## PART 39—AIRWORTHINESS DIRECTIVES

■ 1. The authority citation for part 39 continues to read as follows:

**Authority:** 49 U.S.C. 106(g), 40113, 44701.

**§ 39.13 [Amended]**

■ 2. The FAA amends § 39.13 by adding the following new airworthiness directive:

**2024–03–04 The Boeing Company:** Amendment 39–22673; Docket No. FAA–2024–0224; Project Identifier AD–2024–00055–T.

**(a) Effective Date**

This airworthiness directive (AD) is effective February 12, 2024.

**(b) Affected ADs**

None.

**(c) Applicability**

This AD applies to The Boeing Company Model 737–8, 737–8200, and 737–9 airplanes, certificated in any category, with an original airworthiness certificate or original export certificate of airworthiness issued on or before December 20, 2023.

**(d) Subject**

Air Transport Association (ATA) of America Code 27, Flight controls.

**(e) Unsafe Condition**

This AD was prompted by a report of a missing washer and nut and consequent migrated bolt discovered by an operator during scheduled maintenance. The FAA is issuing this AD to address improper torque of the aft rudder quadrant output rod fasteners, which may cause a disconnect between the aft rudder quadrant and the output rod, which would result in loss of rudder control via the rudder pedals to counter an engine-out scenario during takeoff/climb out or to counter a high crosswind during landing. The unsafe condition, if not addressed, could result in loss of continued safe flight and landing.

**(f) Compliance**

Comply with this AD within the compliance times specified, unless already done.

**(g) Inspection**

Within 30 days after the effective date of this AD, perform a one-time detailed visual inspection or remote video inspection of the aft rudder quadrant for missing bolts, nuts, and washers; a gap between the bolt/nut/washer and quadrant; and insufficient thread protrusion.

**Note 1 to paragraph (g):** Guidance for accomplishing the actions required by paragraph (g) of this AD can be found in Boeing Multi Operator Message MOM–MOM–23–0993–01B, dated December 27, 2023.

**(h) On-Condition Actions**

If any discrepancy is found during the inspection required by paragraph (g) of this AD, do the actions specified in paragraphs (h)(1) through (3) of this AD before further flight.

(1) Do a detailed inspection of the bolt, washer, and nut for damage and, before further flight, replace any missing or damaged bolts, washers, and nuts.

(2) Install each bolt, washer, and nut with a torque of 65 in-lb.

(3) Perform a rudder travel test to ensure that the rudder is operating correctly. If the test fails, before further flight, do applicable corrective actions and repeat until the test is passed.

**Note 2 to paragraph (h) of this AD:** Guidance for accomplishing the actions required by paragraph (h) of this AD can be found in Boeing Multi Operator Message MOM–MOM–23–0993–01B, dated December 27, 2023.

**(i) Credit for Previous Actions**

This paragraph provides credit for the actions specified in paragraphs (g) and (h) of this AD, if those actions were performed before the effective date of this AD using Boeing Multi Operator Message MOM–MOM–23–0993–01B, dated December 27, 2023.

**(j) Alternative Methods of Compliance (AMOCs)**

(1) The Manager, AIR–520, Continued Operational Safety Branch, FAA, has the authority to approve AMOCs for this AD, if requested using the procedures found in 14 CFR 39.19. In accordance with 14 CFR 39.19, send your request to your principal inspector or responsible Flight Standards Office, as appropriate. If sending information directly to the manager of the certification office, send it to the attention of the person identified in paragraph (k)(1) of this AD. Information may be emailed to: *9-ANM-Seattle-ACO-AMOC-Requests@faa.gov.*

(2) Before using any approved AMOC, notify your appropriate principal inspector, or lacking a principal inspector, the manager of the responsible Flight Standards Office.

(3) An AMOC that provides an acceptable level of safety may be used for any repair, modification, or alteration required by this AD if it is approved by The Boeing Company Organization Designation Authorization (ODA) that has been authorized by the Manager, AIR–520, Continued Operational Safety Branch, FAA, to make those findings. To be approved, the repair method, modification deviation, or alteration deviation must meet the certification basis of the airplane, and the approval must specifically refer to this AD.

