manufacturing processes as the changes occur. A sample cover letter for an Amendment to a DMF is provided as Attachment H to this manual. The amendment should be submitted in duplicate.

Generally, when a change is made to one part of a DMF, the entire DMF should not be resubmitted. Nevertheless, FDA now permits, and sometimes even encourages, the reorganization and resubmission of older DMFs in a more user-friendly format. For example, we note that FDA has on file several DMFs that have grown unwieldy over time as a result of the old pagination process whereby a DMF was numbered consecutively throughout, whereas now, as shown in Attachment C to this guidance (“Sample Type III DMF”), it has become common practice to consecutively number only the pages in a particular section of the DMF and then restart the numbering process at the beginning of each new section. Note, however, that reorganizations should not contain substantive changes to a DMF, which should be submitted as separate amendments to the reorganized DMF.

⁹ See 21 C.F.R. § 314.420(d), “Drug Master Files.” A copy of this regulation is provided as Attachment B to this manual.

a) Adding Information on New Products

Information on additional grades of a certain material may easily be incorporated into a DMF that has already been prepared and submitted to FDA. In particular, information on the chemical composition, specifications, and properties of each additional product of interest may be added to the DMF. It should be noted, however, that, if a company plans to submit a DMF that includes information on several different product grades, or if the company plans to expand the DMF to include additional products after the DMF has been filed, each customer authorization letter issued should be drafted to refer only to those products described in the DMF that will be used by the customer of interest. Drafting the customer authorization letters in this way will assist FDA in locating the specific information in the DMF relevant to the Agency's review of a particular new drug application. Further, since drug companies who are authorized to make reference to the DMF must be notified of any substantive changes to the information being referenced, this practice will eliminate the need to notify customers of changes to the file that do not affect the products they use.

A different approach is recommended for DMFs on disparate products or separate product lines. While it is technically permissible to include in a single DMF information on disparate products, this practice is not recommended. DMFs that contain information on a large number of products typically become difficult to manage over the years, particularly if the products described in such files are dissimilar. Furthermore, FDA's new drug reviewers may have difficulty locating relevant information on a particular product if too many products are described in a single DMF. This is due in part to the way in which FDA handles amendments to DMFs. Instead of replacing pages with revised versions, even if asked to do so, the Agency simply adds amendments on top of the existing DMF, never discarding anything. Therefore, over time, a DMF may become unwieldy, particularly if it covers many products. FDA's own DMF maintenance practices in some cases cause the Agency's reviewers to ask unnecessary questions, and DMF holders need to be aware of this situation in structuring and amending DMFs. Eventually, a DMF holder may be served best by filing a new version of the entire DMF instead of making partial amendments. As noted above, FDA now permits and sometimes even encourages this practice.

FDA does not require a filing fee for establishing a DMF; thus, the cost associated with establishing and maintaining separate DMFs on separate product lines is not significantly greater than the cost of establishing a single DMF. Indeed, the cost of maintaining several small DMFs is likely to be lower because of the potential administrative difficulties associated with maintaining a large file. This being the case, it is generally preferable to establish separate DMFs for separate product lines.

b) Notifying Customers of a Change to a DMF

FDA's DMF regulation requires a DMF holder to notify all persons authorized to reference information in a DMF if *any* information in the file is added, changed, or deleted. Such notification is essential to allow the DMF holders' customers to meet their

obligations with respect to product changes, which are further discussed in Section IV of this manual.

Personnel within FDA's Center for Drug Evaluation and Research interpret the notification requirement in a practical manner. Only substantive product modifications require notification of the DMF holder's customers. Thus, all customers need not be notified when, for example, editorial changes are made to the file or a new customer is authorized to reference the DMF.

2. Annual Reports

In addition to reporting changes as they occur, the DMF should be updated annually. The purpose of the "Annual Report" is to update the list of customers who are authorized to reference the DMF, and to identify any changes or additional information incorporated into the DMF since the previous annual report.¹⁰ If no changes have been made, a statement to this effect should be submitted to FDA. The Annual Report should also include an administrative page containing: (1) the holder's name; (2) the address of the corporate headquarters; (3) the name and address of applicable manufacturing site(s); (3) the name and contact details for the contact person for FDA correspondence; and (4) the name and contact details for the U.S. agent, if applicable. Note that FDA does not accept Annual Reports as a means to report changes to a DMF. Thus, Annual Reports and Amendments must be submitted as separate filings, although they may be submitted concurrently to the Agency if appropriate. A sample cover letter for an "Annual Report" is provided as Attachment G to this manual.

