



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 601

[Docket No. FDA-2019-N-1363]

RIN 0910-AH50

Biologics License Applications and Master Files

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend its regulations concerning the use of master files for biological products. This action, if finalized, will allow certain biological products approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act) to continue to incorporate by reference information about drug substances, drug substance intermediates, or drug products contained in master files after those products are deemed to be licensed under the Public Health Service Act (PHS Act) on March 23, 2020. The proposed rule also codifies FDA's practice of permitting applications for biological products submitted under the PHS Act to incorporate by reference information other than drug substance, drug substance intermediate, or drug product information contained in a master file. In addition, the proposed rule codifies FDA's practice of permitting investigational new drug applications to incorporate by reference any information contained in a master file for products subject to licensure under the PHS Act.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2019-N-1363 for “Biologics License Applications and Master Files.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover

sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public docket, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Kavita Vyas, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 4154, Silver Spring, MD 20993-0002, 301-796-4787, kavita.vyas@fda.hhs.gov; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

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I. Executive Summary

A. *Purpose of the Proposed Rule*

FDA proposes to amend its regulations to implement certain aspects of section 7002(e) of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The proposed rule is necessary to avoid unnecessary disruptions with respect to biological products originally approved under section 505 of the FD&C Act (21 U.S.C. 355) when their applications are deemed to be licenses under the PHS Act and to prevent potential drug shortages when those products are transitioned to being regulated under section 351 of the PHS Act (42 U.S.C. 262). The proposed rule will also update the regulation to reflect FDA's longstanding practices regarding the use of master files referenced in applications for biological products submitted under section 351 of the PHS Act.

B. *Summary of the Major Provisions of the Proposed Rule*

FDA proposes to amend its regulations concerning the use of master files for biological products. The proposed rule would allow certain biological products, originally approved in a new drug application (NDA) under the FD&C Act, to continue relying on a drug master file for information on a drug substance, drug substance intermediate, or drug product (DS/DSI/DP) after the NDA is deemed to be a license for a biological product under the PHS Act on March 23, 2020. The proposed rule also codifies FDA's existing practice that a biological product in a biologics license application (BLA) under the PHS Act may rely on a master file, except for information regarding a drug substance, drug substance intermediate, or drug product. In addition, the rule codifies FDA's practice that an investigational new drug application (IND) for a biological product may incorporate by reference any information, including drug substance, drug substance intermediate, and drug product information, contained in a master file.

C. Legal Authority

FDA is proposing to amend its regulations, in part, to implement section 7002(e) of the BPCI Act. FDA's authority for this rule also derives from the biological product provisions of the PHS Act (42 U.S.C. 262 and 264), and the provisions of the FD&C Act (21 U.S.C. 321, *et seq.*) applicable to drugs, including section 701 (21 U.S.C. 371); the FD&C Act provisions are applicable to biological products under section 351(j) of the PHS Act.

D. Costs and Benefits

FDA anticipates that affected entities would incur minimal costs to read and understand the rule. By allowing transitioned products to continue to incorporate by reference information contained in existing master files, FDA avoids imposing a potential new regulatory burden. FDA projects that over 10 years at a discount rate of 7 percent the proposed rule would generate annualized net cost savings ranging from \$0.3 million to \$4.6 million with a primary estimate of \$2.5 million; over 10 years at a discount rate of 3 percent the proposed rule would generate annualized net cost savings ranging from \$0.3 million to \$4.8 million with a primary estimate of \$2.6 million.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
BLA	Biologics License Application
BPCI Act	Biologics Price Competition and Innovation Act of 2009
DMF	Drug Master File
DP	Drug Product
DS	Drug Substance
DSI	Drug Substance Intermediate
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	U.S. Food and Drug Administration
IND	Investigational New Drug Application
NDA	New Drug Application
PHS Act	Public Health Service Act

III. Background

A. Introduction

This proposed rule, when finalized, would amend FDA regulations relating to the use of master files in applications for biological products subject to regulation under the PHS Act. Section 7002(b)(1) of the BPCI Act revised section 351(i) of the PHS Act, in part, to amend the definition of a “biological product” to include a “protein (except any chemically synthesized polypeptide).”¹ A number of products approved in NDAs under section 505 of the FD&C Act meet the revised definition of biological product. Also, section 7002(e)(4) of the BPCI Act provided that, on March 23, 2020, an application for a biological product approved under section 505 of the FD&C Act “shall be deemed to be a license for the biological product under” section 351 of the PHS Act. This rule implements FDA’s interpretation of the “deemed to be a license” provision of the BPCI Act with respect to the use of master files.² In addition, this rule codifies current Agency practices relating to the use of master files referenced in applications for biological products.