**(k) Related Information**

(1) For more information about this AD, contact Anthony Caldejon, Aviation Safety Engineer, FAA, 2200 South 216th St., Des Moines, WA 98198; phone: 206–231–3534; email: *Anthony.V.Caldejon@faa.gov.*

(2) For service information identified in this AD that is not incorporated by reference, contact Boeing Commercial Airplanes, Attention: Contractual & Data Services (C&DS), 2600 Westminster Blvd., MC 110–SK57, Seal Beach, CA 90740–5600; telephone 562–797–1717; website *myboeingfleet.com.*

**(l) Material Incorporated by Reference**

None.

Issued on February 2, 2024.

**Caitlin Locke,**

*Director, Compliance & Airworthiness Division, Aircraft Certification Service.*

[FR Doc. 2024–02930 Filed 2–8–24; 2:00 pm]

**BILLING CODE 4910–13–P**

## 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:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule to amend its regulations to address the use of master files by applications licensed under the Public Health Service Act (PHS Act). This final rule codifies FDA's existing approach that former approved applications for certain biological products under the Federal Food, Drug, and Cosmetic Act (FD&C Act) that have been deemed to be licenses for the biological products under the PHS Act may continue to incorporate by reference drug substance, drug substance intermediate, or drug product (DS/DSI/DP) information contained in a drug master file (DMF) if such information was being referenced at the time the application was deemed to be a license. This final rule also codifies FDA's general practices regarding the referencing of information in master files by applications licensed under the PHS Act, including applications for combination products licensed under the PHS Act, and by investigational new drug applications (INDs) for products that would be subject to licensure under the PHS Act.

**DATES:** This rule is effective March 13, 2024.

**ADDRESSES:** For access to the docket to read background documents or comments received, go to *https://www.regulations.gov* and insert the docket number found in brackets in the heading of this final rule into the ''Search'' box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

**FOR FURTHER INFORMATION CONTACT:** Natalia Comella, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 3141, Silver Spring, MD 20993–0002, 301–796–6226, *natalia.comella@fda.hhs.gov;* or James Myers, 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.

**SUPPLEMENTARY INFORMATION:**

**Table of Contents**



## I. Executive Summary

### *A. Purpose and Coverage of the Final Rule*

This final rule amends FDA's regulations to codify FDA's existing approach that former approved applications for biological products under the FD&C Act that have been deemed, pursuant to the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), to be licenses for the biological products under the PHS Act can continue to incorporate by reference DS/DSI/DP information contained in a DMF if such information was referenced at the time the application was deemed to be a license, in order to avoid the risk of unnecessary disruptions and potential drug shortages for these products. This final rule also amends the regulations to reflect FDA's longstanding practices regarding the referencing of information contained in master files by biologics license applications (BLAs). The final rule codifies FDA's practice and policy that INDs for products that would be subject to licensure under the PHS Act may incorporate by reference any information in a master file. The final rule also amends the regulations to address the use of master files for the constituent parts of combination products licensed under the PHS Act.

### *B. Summary of the Major Provisions of the Final Rule*

Under this final rule, FDA is amending its regulations to address the use of master files by BLAs and INDs for products subject to licensure under the PHS Act. This final rule confirms that former approved applications for biological products in new drug applications (NDAs) under the FD&C Act that have been deemed, pursuant to the BPCI Act, to be licenses for the biological products under the PHS Act may continue relying on DMFs for information on DS/DSI/DP if such information in a master file was relied on at the time the application was deemed to be a license under the PHS Act. For BLAs outside the scope of the circumstances described in the preceding sentence, the final rule also codifies FDA's existing practice that BLAs may not rely on a master file for DS/DSI/DP information but may rely on a master file for other kinds of information.[1] This final rule also codifies FDA's practice that an IND for a product that would be subject to licensure as a BLA may incorporate by reference any information, including DS/DSI/DP information, contained in a master file. This final rule also provides that, while BLAs under the PHS Act may not incorporate by reference DS/DSI/DP information contained in master files for biological product constituent parts of combination products, they may do so for non-biological product constituent parts.

### *C. Legal Authority*

This final rule amends FDA's regulations, as part of FDA's implementation of the BPCI Act, as amended by the Further Consolidated Appropriations Act, 2020 (FCA). FDA's authority for this rule also derives from the biological product licensing provisions of the PHS Act and the provisions of the FD&C Act applicable to drugs; the FD&C Act provisions are applicable to biological products under the PHS Act.