Compliance with the Annual Report requirement is extremely important to ensuring the "active" status of a DMF. Although FDA previously did not strictly enforce this requirement, this is no longer the case. In recent years, FDA has been engaged in the process of sending "Overdue Notification Letters" to DMF holders for DMFs that are overdue for update and then closing and retiring these DMFs if the requisite Annual Report is not submitted within 90 days of the date of the overdue notification letter. Once a DMF is retired by FDA, it is unavailable for review and can only be reactivated through the submission of a reactivation request letter (a sample is provided as Attachment L to this manual) and a complete resubmission of the DMF, including new, signed Manufacturing and Environmental Statements of Commitment. Thus, to ensure the active status of a DMF and avoid delays in FDA's review of your customers' drug submissions, annual reports should be submitted on an annual basis as close as possible to the anniversary date of the DMF. Note that a response to an overdue notice letter to avoid FDA's closure of a DMF is an Annual Report and must contain the information discussed above as required for inclusion in an Annual Report. As we noted elsewhere in

¹⁰ FDA previously used the terminology "Annual Update" to refer to the annual DMF filings as a way of distinguishing them from the "Annual Reports" submitted by drug companies in connection with NDAs. FDA has now done away with the "Annual Update" terminology and insists that the term "Annual Report" be used for such DMF filings.

this guidance, the status of a DMF will be reflected on the electronic inventory of DMFs maintained by FDA.

D. Closing a DMF

In Section C.2 above, we discuss the procedure by which FDA may move to close a DMF for failure to comply with the Annual Report requirement. Additionally, a DMF may also be closed at the request of the holder. For example, a holder may wish to close a DMF because they are no longer producing the product that is the subject of a DMF or because they are no longer selling the product for use in drug applications.

Only the holder of a DMF is allowed to close the file. We provide a sample closure request letter as Attachment K to this manual. In addition, the holder is required to notify, in writing, all companies authorized to reference the DMF of the closure. The closure request letter provided to FDA must confirm that all companies authorized to reference the DMF have been notified of the closure.

E. Transferring a DMF

When ownership of a DMF is transferred from one company to another, both the existing and new holder must submit documentation of the transfer to FDA. More specifically, the original holder should submit an amendment to FDA stating that they are transferring the DMF to the new holder. A sample holder transfer letter is provided as Attachment I to this manual. Similarly, the new holder should submit an administrative amendment to FDA stating that they are accepting responsibility for the DMF from the former holder. Both types of documentation should be submitted as original, signed letters on company letterhead.

The former owner of the DMF is expected to transfer a complete copy of the DMF to the new owner. The new owner is responsible for submitting to FDA (1) an updated administrative page, (2) new, signed Statements of Commitment, and (3), if applicable, a new agent appointment letter.

If the DMF holder simply changes its name internally and there is no transfer of ownership, the holder need only submit a holder name change amendment to FDA. A sample holder name change letter is provided as Attachment J to this manual.

IV. Changes in Drug Packaging Materials

Under Section 314.70 of FDA's New Drug Regulations, drug companies are required to notify FDA of any change to the information provided in an approved New Drug Application.¹¹ As indicated in Section II.B above, depending upon the type of change (*i.e.*, major, moderate, or minor), the drug company is required to provide such notification either in a supplemental new drug application (SNDA), or by including the

¹¹ See 21 C.F.R. § 314.70, "Supplements and other changes to an approved application."

relevant information in its annual report. In addition, to make certain changes that require submission of an SNDA, companies must receive prior FDA approval.