B. FDA’s Current Regulatory Framework

1. What Are Master Files?

Master files are submissions to the Agency that may be used to provide detailed, confidential information to the Agency about facilities, processes, or articles used in the manufacturing, processing, packaging, or storing of one or more human drugs. Information

¹ On December 12, 2018, FDA issued a proposed rule regarding its interpretation of the terms “protein” and “chemically synthesized polypeptide” as used in section 351(i) of the PHS Act (“Definition of the term ‘Biological Product’”, 83 FR 63817).

² For more information about FDA’s interpretation of the “deemed to be a license” provision of the BPCI Act, see guidance for industry entitled “Interpretation of the ‘Deemed to be a License’ Provision of the Biologics Price Competition and Innovation Act of 2009” (December 2018). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

contained in a master file can be used to support a submission to FDA by an applicant or sponsor. The holder of a master file can authorize one or more applicants or sponsors to incorporate by reference information contained in the master file to support a submission to FDA without having to disclose the information in that master file (which may contain trade secrets or other confidential commercial information) to the applicants or sponsors.^{3,4} The submission of a master file is at the sole discretion of the master file holder. Ordinarily, FDA neither independently reviews nor approves submissions to a master file; instead, the Agency reviews such information only in the context of an application that incorporates by reference information contained in that master file.

a. Drug master files. Some master files contain information that is relevant to applications for drug products. For products regulated under section 505 of the FD&C Act, FDA defines the term “drug master file” (DMF) in its drug regulations (§ 314.420(a) (21 CFR 314.420(a))) and explicitly provides that “[a]n 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 of the master file authorizes the incorporation (§ 314.420(b)). Section 314.420 also describes several types of DMFs, each of which typically contains certain kinds of information (§ 314.420(a)): drug substance, drug substance intermediate, and materials used in their preparation, or drug product (referred to as Type II DMFs); packaging materials (Type III); excipient, colorant, flavor, essence, or materials used in their preparation (Type IV); and FDA-accepted reference information (Type V). (See also FDA Guidance for Industry entitled “Drug Master Files:

³ See, e.g., 21 CFR 314.420 and 47 FR 46622 at 46642 (October 19, 1982).

⁴ The holder of a master file (including a drug master file) who expects that information in the file will be incorporated by reference both in a BLA and in an NDA or abbreviated new drug application (ANDA) need only submit the master file to the Agency once.

Guidelines,” September 1989, available at

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm> (accessed March 2019).)

b. Other master files. FDA also permits reference to master files that are not addressed by § 314.420, some of which contain information that is relevant to applications for biological products.⁵ The Agency’s approach to the terminology for types of master files used for products regulated under the PHS Act has generally tracked its approach to the types of DMFs (e.g., Type II, Type III) used for products regulated under the FD&C Act.

2. Biologics License Applications and Master Files

a. FDA generally permits BLAs to incorporate by reference information contained in master files. Just as FDA permits NDAs and ANDAs under the FD&C Act to incorporate by reference certain information contained in DMFs, the Agency also generally permits applications under the PHS Act (BLAs) to incorporate by reference certain information contained in master files, including DMFs.