### *D. Costs and Benefits*

By allowing certain BLAs to continue referencing a DMF for DS/DSI/DP information, FDA avoids imposing a potential new regulatory burden. Affected entities will incur minimal costs to read and understand the rule. FDA estimates that over 10 years at a discount rate of 7 percent, the final rule will generate annualized net cost savings ranging from $0.40 million to $5.19 million with a primary estimate of $2.80 million; at a discount rate of 3 percent, the final rule will generate annualized net cost savings ranging from $0.37 million to $5.17 million with a primary estimate of $2.77 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. |
| FCA Act | Further Consolidated Appropriations Act, 2020. |
| IND | Investigational New Drug Application. |
| IVD | In Vitro Diagnostic. |
| NDA | New Drug Application. |
| PHS Act | Public Health Service Act. |

## III. Background

### *A. History of This Rulemaking*

In the proposed rule,[2] FDA announced its intention to amend its regulations to address the use of master files by BLAs. Section 7002(b)(1) of the BPCI Act revised section 351(i) of the PHS Act (42 U.S.C. 262(i)), in part, to amend the definition of a ''biological product'' to include a ''protein (except any chemically synthesized polypeptide).'' Section 605 of the FCA Act (Pub. L. 116–94) later amended this definition to remove the parenthetical ''(except any chemically synthesized polypeptide).'' [3] Also, section 7002(e)(4) of the BPCI Act provided that, on March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act (21 U.S.C. 355) ''shall be deemed to be a license for the biological product under'' section 351 of the PHS Act.[4] A number of products that were

[1] FDA notes that an applicant may seek guidance from the relevant review division at the Agency if the applicant is unsure whether information in a master file constitutes DS/DSI/DP information in the context of a particular BLA.

[2] ''Biologics License Applications and Master Files,'' 84 FR 30968 (June 28, 2019).

[3] See FDA's final rule issued on February 21, 2020, regarding its interpretation of the term ''protein'' as used in section 351(i)(1) of the PHS Act (definition of the term ''Biological Product,'' 85 FR 10057).

[4] Section 607 of Division N of the FCA Act, 2020 (Pub. L. 116–94, 133 Stat 3127), amended section

approved in NDAs under section 505 of the FD&C Act met the revised definition of a biological product and the applications for these products were deemed to be biologics license applications on March 23, 2020 (deemed BLAs). The proposed rule described FDA's interpretation of the ''deemed to be a license'' provision of the BPCI Act with respect to the use of master files by BLAs.[5]

The preamble to the proposed rule described FDA's current regulatory framework and practices regarding the use of master files by BLAs and INDs. The proposed rule also described a mechanism to provide for continued use of DMFs referenced by deemed BLAs. The preamble to the proposed rule further noted that there are combination products approved in BLAs under the PHS Act and that the rationale described in the proposed rule for the Agency's proposed approach to BLAs also applied to the biological product constituent part(s) of such combination products. FDA sought 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 product constituent part (for example, the drug constituent part of an antibody-drug conjugate).

In this final rule, FDA is finalizing the approach described in the proposed rule with several changes. Based on comments received, FDA is adding provisions codifying the use of master files by BLAs under the PHS Act for combination products. In addition, FDA is making nonsubstantive changes to the structure of the codified language to improve its readability.

7002(e)(4) of the BPCI Act to provide that FDA will continue to review an application for a biological product under section 505 of the FD&C Act after March 23, 2020, so long as that application was submitted under section 505 of the FD&C Act, is filed not later than March 23, 2019, and is not approved as of March 23, 2020. If such an application is approved under section 505 of the FD&C Act before October 1, 2022, it will be deemed to be a license for the biological product under section 351 of the PHS Act upon approval (see section 7002(e)(4)(B)(iii) and (vi) of the BPCI Act).

[5] For more information about FDA's interpretation of the ''deemed to be a license'' provision of the BPCI Act, see the guidance for industry entitled ''Interpretation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009'' (Ref. 1). 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/guidance-compliance-regulatory-information/guidances-drugs.*

*B. Summary of Comments to the Proposed Rule*

We received fewer than 30 comment letters on the proposed rule. Several comments generally support the proposed rule, in whole or in part. Several comments recommend revisions to, or disagree with, individual provisions in the proposed rule. Some comments address the use of master files for combination products in response to FDA's request for public comment in the preamble to the proposed rule.