A. Major Changes

Under Section 314.70(b)(2)(vi), a change from one container and closure system to another is a major change that requires the submission of an SNDA, as well as prior FDA approval; a major change is one that “has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.” The following three types of container changes are cited in the regulation as examples of major changes that would require prior Agency approval: (1) a change from glass to high density polyethylene (HDPE); (2) a change from HDPE to polyvinyl chloride (PVC); and (3) a change from one HDPE resin to another HDPE resin in a packaging component that may affect the impurity profile of the drug product.¹² FDA provides additional examples of “major” post-approval packaging changes in FDA’s Guidance for Industry: Changes to an Approved NDA or ANDA (April 2004), which is available at:

<http://www.fda.gov/OHRMS/DOCKETS/98fr/1999d-0529-gdl0003.pdf>

B. Minor Changes

A change *within* the container and closure system for a drug product, however, does not always require prior FDA approval and the submission of an SNDA. Under Section 314.70(d)(2)(v), a change within the container and closure system for a *nonsterile* drug product is a minor change, one that may simply be described to the Agency in the drug company’s annual report if the new container and closure system is shown to be equivalent to the approved container and closure system based on “a protocol approved in the application or published in an official compendium.”¹³ A minor change is one that has “a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety of effectiveness of the drug product.” As noted above, minor changes can be documented in the manufacturer’s next annual report. FDA’s Guidance for Industry: Changes to an Approved NDA or ANDA (April 2004) elaborates on the types of changes that the

¹² Prior to June 22, 2004, the regulation cited a change from one HDPE to another HDPE pursuant to an approved protocol or official compendium as being minor for solid oral dosage forms without reference to the purity profile of the packaged drug. Under the regulation, this type of change could be notified in an annual report rather than an SNDA. (*See* the Final Rule published in 69 *Fed. Reg.* 18727-18767 (April 8, 2004).) The change in the regulation to clarify the potential for a heightened reporting requirement in certain cases was precipitated by an increased concern on the part of FDA that post-approval packaging changes within a container/closure system for certain dosage forms (*i.e.*, sterile liquids) could adversely impact the identity, strength, quality, purity, or potency of the drug product, if the changes were made pursuant to an approved protocol or official compendium.

¹³ *See* 21 C.F.R. § 314.70(d)(2)(v). The official compendia referenced in the Federal Food, Drug, and Cosmetic Act (§ 321(j)) are the U.S. Pharmacopeia, the Homeopathic Pharmacopeia of the United States, and the National Formulary.

Agency considers to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. One such example is a change in the container closure system of a solid oral dosage form drug product from one HDPE resin to another HDPE resin.¹⁴

Equivalency between HDPE containers for packaging solid oral dosage forms may be shown based on compliance with the standards published in the United States Pharmacopeia (USP). Section 661 of the USP contains standards applicable to various types of drug containers, including standards for characterizing polyethylene containers that are interchangeably suitable for packaging dry oral dosage forms. Thus, for example, if a drug company using an HDPE container that meets the standards set forth in section 661 of the USP to package its dry drug product wishes to change to another HDPE container, a showing that the new container also meets the same requirements under section 661 is sufficient to demonstrate equivalency. In this situation, the drug company making such a change need only reference the change in its annual report.¹⁵

If a proposed change within a drug container and closure system for a nonsterile drug product is not covered by a protocol published in an official compendium, the drug company must either confirm that the two systems are equivalent based upon a protocol contained in its approved NDA, or otherwise demonstrate that the change has a minimum potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. Otherwise, the drug company must file a supplemental submission with FDA. Many NDAs do not contain suitable protocols for showing equivalency between container and closure systems. Therefore, the requirements applicable to these types of changes must be determined on a case-by-case basis in accordance with the contents of the particular NDA.

FDA has published a draft guidance document describing additional post-approval manufacturing changes to NDAs and ANDAs that are considered to be “minor” and, therefore, may be categorized as a change reportable in an annual report rather than an SNDA. (See Guidance for Industry: CMC Postapproval Manufacturing Changes Reportable in Annual Reports (June 2010), available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM217043.pdf>.) One such example is a “change in the container/closure system for the storage of a nonsterile drug substance when the proposed container/closure system

¹⁴ In addition, FDA’s guidance caveats that the new package provide the same or better protective properties and that any new primary packaging component materials must have been used in and been in contact with CDER-approved solid oral dosage form drug products.