For most categories of information and most application types (including BLAs and INDs), the needs of master file holders, applicants and sponsors, and FDA have been adequately met through this incorporation-by-reference mechanism. This mechanism allows applicants and sponsors to refer to information contained in master files without having knowledge of the contents of those master files (§ 314.420; 47 FR 46622 at 46642). For products licensed under section 351 of the PHS Act, FDA has permitted, and will generally continue to permit, the use of information contained in most types of master files (such as information about excipients, stabilizers, penetrants, or materials used in the preparation of DS/DSI/DP) because the applicant

⁵ See, e.g., 21 CFR 601.51(a).

generally has the ability to independently identify and mitigate the risk posed to product quality by such components. For example, applicants are permitted to incorporate by reference in their BLA information on container closures contained in a master file. This is the case because an applicant can independently identify the risk to product quality posed by a container closure (for example, by leachables in the closure) by performing appropriate studies on stability and adequateness for intended use and then taking steps to mitigate any risks identified (for example, by implementing appropriate testing and controls). Thus, in such cases, the feasibility of testing to confirm the adequateness of intended container closures mitigates the risks to quality arising from the applicant's lack of access to the information contained in the master file.

Accordingly, proposed § 601.2(i) would codify FDA's longstanding practice of permitting biological products in BLAs to incorporate by reference most categories of information contained in master files (other than information about DS/DSI/DP, discussed below).

b. FDA currently does not permit biological products in BLAs to incorporate by reference drug substance, drug substance intermediate, or drug product information in master files. Although FDA's approach to the use of master files in BLAs largely parallels its approach to the use of DMFs in applications under the FD&C Act, there is a significant difference: unlike applications submitted under section 505 of the FC&C Act, for biological products in BLAs, the Agency has, as a scientific matter, expected applicants to submit information about DS/DSI/DP directly to the BLA rather than incorporating it by reference to a master file. (See, e.g., FDA Guidance for Industry entitled "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" April 2015, available at

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf> (accessed March 2019).)

The risk associated with the manufacture of complex biological products is generally significantly higher than that associated with the manufacture of chemical entities, which are often less complex.⁶ This is because most biological products tend to have certain features (e.g., amino acid sequence, glycosylation, folding, cellular phenotype) essential to their intended effect and can be very sensitive to changes to their manufacturing process. In addition, biological products derived from biological sources may be complex heterogeneous mixtures, which provides another basis for having consistent process controls to ensure quality.

For these reasons, the Agency considers the establishment and function of a robust quality assurance program, with intimate knowledge of all manufacturing steps, to be essential for controlling and evaluating the process and the biological product, and for mitigating product quality risks. The applicant for a BLA is expected to have knowledge of and direct control over the manufacturing process for the DS/DSI/DP for a biological product (21 CFR 601.2 and 601.20). Absent this knowledge and control, the applicant generally cannot operate a robust quality assurance program that independently identifies and mitigates quality risks, which is critical to assuring the quality of a biological product.

As a scientific matter, given the complexity of biological products, the Agency considers it generally impractical for the applicant to confirm the DS/DSI/DP quality characteristics of a biological product without complete knowledge of, and control over, all aspects of the manufacturing process. FDA has concluded that the risk to quality arising from the

⁶ The Agency recognizes that, in limited circumstances, this may not always be the case; however, for purposes of administrative efficiency and predictability, the Agency is proposing a bright line between BLAs and NDAs regarding the referencing of master files for DS/DSI/DP information for biological products.

fragmentation of information about DS/DSI/DP for a biological product between a master file and a BLA is very difficult to mitigate. As a result, FDA believes that this type of information is generally best submitted to the Agency directly in the BLA, and that a BLA that incorporates by reference DS/DSI/DP information for a biological product contained in a master file is generally inconsistent with biological product licensing requirements.^{7,8}

Accordingly, proposed § 601.2(g) would codify FDA's longstanding practice of not permitting a biological product in a BLA to incorporate by reference information regarding DS/DSI/DP contained in master files.

3. The Biologics Price Competition and Innovation Act of 2009

Section 7002(b) of the BPCI Act amended, in part, the definition of a “biological product” in the PHS Act to include a “protein (except any chemically synthesized polypeptide).”⁹ Accordingly, under section 351(i) of the PHS Act, a “biological product” is now defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, *protein (except any chemically synthesized polypeptide)*, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings” (section 351(i) of the PHS Act; emphasis added).

⁷ FDA may permit, and generally will continue to permit, an applicant to incorporate by reference certain information about a product that is not the subject of the applicant's own BLA, such as information about a comparator product used in studies intended to support approval of the applicant's BLA. Incorporation of such information by reference generally does not raise similar concerns relating to an applicant's knowledge and control over all aspects of the manufacturing process for the product that is the subject of the applicant's own BLA.