## IV. Legal Authority

We are issuing this final rule under section 7002(e) of the BPCI Act, as amended by section 607 of the FCA Act. FDA's authority for this final 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 potent and manufactured in accordance with current good manufacturing practice. FDA also has general authority to issue regulations for the efficient enforcement of the FD&C Act under section 701 of the FD&C Act, which is applicable to biological products pursuant to section 351(j) of the PHS Act.

## V. Comments on the Proposed Rule and FDA Response

*A. Introduction*

We received fewer than 30 comment letters on the proposed rule by the close of the comment period, each addressing one or more issues. We received comments from industry, individuals, and a trade organization.

We describe and respond to the comments in section V.B below. We have numbered each comment topic to help distinguish between the issues raised in the comments. We have grouped similar comments together under the same number, and, in some cases, we have separated different issues discussed in the same comment for purposes of our responses. The number assigned to each comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

In addition, FDA has restructured the codified language to address comments and for ease of reading. The paragraph numbers in the codified text and preamble of this final rule differ from those used in the proposed rule. Where applicable in this preamble, we identify the paragraphs as numbered in the proposed, as well as final, codified language. Although the codified language has been restructured for ease of reading into a new § 601.2(g), the separate paragraphs of this rule, applicable to certain deemed BLAs, to INDs for products that would be subject to licensure as a BLA, and to non-biological product constituent parts of combination products regulated under the PHS Act, each function independently to address specific circumstances and codify FDA's practices for those circumstances. In the event of a stay or invalidation of any paragraph of new § 601.2(g), those paragraphs that remain in effect would continue to function sensibly [6] to address their respective circumstances. For example, invalidation of § 601.2(g), which is specific to certain deemed BLAs, would have no effect on the provisions applicable to applications outside the scope of that paragraph.

*B. Specific Comments and FDA Response*

1. Final § 601.2(g)(1) (Proposed § 601.2(g))

We proposed that an application for a biological product submitted to FDA for licensure under section 351 of the PHS Act, licensed under section 351 of the PHS Act, or, except as provided in proposed § 601.2(h), deemed to be licensed under section 351 of the PHS Act, may not incorporate by reference DS/DSI/DP information contained in a master file (see proposed § 601.2(g)). We also proposed that amendments and supplements to these applications may not incorporate by reference such information contained in a master file.

FDA received several comments addressing this aspect of the proposed rule, some of which agree with the need for the provision and with FDA's rationale, and some of which disagree. Some of the comments that disagree propose that FDA permit BLAs more generally to incorporate by reference information on DS/DSI/DP contained in master files or permit this on a case-by-case basis. A few comments suggest that BLAs should be permitted to incorporate certain kinds of DS/DSI/DP information by reference or that BLAs for certain products should be permitted to incorporate by reference DS/DSI/DP

[6] See, *e.g., Belmont Mun. Light Dep't* v. *FERC*, 38 F.4th 173, 188 (D.C. Cir. 2022) (finding severability of portion of an administrative action, applying principle that severability is appropriate where ''the agency prefers severability to overturning the entire regulation'' and where the remainder of the regulation ''could function sensibly without the stricken provision'') (citations omitted).

information. For the reasons described below, we are not changing our approach in finalizing this proposal. However, because the final regulation also addresses combination products licensed in BLAs, final § 601.2(g)(1) (as well as final § 601.2(g)(3)) includes references to such applications. In addition, because § 601.2(g)(1) applies to a BLA regardless of submission type (*e.g.,* application for approval, licensed BLA, amendment, supplement), we have removed the reference to ''amendments'' and ''supplements.''

(Comment 1) FDA received three comments disagreeing with FDA's proposed approach and suggesting that FDA instead permit BLAs more generally to incorporate by reference DS/DSI/DP information contained in master files on a case-by-case basis. One of these comments asserts that FDA's proposal is inconsistent with applying a risk-based approach to regulatory review of applications, and, in support of a case-by-case approach, specifically suggests that FDA permit BLAs to incorporate by reference this information when it does not increase risk to the patient.