¹⁵ Drug stability studies using the new polyethylene container need not be completed prior to making a change from one polyethylene container to another equivalent polyethylene container. However, in accordance with the USP standard, where stability studies have been performed to establish the expiration date for a dry oral dosage form, the appropriate stability programs must be expanded to include the alternative container to ensure that the identity, strength, quality, and purity of the drug are maintained throughout the expiration period. *See* United States Pharmacopeia 35, Section 661, at 276.

has no increased risk of leachable substances in the extractable profile (for liquids) and equivalent protection properties.”

C. Moderate Changes

A moderate change is described in Section 314.70(c) as one that has a “moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety of effectiveness of the product.” Section 314.70(c)(2)(i) provides that any change in a container closure system that does not affect the quality of the drug product, and is not deemed to be a major change requiring prior approval under Section 314.70 (b) or to be a minor change under Section 314.70 (d), is a moderate change. There are two types of reporting requirements for moderate changes (“changes being effected”): one requires submission of an SNDA at least 30 days prior to distribution of the drug product made using the change, while the other allows distribution of the drug product once FDA receives the SNDA. FDA’s Guidance for Industry: Changes to an Approved NDA or ANDA (April 2004) provides further examples of both types of categories of moderate changes to a container closure system.

V. Principal Points to Remember

The essential points to remember in submitting and maintaining a DMF are as follows:

- (1) Include whatever information you anticipate FDA will require, and designate as confidential information that should be kept confidential within the meaning of Section 314.430 of the New Drug Regulations and Section 20.61 of FDA’s public information regulations.
- (2) Submit Annual Reports on a regular basis (as close as possible to the anniversary date of the original submission) to ensure the active status of the DMF and avoid delays in FDA’s review of your customers’ drug submissions.
- (3) Notify your drug customers and update your DMF whenever a change is made to the products covered by the information already in the file (administrative or editorial changes may not require notice to customers).
- (4) Stand ready to cooperate with the drug customer to the degree necessary in supplying additional information if it is requested.
- (5) Submit the information in such a way as to permit as much flexibility as possible in making non-substantive changes, while avoiding delays in FDA review of customers’ drug applications.

With respect to items (3) and (5) and the types of materials that may be considered “interchangeably suitable” for use in drug packaging applications, as indicated above, some groundwork in the area of developing protocols for the interchangeability of certain types of containers has already been accomplished with the aid of SPI’s Food, Drug, and Cosmetics Packaging Materials Committee, Drug Packaging Subcommittee. For example, the Committee assisted FDA in completing a study comparing the properties of HDPE containers made using virgin materials with HDPE made using regrind for use in packaging solid oral dosage forms.¹⁶ The results of the studies showed that all of the containers tested passed the requirements of the United States Pharmacopeia (USP) for HDPE containers used to package dry drugs, whether the containers were produced using regrind or virgin resin. Therefore, based on this study, it is not necessary to differentiate in a DMF between HDPE resin produced using virgin materials and HDPE resin produced using regrind.

Finally, it is important to keep in mind that FDA is scrutinizing DMFs more closely than ever before. With the considerable increase in the number of DMF submissions and FDA’s interest in keeping track of such filings electronically, FDA’s procedures for DMFs have grown more bureaucratic in nature and FDA more stringently insists on uniformity in DMF submissions in accordance with its current administrative guidelines. Thus, more than ever before, it is important to consult FDA’s current DMF guidance when preparing DMF submissions and to adhere to FDA’s requirements for various types of DMF filings.¹⁷ Moreover, to maintain the active status of a DMF and ensure that it is not retired by FDA making it unavailable for review, it is important to regularly comply with FDA’s Annual Report requirement.

¹⁶ The term “regrind” as used here means resin from a fabricator’s own production that has been reground after having been processed; it is not intended to refer to post-consumer material.

¹⁷ As noted in footnote 2 above, FDA provides several sources of useful guidance for DMFs:
(1) FDA’s website, available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFiles/DMFs/default.htm> (last updated 5/11/2012);
(2) FDA’s “Guideline for Drug Master Files,” (September 1989);
(3) FDA’s Guidance for Industry: “Container Closure Systems for Packaging Human Drugs and Biologics: and (4) FDA’s Manual of Policies and Procedures (MAPP 5015.5).