⁸ In lieu of the use of master files, other types of contract manufacturing arrangements can be considered if the sponsor does not intend to manufacture all aspects of the product for licensure and the licensee assumes responsibility for compliance with the applicable product and establishment standards. (See, e.g., FDA guidance for industry entitled “Cooperative Manufacturing Arrangements For Licensed Biologics,” November 2008, available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-bio-gen/documents/document/ucm069908.pdf> (accessed March 2019).)

⁹ See footnote 1.

Some protein products have historically been approved under section 505 of the FD&C Act. However, section 7002(e) of the BPCI Act provides that a marketing application for a “biological product” must be submitted under section 351 of the PHS Act (subject to certain exceptions during a transition period ending on March 23, 2020). Section 7002(e) of the BPCI Act also provides that, on March 23, 2020, an application for a biological product approved under section 505 of the FD&C Act “shall be deemed to be a license for a biological product under section 351” of the PHS Act.¹⁰ Such approved applications are referred to as “deemed BLAs” in this document.

C. Need for the Regulation

1. The Biologics Price Competition and Innovation Act of 2009 and the Use of Drug Master Files in BLAs

The BPCI Act is silent about implementation of the “deemed to be a license for a biological product” provision. In March 2016, FDA published a draft guidance for industry entitled “Interpretation of the ‘Deemed to be a License’ Provision of the Biologics Price Competition and Innovation Act of 2009” (see 81 FR 13373, March 14, 2016). Footnote 12 of that draft guidance explained that for sponsors of proposed protein products who intend to submit a BLA, a Type II DMF for a drug substance, drug substance intermediate, or drug product would not be acceptable for a BLA because a license holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license. The footnote went on to provide that FDA is considering a mechanism that, in limited circumstances, would allow holders of approved applications under section 505 of the

¹⁰ See FDA Guidance for Industry entitled “Interpretation of the ‘Deemed to be a License’ Provision of the Biologics Price Competition and Innovation Act of 2009” (December 2018). Available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf> (accessed March 2019).

FD&C Act that reference a Type II DMF to continue to reference the DMF after the application is deemed to be a license under the PHS Act on March 23, 2020. FDA finalized this guidance in December 2018 (available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf> (accessed March 2019)), after considering comments in its draft recommendations and without including the corresponding footnote from the draft guidance because this proposed rule would establish such a mechanism, while also codifying the general longstanding practice that BLAs and INDs for biological products can reference information in master files except, in the case of BLAs, for DS/DSI/DP information for a biological product.

2. Mechanism To Permit the Continued Use of Currently Referenced DMFs by “Deemed BLAs”

Biological products regulated under the FD&C Act have been able to incorporate by reference DS/DSI/DP information contained in DMFs to support the approval of NDAs. As explained above, for biological products licensed under section 351 of the PHS Act, incorporating by reference information contained in master files on DS/DSI/DP generally is not permitted.

This proposed regulation addresses, in part, a specific issue related to implementation of the “deemed to be a license” provision of the BPCI Act: whether applications approved under section 505 of the FD&C Act may continue to incorporate by reference DS/DSI/DP information contained in DMFs once the applications are deemed to be BLAs subject to licensure and regulation under the PHS Act.

To date, FDA has identified approximately 89 applications approved under the FD&C Act that will be deemed licensed under the PHS Act on March 23, 2020. Approximately 17 of

these applications incorporate by reference information on DS/DSI/DP contained in DMFs. Furthermore, the DS/DSI/DP information incorporated by reference into these 17 applications is drawn from only 7 DMFs. Thus, this use of DMFs for DS/DSI/DP information involves a small subset of the deemed BLAs and only a very small number of DMFs.

In light of FDA's longstanding practice of not permitting a biological product in a BLA to incorporate by reference information regarding DS/DSI/DP contained in a master file, the Agency is considering the appropriate regulatory approach to the relatively few deemed BLAs that reference DS/DSI/DP information contained in DMFs. The Agency is evaluating the risks and benefits of allowing these deemed BLAs to continue incorporating by reference this type of information from those DMFs. The analysis takes into account clinical considerations and product availability, as well as the limited number of applications and the limited number of DMFs that are involved. Based on this analysis, the Agency proposes that for biological products, the appropriate mechanism with respect to addressing incorporation by reference of DS/DSI/DP information contained in DMFs would be to implement the least disruptive approach.