(Response 1) FDA disagrees that its proposal is inconsistent with applying a risk-based approach and declines to revise its proposal to permit incorporation by reference of DS/DSI/DP information contained in a master file on a case-by-case basis.

FDA agrees that it is important to employ a science- and risk-based approach to its regulation of BLAs. Accordingly, FDA considers the establishment and function of a robust quality assurance program to be essential for evaluating, controlling, and mitigating product quality risks. The Agency has carefully considered the (generally) complex characteristics of most biological products and the risks to product quality inherent in the manufacture of these products. As stated in the preamble to the proposed rule, 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 the manufacturing process. In addition, biological products isolated from biological sources may be complex heterogeneous mixtures. As a result of such characteristics, the manufacture of most biological products carries increased potential risk to product quality. As a scientific matter, for biological products, the Agency considers it to be generally impractical for the applicant to confirm DS/DSI/DP quality characteristics without complete knowledge of, and control over, all aspects of the manufacturing process, including the manufacturing process for the DS/DSI/DP. Absent such knowledge and control, the applicant generally cannot operate a quality assurance program that independently identifies, assesses, and mitigates quality risks, which is critical to assuring the quality of a biological product.

For biological products, FDA has found that the fragmentation of DS/DSI/DP information between a master file and a BLA results in a risk to quality that is very difficult to mitigate. Therefore, requiring DS/DSI/DP information to be submitted as part of the BLA, rather than incorporated by reference to a master file, is consistent with FDA's scientific assessment of the risks associated with this category of products and the need for BLA applicants to have direct knowledge of and control over the entire manufacturing process.

As we acknowledged in the preamble to the proposed rule, there may be some biological products for which referencing a DMF for DS/DSI/DP information presents somewhat less risk. However, FDA declines to adopt a case-by-case approach to BLAs incorporating by reference DS/DSI/DP information contained in master files. Given the complex characteristics of most biological products, the importance of the applicant's knowledge of and direct control over the manufacturing processes for biological products, and the advantages in administrative efficiency and predictability, the Agency is proceeding with an approach that draws a distinction between BLAs and NDAs with regard to the referencing of master files for DS/DSI/DP information, except for certain deemed BLAs (see section V.B.2).

(Comment 2) One comment suggests that it would be unfair to prohibit sponsors of applications for ''biological products'' from incorporating by reference DS/DSI/DP information contained in master files while permitting sponsors of applications for ''drug products'' to do so because it would create unequal starting points and incentives for product development.

(Response 2) FDA disagrees that it would be unfair to prohibit BLAs from incorporating by reference DS/DSI/DP information contained in master files while permitting applications under the FD&C Act to do so. FDA's longstanding practice of not permitting BLAs to incorporate by reference DS/DSI/DP information contained in master files is based on the differences in risk generally associated with products regulated under the PHS Act and products regulated under the FD&C Act, as described above and in the preamble to the proposed rule.

With regard to a difference in starting points and incentives, nothing in this rule prohibits an IND for a product that would be subject to licensure under section 351 of the PHS Act from incorporating by reference DS/DSI/DP information contained in a master file, in the same way that an IND can for a product that would be subject to approval under the FD&C Act. Therefore, the starting points for INDs for products that would be regulated under the PHS Act and products that would be regulated under the FD&C Act are the same in this regard. Furthermore, it should be noted that at the BLA stage the inability to incorporate by reference DS/DSI/DP information contained in a master file does not remove BLA applicants' incentives or ability to proceed with product development. An applicant who does not intend to manufacture all aspects of the product for licensure may, as stated in the preamble to the proposed rule, consider other types of cooperative manufacturing arrangements, while still assuming responsibility for meeting the applicable product and establishment standards.[7] These other arrangements would provide alternatives in cases where the incorporation by reference of a master file is not permitted.

(Comment 3) Two comments assert that BLAs should be permitted to incorporate by reference DS/DSI/DP information contained in master files because IND applications are permitted to do so.

(Response 3) FDA disagrees with these comments. FDA requires an applicant to be able to submit DS/DSI/DP information directly to the BLA because, at the time a BLA is submitted, FDA expects the sponsor to have knowledge of and direct control over the manufacturing process.