ATTACHMENT A

21 C.F.R. § 314.420 “Drug Master Files”

of the labeling required for, the approved drug product.

(3) Insulin or an antibiotic drug may be exported without regard to the requirements in section 802 of the act if the insulin or antibiotic drug meets the requirements of section 801(e)(1) of the act.

[50 FR 7493, Feb. 22, 1985, unless otherwise noted. Redesignated at 57 FR 17983, Apr. 28, 1992, and amended at 64 FR 402, Jan. 5, 1999]

§ 314.420 Drug master files.

(a) A drug master file is a submission of information to the Food and Drug Administration by a person (the drug master file holder) who intends it to be used for one of the following purposes: To permit the holder to incorporate the information by reference when the holder submits an investigational new drug application under part 312 or submits an application or an abbreviated application or an amendment or supplement to them under this part, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person. FDA ordinarily neither independently reviews drug master files nor approves or disapproves submissions to a drug master file. Instead, the agency customarily reviews the information only in the context of an application under part 312 or this part. A drug master file may contain information of the kind required for any submission to the agency, including information about the following:

(1) [Reserved]

(2) Drug substance, drug substance intermediate, and materials used in their preparation, or drug product;

(3) Packaging materials;

(4) Excipient, colorant, flavor, essence, or materials used in their preparation;

(5) FDA-accepted reference information. (A person wishing to submit information and supporting data in a drug master file (DMF) that is not covered by Types II through IV DMF's must first submit a letter of intent to the Drug Master File Staff, Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852). FDA will

then contact the person to discuss the proposed submission.

(b) An investigational new drug application or an application, abbreviated application, amendment, or supplement may incorporate by reference all or part of the contents of any drug master file in support of the submission if the holder authorizes the incorporation in writing. Each incorporation by reference is required to describe the incorporated material by name, reference number, volume, and page number of the drug master file.

(c) A drug master file is required to be submitted in two copies. The agency has prepared guidance that provides information about how to prepare a well-organized drug master file. If the drug master file holder adds, changes, or deletes any information in the file, the holder shall notify in writing, each person authorized to reference that information. Any addition, change, or deletion of information in a drug master file (except the list required under paragraph (d) of this section) is required to be submitted in two copies and to describe by name, reference number, volume, and page number the information affected in the drug master file.

(d) The drug master file is required to contain a complete list of each person currently authorized to incorporate by reference any information in the file, identifying by name, reference number, volume, and page number the information that each person is authorized to incorporate. If the holder restricts the authorization to particular drug products, the list is required to include the name of each drug product and the application number, if known, to which the authorization applies.

(e) The public availability of data and information in a drug master file, including the availability of data and information in the file to a person authorized to reference the file, is determined under part 20 and § 314.430.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 53 FR 33122, Aug. 30, 1988; 55 FR 28380, July 11, 1990; 65 FR 1780, Jan. 12, 2000; 65 FR 56479, Sept. 19, 2000; 67 FR 9586, Mar. 4, 2002]

ATTACHMENT B

Sample Cover Letter for Original DMF Submission

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: Holder:

Manufacturing Location(s):

Subject:

DMF Type: III

Title: Original Submission

Dear Sir or Madam:

On behalf of [name of company], we request that you establish a Type III Drug Master File (DMF) for [name of product]. **[If an agent is authorized to submit and amend the DMF on behalf of the DMF holder, the following language should be included: Pursuant to the attached letter from [name of appropriate official], we hereby appoint [name of agent] to act on behalf of [company name] with respect to all matters concerning this DMF.]**

We understand that the DMF procedure has been developed solely as a means of making data available to the Food and Drug Administration (FDA) to assist in its review of drug submissions and that the information included in this DMF, and any information that may be added subsequently, will be afforded appropriate confidential treatment in accordance with 21 C.F.R. § 314.430 and FDA's public information regulations set forth in 21 C.F.R. Part 20.

In addition to a complete copy of the original submission, we also are enclosing a duplicate copy of this forwarding letter for your use in acknowledging receipt. Should you have any questions regarding this matter, please do not hesitate to contact us, preferably by telephone, so that we may respond as quickly as possible. Thank you for your assistance in this matter.