Some of the deemed BLAs that currently incorporate by reference information contained in DMFs to support the application were approved by the Agency based in part on DS/DSI/DP information contained in those DMFs. Many of these products have been marketed for decades. Over this period, none of these products have been withdrawn or removed from the market for reasons of safety or effectiveness. For these products, the Agency has no reason to believe that the March 23, 2020, transition in and of itself introduces new risks to product safety, purity, and potency.

For some biological products, such as certain reproductive hormones, treating the deemed BLAs like other applications for biological products under the PHS Act with regard to the use of DS/DSI/DP information contained in a DMF would present a considerable challenge. Nearly all approved applications for these biological products incorporate by reference DS/DSI/DP information contained in a DMF. This incorporation by reference has resulted in drug substances for these products of acceptable quality for decades. For example, multiple Human Chorionic Gonadotropins from urinary sources have been on the market since the mid-1970s using DMFs for information on the drug substance, with changes to the product being handled through the DMF pathway. Disallowing use of DMFs for these deemed BLAs would curtail or halt production of these products, resulting in imminent or immediate drug shortages with considerable negative impacts on public health. FDA does not believe it was Congress's intent when enacting section 7002(e) of the BPCI Act that deemed BLAs would need to be removed from the market on March 23, 2020.

Furthermore, the general concern about fragmentation of DS/DSI/DP information associated with the use of DMFs is lessened in the case of the deemed BLAs by the existence of generally longstanding relationships between the deemed-BLA applicants and the DMF holders. For example, the license holder of a deemed BLA may have accumulated knowledge about the quality of the biological product supplied by the DMF holder over an extended period. This accumulated knowledge allows the deemed BLA holder to implement a more robust control strategy to mitigate the risk to product quality posed by the applicant's limited knowledge of the manufacturing process described in the DMF.

In light of these facts, FDA believes that permitting a limited number of deemed BLAs to continue to incorporate by reference DS/DSI/DP information contained in a limited number of

DMFs will, on balance, protect and promote the public health. In contrast, if non-deemed BLAs were to reference an existing DMF, they would generally not have the benefit of this accumulated knowledge, and thus would not be able to mitigate the resulting fragmentation of information and risk to product quality as effectively. Similarly, while the lack of overt safety signals and the absence of concerns about efficacy provide a rationale for allowing a deemed BLA to continue to rely on DS/DSI/DP information contained in a DMF, it may not be appropriate to extend this rationale to a non-deemed BLA. For these reasons, in proposed § 601.2(h), FDA would permit only deemed BLAs that incorporate by reference information on DS/DSI/DP contained in particular DMFs in their approved applications under section 505 of the FD&C Act to continue doing so after these products are deemed to be licensed under the PHS Act on March 23, 2020. BLAs for other biological products will continue to not be permitted to incorporate by reference DS/DSI/DP information contained in a master file, consistent with FDA's longstanding practice. Also, to enable innovation for deemed BLAs that reference an existing DMF, it is important to preserve the ability to make changes to the existing DMFs. Therefore, the proposed rule will permit holders of existing DMFs referenced for deemed BLAs before transition to modify these DMFs under § 314.420 after March 23, 2020.

3. Investigational New Drug Applications and Master Files

Section 314.420(b) provides that “[a]n investigational new drug application ... may incorporate by reference all or part of the contents of any drug master file in support of the submission” with the DMF holder's consent. In addition, FDA typically permits an IND for a biological product to incorporate by reference information contained in other master files, in addition to DMFs. Furthermore, it has been FDA's practice to permit sponsors of INDs for

biological products to incorporate by reference DS/DSI/DP information contained in a master file.

FDA permits the use of DS/DSI/DP master files in biological product INDs for several reasons. Exposure to the investigational product is limited in the IND stage because it is only administered to subjects enrolled in clinical trials, which are typically carried out in controlled settings. Accordingly, the sponsor and FDA can mitigate risk more effectively by closely monitoring patients in those trials, in order to evaluate the safety of the investigational product, which is a necessary component of the licensing process.