As described in the preamble to the proposed rule, INDs are permitted to incorporate by reference DS/DSI/DP information contained in master files for several reasons, including the following: exposure to the investigational product is limited to subjects enrolled in clinical trials, which are typically carried out in controlled settings; the sponsor and FDA can mitigate risk by closely monitoring patients in clinical trials to evaluate the safety of the investigational

[7] See the guidance for industry ''Cooperative Manufacturing Arrangements for Licensed Biologics'' (Ref. 2).

product; and permitting INDs to incorporate by reference DS/DSI/DP information contained in master files may facilitate product development because a sponsor might otherwise choose not to make the significant investment to manufacture the DS/DSI/DP for the product at the early, investigational stage. None of these situations apply at the time of BLA submission.

Because the rationale for permitting INDs to incorporate by reference DS/DSI/DP information contained in a master file does not apply at the BLA stage, FDA declines to change its approach and permit BLAs to incorporate such information by reference.

(Comment 4) One comment contends that BLAs should be permitted to incorporate by reference DS/DSI/DP information contained in master files because, if there are concerns with the safety of a product during the BLA review process, FDA can issue a complete response letter or request mandatory postmarketing studies and postmarketing surveillance.

(Response 4) Complete response letters are regulatory responses that convey deficiencies identified by FDA during the review and evaluation of an application. Postmarketing requirements, postmarketing commitments, and postmarketing surveillance are regulatory tools that can be used to assess and address potential product risks after the product is licensed. Complete response letters, postmarketing study commitments, and postmarketing surveillance are application-specific actions. For the reasons discussed above, FDA declines to take a case-by-case (*i.e.,* application-specific) approach to BLAs' incorporation by reference of DS/DSI/DP information contained in master files. Furthermore, complete response letters, postmarketing study commitments, and postmarketing surveillance are relevant only after the product has been developed and an application has been submitted to and reviewed and evaluated by the Agency. In contrast, given the importance of the applicant's knowledge of and direct control over the manufacturing processes for biological products, a clear rule that applies to all BLAs provides all applicants with administrative efficiency and predictability early in the development process about the Agency's expectations regarding the use of master files, allowing applicants to take these expectations into account in their product development plan and when preparing content to be submitted in the application.

For the reasons discussed above, FDA declines to take a case-by-case approach, and has concluded that the availability of complete response letters, postmarketing study commitments, and postmarketing surveillance does not provide a suitable alternative to FDA's approach, which is, among other things, intended to provide predictability regarding the use of master files for BLAs.

(Comment 5) One comment proposes that FDA permit BLAs to incorporate by reference certain kinds of DS/DSI/DP information contained in a master file, advocating for the ability of BLAs to reference DS/DSI/DP information that is not ''highly product-specific.'' As an example, the comment asserts that ''drug product information'' could be interpreted to encompass extensive aseptic processing information and, in certain circumstances, this information could be appropriately managed in a master file because elements of aseptic processing can cut across multiple products and very few elements of aseptic processing are drug product-specific. The comment also suggests that platform data to support viral clearance could be more appropriately captured once in a DMF instead of being repeated in multiple BLAs, thereby reducing burden on the Agency and sponsors.

(Response 5) FDA declines to change its approach in order to permit BLAs to incorporate by reference certain DS/DSI/DP information contained in a master file as suggested by the comment.

The comment uses, but does not explain what it means by, the term ''highly product-specific information,'' other than providing examples of information that the comment considers not to be ''highly product-specific,'' such as platform data to support viral clearance and aseptic processing information. It is unclear whether these examples would, in fact, be DS/DSI/DP information in the context of a particular BLA. FDA notes that an applicant may seek guidance from the relevant review division at the Agency if the applicant is unsure whether information in a master file constitutes DS/DSI/DP information in the context of a particular BLA.

Accordingly, FDA declines to change this provision to treat DS/DSI/DP information that is not ''highly product-specific'' different from any other kind of DS/DSI/DP information contained in master files.