Sincerely yours,

[signature and title of company official]

Enclosures

ATTACHMENT C

Sample Type III DMF

Binder Cover (Original Submission)

The binder cover (available as Form FDA 3316a, blue review binder; and Form FDA 3316, red archive binder), includes the following information:

1. Name of company that is submitting the DMF.
2. The type of DMF and subject matter title.
3. Volume number and the total number of volumes.

[Example Binder Cover]

[NAME OF DMF HOLDER]

TYPE III DRUG MASTER FILE

No. _____

**COVERING
[INSERT SUBJECT]**

VOLUME ___ OF ___

INFORMATION PRESENTED IN THIS DOCUMENT IS CONFIDENTIAL

Portions of the file **[insert specific areas]** are trade secrets which may not be disclosed outside the Food and Drug Administration without prior written consent of **[insert holder name]**.

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Administrative Information

1. DMF Holder

[insert company name]

2. Corporate Headquarters

[insert company's corporate headquarter address]

3. Manufacturing/Processing Facility

[insert addresses of all facilities that produce product(s)]

4. Contacts for FDA Correspondence

[insert name, title, mailing address, telephone number, fax number, and email address of company contact person]

[if applicable, insert name, title, mailing address, telephone number, fax number, and email address of the agent contact person]

[Company Letterhead]

B. STATEMENT OF COMMITMENT

1. Manufacturing

[Insert company name] certifies that the information contained in this DMF is current and that the statements, manufacturing processes, specifications, and controls for the products identified in this Drug Master File will be met and complied with during manufacture.

[signature of appropriate company official and date]
[printed name of appropriate company official
[name of company]

[Company Letterhead]

B. STATEMENT OF COMMITMENT

2. Environmental

[Insert company name] certifies that our facilities will be operated in substantial compliance with all applicable environmental laws relating to the manufacture of the products identified in this Drug Master File.

[signature of appropriate company official and date]
[printed name of appropriate company official
[name of company]

PERSONS CURRENTLY AUTHORIZED TO INCORPORATE

THIS DMF BY REFERENCE

Name of Company

Description of Product(s)

Location in DMF

[e.g., all products or a specific product] [e.g., Section or page
number]

D. CONFIDENTIAL FORMULATION

[Insert formulation - use ranges and examples of potential suppliers, where possible.

FDA status of individual components may also be provided, if applicable.]

E. SPECIFICATIONS

[Insert product specifications]

F. TEST METHODS

**[Insert test methods used to demonstrate that the product
complies with listed specifications]**

ATTACHMENT D

Sample Agent Appointment Letter

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: DMF Number: [Enter DMF Number or “Not Yet Assigned”]

Holder: [Enter name of Holder]

Subject: [Enter the subject of the DMF]

Submission Information: Agent Appointment

Dear Sir or Madam:

This letter serves to advise your office that we have appointed the following company as our U.S. Agent for Drug Master File (DMF) purposes:

Company Name:
Contact person’s Name:
Title:
Telephone number:
Address:
Fax number:
E-mail address:

We hereby appoint **[insert name of agent]** to act on our behalf before the Food and Drug Administration (FDA) in all matters concerning our Type III DMF for **[insert holder’s name]’s [insert subject of DMF]**. **[Insert name of agent]** also is hereby authorized to obtain a copy of the DMF on our behalf, and should be copied on any correspondence from FDA to **[insert holder’s name]** regarding this DMF.

If you have any questions regarding this agent appointment, please do not hesitate to contact us. Thank you for your assistance in this matter.

Sincerely yours,

[signature and title of company official]

ATTACHMENT E

Sample Letter of Authorization

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: DMF Number:

Holder:

Subject:

Letter of Authorization for: [Enter the name of the Item being Referenced]

Dear Sir or Madam:

This letter authorizes the U.S. Food and Drug Administration (FDA) to make reference to **[insert holder's name]** DMF No. **[insert DMF number]** in connection with any New Drug Application, Abbreviated New Drug Application, Investigational New Drug Application, or supplements thereto involving the use of **[insert product name]** submitted by:

[insert customer name in bold font]
[insert customer's address in bold font]

DMF No. **[insert DMF number]** was filed initially on **[insert date]**. Information on this product is located in our initial submission in Section **[insert Section number]** at pages **[insert page numbers]** and in Amendment **[insert number and/or date]** at pages **[insert page numbers]**.