Permitting the sponsor of an IND for a biological product to incorporate by reference DS/DSI/DP information contained in master files may also facilitate product development. Without this option, a sponsor might choose not to make the significant investment to manufacture the necessary DS/DSI/DP for a biological product at this early stage of development. However, even in cases where an IND sponsor of a biological product incorporates by reference DS/DSI/DP information contained in a master file, FDA expects the sponsor to have knowledge of and direct control of the manufacturing process by later stages of development.

Therefore, in proposed § 601.2(j), FDA clarifies and codifies this practice.

D. History of the Rulemaking

In response to the BPCI Act, public meetings were held to discuss various aspects of the statute. Also, public comments on the current FDA practice for biological products of not accepting DMFs for biological products in BLAs were received in the context of the draft guidance for industry entitled “Interpretation of the ‘Deemed to be a License’ Provision of the Biologics Price Competition and Innovation Act of 2009” (see 81 FR 13373). Comments, in

part: (1) urged FDA to clarify its position on the use of Type II DMFs for applications that will be deemed BLAs on March 23, 2020, and, at least for pancreatic enzyme products, recommended FDA permit applications to reference Type II DMFs after March 23, 2020, even if the application was not approved as an NDA prior to the transition date;¹¹ (2) urged FDA to adopt a flexible approach toward the continued referencing of existing DMFs;¹² and (3) sought clarity on the use of other categories of DMFs (e.g., Type III DMFs).¹³ FDA finalized this guidance in December 2018 after considering comments in its draft recommendations. With respect to the comments concerning DMFs, the Agency undertook an analysis of the number of DMFs, the number of applications referencing these DMFs, and considered the consequences of not taking any action or taking the proposed action. The Agency addressed all the concerns identified in the public comments through the actions described in this proposed rule, which includes allowing the incorporation by reference of DS/DP/DSI information contained in DMFs, provided the DMFs were referenced prior to the application being deemed a BLA on March 23, 2020, and providing clarity on the use of other categories of DMFs in BLAs.

IV. Legal Authority

FDA is proposing to amend its regulations, in part, to implement certain aspects of section 7002(e) of the BPCI Act. FDA's authority for this proposed rule also derives from the biological product licensing provisions of the PHS Act and the provisions of the FD&C Act (21 U.S.C. 321, *et seq.*) applicable to drugs. Under these provisions, FDA has the authority to issue regulations designed to ensure, among other things, that biological products are safe, pure, and

¹¹ See Comment from Curemark, LLC to Docket No. FDA-2015-D-4750 (available at <https://www.regulations.gov>).

¹² See Comment from Pharmaceutical Research and Manufacturers of America (PhRMA) to Docket No. FDA-2015-D-4750 (available at <https://www.regulations.gov>).

¹³ See Comments from Biotechnology Innovation Organization and from Novo Nordisk, Docket No. FDA-2015-D-4750.

potent and manufactured in accordance with current good manufacturing practice. FDA also has general authority to promulgate regulations for the efficient enforcement of the FD&C Act and the PHS Act, under section 701 of the FD&C Act and section 351(j) of the PHS Act.

V. Description of the Proposed Rule

We propose to amend § 601.2 to add new paragraphs (g), (h), (i), and (j). Specifically, the proposed rule will allow applications for biological products approved under section 505 of the FD&C Act to continue to incorporate by reference DS/DP/DSI information contained in DMFs, provided the DMFs were referenced before March 23, 2020. Also, this proposed rule essentially codifies, for biological products, the longstanding Agency practices of permitting BLAs to incorporate by reference information other than on DS/DP/DSI contained in master files and INDs to incorporate any information contained in master files. FDA is aware that there are combination products approved in BLAs under the PHS Act and ~~considers that~~ the rationale described in this rule for biological products also applies to the biological constituent part of such combination products. FDA seeks comments on whether applications for combination products submitted in BLAs under the PHS Act should be permitted to incorporate by reference DS/DSI/DP information for any non-biological constituent part (for example, the drug constituent part of an antibody drug conjugate).