(Comment 6) One comment largely agrees with FDA's proposal and the rationale provided to support it but expresses concern about its application to purely synthetic drug substance intermediates, asserting that the considerations articulated in the proposed rule are appropriate only for biological products. The comment notes that a chemically synthesized polypeptide does not meet the definition of a biological product under section 7002(b) of the BPCI Act, which amended, in part, the definition of a ''biological product'' in the PHS Act to include a ''protein (except any chemically synthesized polypeptide).'' The comment requests clarity on the use of DMFs for drug substance intermediates for chemically synthesized polypeptides. The comment contends that some biological products may integrate drug substance intermediates that are chemically synthesized polypeptides. The comment asserts that the potential risks to quality are less significant in such cases because, according to the comment, these chemically synthesized polypeptides are not technically biological products. The comment contends that, under such circumstances, reliance on a DMF may be appropriate, and proposes that FDA allow reliance on a DMF for a drug substance intermediate that is purely synthetic.

(Response 6) FDA notes that, after the comment period for the proposed rule closed, section 605 of the FCA Act further amended the definition of a ''biological product'' in section 351(i) of the PHS Act to remove the parenthetical exception for ''any chemically synthesized polypeptide'' from the statutory category of ''protein.'' Accordingly, the comment's assertion that BLAs should be permitted to reference a DMF for information about a drug substance intermediate that is a chemically synthesized polypeptide because a chemically synthesized polypeptide does not meet the definition of a biological product is no longer applicable.

In addition, the inclusion of chemically synthesized polypeptides into the definition of a biological product does not change our overall concerns and approach with respect to biological products. Because chemically synthesized polypeptides can present many of the same issues and concerns as do other biological products, FDA's approach should be the same. When manufacturing processes for chemically synthesized polypeptides are appropriately designed, manufacturers can control the amino acid sequence and modifications to amino acids; however, the manufacturing of chemically synthesized polypeptides may still present risks to quality. As stated in the preamble to the proposed rule, most biological products tend to be

very sensitive to changes in their manufacturing process. For example, aspects of the manufacturing process (*e.g.,* temperature) can affect the folding of polypeptides. Therefore, even for chemically synthesized polypeptides, it is important for the applicant to have knowledge of and control over all aspects of the manufacturing process and to implement a robust quality assurance program. For this reason, the final rule requires that information about chemically synthesized drug substance intermediates be submitted directly to the application, rather than be incorporated by reference to a master file.

(Comment 7) One comment requests that BLAs for in vitro diagnostic (IVD) products, including those for licensed donor IVD screening tests, be excluded from the limitation on BLAs' incorporating by reference DS/DSI/DP information contained in master files, asserting that the reasons for limiting the use of master files for this kind of information in BLAs for therapeutic products do not apply to BLAs for IVDs.

(Response 7) FDA declines to exclude BLAs for IVD devices from the limitation on BLAs' use of master files for DS/DSI/DP information because such an exclusion is generally not necessary.

IVD devices subject to a BLA are intended for use in screening donated human cells, tissues, and cellular and tissue-based products (HCT/Ps) and donated blood in order to ensure the compatibility between donors and recipients and the absence of infectious agents. These assays are performed on samples collected from the HCT/P or blood donor.

Generally, the terms drug substance, drug substance intermediate, and drug product are not applicable to IVD devices. Therefore, the limitation in this rule on BLAs' use of master files for DS/DSI/DP information is not expected to affect BLAs for IVD devices. For this reason, the Agency considers it unnecessary to exclude BLAs for IVD devices from the scope of the rule's limitation on BLAs' use of master files for DS/DSI/DP information.

2. Final § 601.2(g)(2) (Proposed § 601.2(h))

Final § 601.2(g)(2) (proposed § 601.2(h)) addresses applications that have been deemed to be BLAs pursuant to section 7002(e)(4) of the BPCI Act, as amended by the FCA Act. This paragraph provides that a deemed BLA can continue to incorporate by reference DS/DSI/DP information contained in a DMF if such information was referenced at the time the application was deemed to be a BLA. We received several comments on this provision, most of which agree with this provision and the rationale provided in the proposed rule. A few comments disagree and several request clarification regarding certain aspects of this paragraph. For the reasons given below, we decline to make the changes suggested by the comments and are, therefore, finalizing this requirement without substantive change.

(Comment 8) One comment requests clarification regarding proposed § 601.2(h). The comment requests that FDA explain whether all biological products approved in NDAs will be permitted to continue incorporating by reference DS/DSI/DP information contained in DMFs or whether it is only a specific subset of biological products, because the preamble to the proposed rule notes that it would allow ''certain'' biological products originally approved in an NDA under the FD&C Act to continue relying on a DMF for information on DS/DSI/DP after the NDA is deemed to be a license for the biological product.