The information contained in this letter does not reflect any substantive change with regard to the chemical composition, quality control procedures, or manufacturing methodology for the product, and is intended to assist FDA in its review of applications filed with respect to new drugs in accordance with Section 341.420 of the New Drug Regulations. It is our understanding that the information included in DMF No. **[insert DMF number]**, and any information that may be added subsequently, will be afforded appropriate confidential treatment in accordance with the protective provisions of Section 314.430, dealing with the confidentiality of data in New Drug Applications and Abbreviated New Drug Applications, and FDA's Public Information Regulations set forth in 21 C.F.R. Part 20.

Following the required procedure, we are submitting a duplicate of this letter of authorization, as well as an additional copy of this letter for your use in acknowledging receipt. Thank you for your assistance with this matter.

Sincerely yours,

[signature and title of company official]

Enclosures

ATTACHMENT F

Sample Withdrawal of Authorization

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: DMF Number:

Holder:

Subject:

Withdrawal of Authorization for: [Enter the name of the Item being Referenced]

Dear Sir or Madam:

This letter withdraws authorization for the U.S. Food and Drug Administration (FDA) to make reference to **[insert holder's name]** DMF No. **[insert DMF number]** in connection with any New Drug Application, Abbreviated New Drug Application, Investigational New Drug Application, or supplements thereto involving the use of **[insert product name]** submitted by:

[insert customer name in bold font]
[insert customer's address in bold font]

The original Letter of Authorization was submitted on **[insert date]**. *If the DMF covers multiple items, also including the following language: Information on the product for which authorization is now being withdrawn is located in our initial submission in Section **[insert Section number]** at pages **[insert page numbers]** and in Amendment **[insert number and/or date]** at pages **[insert page numbers]**.*

Following the required procedure, we are submitting a duplicate of this withdrawal of authorization letter, as well as an additional copy of this letter for your use in acknowledging receipt. Thank you for your assistance with this matter.

Sincerely yours,

[signature and title of company official]

Enclosures

ATTACHMENT G

Sample Annual Report

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: Annual Report for Type III Drug Master File No. [Insert number]

Holder:

Manufacturing Site:

Subject:

Dear Sir or Madam:

We hereby submit to the U.S. Food and Drug Administration (FDA) an annual report to **[insert holder's name]** Type III Drug Master File (DMF) No. **[insert DMF number]**, which covers the use of **[insert subject of DMF]**. The last annual report for DMF **[insert DMF number]** was submitted on **[insert date of last annual report or the date of original submission, if most recent]**.

[List the dates of any amendments reporting changes to the DMF since the last Annual Report (or the original DMF filing date if most recent), or provide a statement that no amendments have been made.]

Additionally, enclosed is an updated list of customers authorized to make reference to the file. **[Alternatively, provide a statement that no changes have been made to the list of authorized customers since the last Annual Report or the original DMF filing date, whichever is most recent.] [If applicable, list all customers whose authorization has been withdrawn.]**

Finally, we have enclosed with this Annual Report an "Administrative Information" page.

We note that the information contained in the enclosed submission is intended to assist FDA in its review of applications filed with respect to new drugs in accordance with Section 314.420 of the New Drug Regulations. It is our understanding that the information included in DMF No. **[insert DMF number]**, and any information that may be added subsequently, will be afforded appropriate confidential treatment in accordance with the protective provisions of Section 413.430, dealing with the confidentiality of data

ATTACHMENT H

Sample Cover Letter for DMF Amendment

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: Amendment for Type III Drug Master File No. [Insert number]

Holder:

Manufacturing Site:

Subject:

Dear Sir or Madam:

We hereby submit to the U.S. Food and Drug Administration (FDA) an amendment to **[insert holder's name]** Type III Drug Master File (DMF) No. **[insert DMF number]**, which covers the use of **[insert subject of DMF]**. This amendment **[insert list of changes to the DMF and, if possible, identify the sections of the DMF to which information should be added or documents replaced or removed]**.