A. Proposed Provision of Paragraph (g)

Proposed new paragraph (g) codifies the Agency's practice of not permitting applications for biological products submitted under section 351 of the PHS Act to incorporate by reference information on DS/DSI/DP contained in a master file. Deemed BLAs are excluded from this provision and are addressed in proposed new paragraph (h).

B. Proposed Provision of Paragraph (i)

Proposed new paragraph (i) codifies the Agency's practice of permitting applications for biological products submitted under section 351 of the PHS Act to incorporate by reference information other than DS/DSI/DP information contained in master files, including in DMFs.

C. Proposed Provision of Paragraph (j)

Proposed new paragraph (j) codifies the Agency's practice of permitting INDs to incorporate by reference information contained in master files, including information on DS/DSI/DP.

D. Proposed Provision of Paragraph (h)

Proposed new paragraph (h) addresses applications transitioning on March 23, 2020, under section 7002(e) of the BPCI Act. It allows an application for a biological product that has been approved under section 505 of the FD&C Act and that incorporates by reference DS/DSI/DP information contained in a DMF to continue to do so after that application is deemed to be a BLA.

The proposed rule is intended to preserve the status quo both for the small number of deemed BLAs and for all other applications for biological products submitted under section 351 of the PHS Act: deemed BLAs that incorporate by reference information on DS/DSI/DP contained in a DMF at the time of their transition will be permitted to continue to do so, but no other applications for biological products will be permitted to incorporate by reference DS/DSI/DP information contained in any master files.

The proposed rule is not intended to alter a license holder's ability to modify a product under § 601.12 (21 CFR 601.12). The proposed rule is also not intended to expand or reduce the changes allowed to a deemed BLA that incorporates by reference information contained in

master files. Under the proposed rule, an applicant would be permitted to supplement a deemed BLA within the same application, as it would any other BLA under § 601.12 and the applicable bundling policy.¹⁴ However, if modifications to the deemed BLA are required that could not be effected in a supplement and a new application is required, that new BLA would not be considered a deemed BLA. As is the case with other (non-deemed) applications for biological products, the new BLA would not be permitted to reference DS/DSI/DP information contained in any master file and would need to submit this information as part of the new BLA itself.

The proposed rule is also not intended to limit or restrict the changes that may be made to any master file, including a DMF for DS/DSI/DP information.

The proposed rule thus preserves the relationship between a DMF and the application that references it. This ensures that the transition to regulation under the PHS Act does not interrupt the supply of biological products that have already been shown to be safe and effective.

E. Proposed Records/Record Retention Requirements

None; existing records and retention requirements will continue to apply.

F. Proposed Enforcement Provisions

None; existing enforcement regulations will continue to apply.

G. Proposed Technical/Conforming Amendments

None necessary.

VI. Proposed Effective/Compliance Dates

If finalized on or before February 22, 2020, this rule would take effect on March 23, 2020.

¹⁴ See guidance for industry entitled “Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees” (December 2004). Available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm079320.pdf>. (accessed March 2019).

VII. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations “shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.” We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule does not impose any new burdens, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$154 million, using the most current (2018) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

Table 1 summarizes our estimate of the annualized costs and the annualized cost-saving benefits of the proposed rule.

Table 1.--Summary of Benefits, Costs, and Distributional Effects of Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized \$millions/year	\$2.48	\$0.33	\$4.64	2017	7%	10 years	Cost savings
		\$2.56	\$0.32	\$4.80	2017	3%	10 years	Cost savings
	Annualized Quantified					7%		
						3%		
Qualitative								
Costs	Annualized Monetized \$millions/year	\$0.00	\$0.00	\$0.00	2017	7%	10 years	
		\$0.00	\$0.00	\$0.00	2017	3%	10 years	
	Annualized Quantified					7%		
						3%		
Qualitative								
Transfers	Federal Annualized Monetized \$millions/year					7%		
						3%		
	From/To	From:			To:			
	Other Annualized Monetized \$millions/year					7%		
						3%		
From/To	From:			To:				
Effects	State, Local or Tribal Government: None Small Business: None Wages: None Growth: None							

In line with Executive Order 13771, in table 2 we estimate present and annualized values of costs and cost savings over an infinite time horizon. Based on these cost savings, this proposed rule would be considered a deregulatory action under Executive Order 13771.

Table 2.--EO 13771 Summary Table (\$ million in 2016 dollars over an infinite horizon)

	Lower Bound	Primary (7%)	Upper Bound	Lower Bound	Primary (3%)	Upper Bound

	(7%)		(7%)	(3%)		(3%)
Present Value of Costs	\$0.02	\$0.02	\$0.02	\$0.02	\$0.02	\$0.03
Present Value of Cost-Savings	\$2.49	\$18.66	\$34.83	\$2.80	\$22.47	\$42.14
Present Value of Net Costs	(\$2.47)	(\$18.64)	(\$34.81)	(\$2.77)	(\$22.45)	(\$42.12)
Annualized Costs	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00
Annualized Cost-Savings	\$0.17	\$1.31	\$2.44	\$0.08	\$0.67	\$1.26
Annualized Net Costs	(\$0.17)	(\$1.30)	(\$2.44)	(\$0.08)	(\$0.67)	(\$1.26)

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 1) and at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This proposed rule refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 314 and 21 CFR part 601 have been approved under OMB control numbers 0910-0001 and 0910-0338, respectively.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies

that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. Reference

The following reference is on display at the Dockets Management Staff (see ADDRESSES) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at <https://www.regulations.gov>.

1. FDA, Preliminary Regulatory Impact Analysis, “Biologics License Applications and Master Files.”

List of Subjects

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 601 be amended as follows:

PART 601--LICENSING

1. The authority citation for part 601 is revised to read as follows:

Authority: 15 U.S.C. 1451-1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105-115, 111 Stat. 2322 (21 U.S.C. 355 note), sec 7002(e), Pub. L. 111-148, 124 Stat.817.

2. Amend § 601.2 by adding paragraphs (g), (h), (i), and (j) to read as follows:

§ 601.2 Applications for biologics licenses; procedures for filing.

* * * * *

(g) Except as provided in paragraph (h) of this section, an application for a biological product submitted to the Food and Drug Administration for licensure under section 351 of the Public Health Service Act; licensed under section 351 of the Public Health Service Act; or deemed, under section 7002(e) of the Biologics Price Competition and Innovation Act of 2009, to be licensed under section 351 of the Public Health Service Act may not incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a master file, including a drug master file submitted under § 314.420 of this chapter.

Amendments and supplements submitted in support of these applications also may not incorporate by reference such information contained in a master file.

(h) An application for a biological product that:

(1) Was approved under section 505 of the Federal Food, Drug, and Cosmetic Act;

(2) Was deemed on March 23, 2020, to be a license for the biological product under section 351 of the Public Health Service Act; and

(3) On March 23, 2020, incorporated by reference drug substance, drug substance intermediate, and/or drug product information contained in a drug master file submitted under § 314.420 of this chapter may continue to incorporate by reference the information contained in that drug master file after March 23, 2020. Amendments and supplements submitted in support of these applications may also incorporate by reference the information contained in that drug master file.

(i) Nothing in paragraph (g) of this section limits or restricts an application for a biological product submitted to the Food and Drug Administration for licensure under section 351 of the Public Health Service Act; licensed under section 351 of the Public Health Service Act; or deemed, under section 7002(e) of the Biologics Price Competition and Innovation Act of 2009, to be licensed under section 351 of the Public Health Service Act from incorporating by reference information contained in any master file, including a drug master file submitted under § 314.420 of this chapter, that is not drug substance, drug substance intermediate, or drug product information. Amendments and supplements submitted in support of these applications may also incorporate by reference such information contained in a master file.

(j) Nothing in paragraph (g) of this section limits or restricts an investigational new drug application for a biological product from incorporating by reference any information, including drug substance, drug substance intermediate, and drug product information, contained in a master file, including a drug master file submitted under § 314.420 of this chapter.

Dated: June 17, 2019.

Norman E. Sharpless,
Acting Commissioner of Food and Drugs.

Dated: June 21, 2019.

Eric D. Hargan,
Deputy Secretary,
Department of Health and Human Services.

[FR Doc. 2019-13753 Filed: 6/27/2019 8:45 am; Publication Date: 6/28/2019]