[If applicable, state that you are including with this amendment an updated Table of Contents for the DMF.]

We request that all information in this file be treated as confidential to the extent possible in accordance with 21 CFR 314.430 and 21 CFR 20.61, and that no information from this file be provided to any unauthorized persons without our written consent.

We are submitting a duplicate copy of this submission, as well as an additional copy of this transmittal letter for your use in acknowledging receipt. Should you have any questions regarding this submission, please do not hesitate to contact us, preferably by telephone, so that we may respond to your request as quickly as possible. We appreciate your attention to this matter.

Sincerely yours,

[signature and title of company official]

Enclosures

ATTACHMENT I

Sample Holder Transfer Letter

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: DMF Number:

Holder:

Subject:

Submission Information: Change in Holder - Transfer to New Holder

New Holder Name:

Dear Sir or Madam:

The purpose of this letter is to provide notification to the U.S. Food and Drug Administration (FDA) of a change in the identity of the holder for Drug Master File (DMF) No. [insert DMF number]. Specifically, DMF No. [insert DMF number] is being transferred from [insert name of current holder] to [insert name of new holder]. In this regard, [insert name of current holder] has received a complete copy of the existing DMF.

Following the required procedure, we are submitting a duplicate of this holder transfer letter, as well as an additional copy of this letter for your use in acknowledging receipt. Should you have any questions regarding this matter, please do not hesitate to contact us. Thank you for your assistance.

Sincerely yours,

[signature and title of company official]

Enclosures

ATTACHMENT J

Sample Holder Name Change Letter

[Company Letterhead Reflecting the Internal Name Change]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: DMF Number:

Holder:

Subject:

Submission Information: Change in Holder - Internal Name Change

New Holder Name:

Dear Sir or Madam:

The purpose of this letter is to provide notification to the U.S. Food and Drug Administration (FDA) that the holder of Drug Master File (DMF) No. **[insert DMF number]** has changed its name from **[insert former name of holder]** to **[insert new name of holder]**.

Following the required procedure, we are submitting a duplicate of this holder name change letter, as well as an additional copy of this letter for your use in acknowledging receipt. Should you have any questions regarding this matter, please do not hesitate to contact us. Thank you for your assistance.

Sincerely yours,

[signature and title of company official]

Enclosures

ATTACHMENT K

Sample DMF Closure Request

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: DMF Number:

Holder:

Subject:

Submission Information: Request for Closure

Dear Sir or Madam:

The purpose of this letter is to request that the U.S. Food and Drug Administration (FDA) close Drug Master File (DMF) No. **[insert DMF number]** covering **[insert holder's name]** **[insert subject of DMF]**, as **[insert reason for closure]**.

All parties authorized to reference DMF No. **[insert DMF number]** have been notified of our intention to close this DMF, namely, **[insert list of customers authorized to reference the DMF]**.

We understand that this DMF will no longer be available for review and, if we decide to re-activate the DMF, a complete new document will need to be submitted requesting reactivation of the original number.

In addition to the requisite duplicate copy of this closure letter, we are submitting an additional copy for your use in acknowledging receipt. Should you have any questions regarding this matter, please do not hesitate to contact us. Thank you for your assistance.

Sincerely yours,

[signature and title of company official]

Enclosures

ATTACHMENT L

Sample Cover Letter for Reactivation of a Closed DMF

[Company Letterhead]

[Date]

Drug Master File Staff
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: DMF Number:

Holder:

Subject:

Submission Information: Reactivation of a Closed DMF

Dear Sir or Madam:

The purpose of this letter is request that the U.S. Food and Drug Administration (FDA) reactivate Drug Master File (DMF) No. [insert DMF number] covering [insert holder's name] [insert subject of DMF]. A complete resubmission is enclosed, including new, original, signed Statements of Commitment.

In addition to the requisite duplicate copy of this letter and its enclosure, we are submitting an additional copy of this letter for your use in acknowledging receipt. Should you have any questions regarding this matter, please do not hesitate to contact us. Thank you for your assistance.

Sincerely yours,

[signature and title of company official]

Enclosures

4850-5672-6288, v. 2