(Response 8) As explained in the preamble to the proposed rule and described in proposed § 601.2(h), a deemed BLA that was relying on DS/DSI/DP information in a DMF at the time the application was deemed a BLA may continue to incorporate by reference that DS/DSI/DP information contained in that DMF. The reference in the preamble to the proposed rule to ''certain'' applications refers to deemed BLAs that incorporated by reference DS/DSI/DP information contained in a DMF at the time the application was deemed a BLA. These are the same applications specified in § 601.2(g)(2) in this final rule.

(Comment 9) One comment requests clarification regarding whether applications that reference DMF information may continue referencing the DMF if changes are made to the DMF.

(Response 9) The preamble to the proposed rule explains that the rule is not intended to limit or restrict the changes that may be made to any master file, including a DMF containing DS/DSI/DP information. Changes made to such a DMF, including changes to previously referenced DS/DSI/DP information, do not restrict the ability of a deemed BLA to continue to incorporate by reference the DS/DSI/DP information in that DMF for the same purpose for which it was incorporated by reference at the time the application was deemed to be a BLA. For example, consider a former NDA that incorporated by reference information contained in a DMF regarding the manufacture of its drug substance and that, after the application was deemed to be a BLA, continues to incorporate by reference that drug substance information. If the DMF holder subsequently modifies drug substance manufacturing (for example, by making changes to the analytical methods or purification process for the drug substance), the deemed BLA may continue to incorporate by reference this modified drug substance information, provided that the BLA applicant informs the Agency of the change in the BLA in accordance with § 601.12 (21 CFR 601.12). Alternatively, if the DMF holder adds information about manufacturing of drug product to the same DMF, FDA does not intend to permit the deemed BLA to incorporate by reference that new drug product information because it is not the type of information that was referenced by the former NDA at the time it was deemed to be a BLA.

(Comment 10) One comment requests further information on the circumstances in which submission of a supplement to a BLA would not be sufficient and the submission of a new BLA would be required.

(Response 10) FDA notes that a description of the kinds of changes that cannot be addressed through a supplement is outside the scope of this rule. The Agency has generally described its thinking on what constitutes a separate original application, amendment, or supplement.[8]

(Comment 11) One comment suggests that deemed BLAs are best described as ''expected to transition.''

(Response 11) The applications described in § 601.2(g)(2) in this final rule have already been deemed to be BLAs by operation of the statute (section 7002(e)(4) of the BPCI Act, as amended by section 607 of the FCA Act). Therefore, referring to deemed BLAs as ''expected to transition'' would be inaccurate.

(Comment 12) One comment suggests that FDA change proposed § 601.2(h) to state that any new BLAs will not be allowed to incorporate by reference DS/DSI/DP information contained in master files after March 23, 2020.

(Response 12) The Agency declines to make the suggested change. Except as noted in final § 601.2(g)(2) and (3), final § 601.2(g)(1) applies to all BLAs, whether new or existing. Therefore, the suggested change is not needed because,

[8] For example, see the guidance for industry and FDA Staff ''Bundling Multiple Devices or Multiple Indications in a Single Submission'' (Ref. 3).

under the final codified, a new BLA may not incorporate by reference DS/DSI/DP information contained in any master file.

(Comment 13) One comment asserts that the BPCI Act was enacted to guarantee appropriate regulation of biological products to support public health and to ensure that only safe and effective products enter the market. The comment further maintains that the intent of the deemed BLA provision of section 7002(e)(4) of the BPCI Act is to ensure that scientific and technical complexities associated with the generally larger and typically more complex structure of biological products, as well as the processes by which such products are manufactured, are not overlooked. The comment asserts that it would therefore defeat the purpose of the BPCI Act to allow biological products initially approved in an NDA under the FD&C Act to continue to rely on a DMF for DS/DSI/DP information after the NDA is deemed to be a license for the biological product under the PHS Act. The comment recommends that deemed BLAs be regulated like other biological products with respect to use of master files.

(Response 13) FDA agrees that, in general, scientific and technical complexities associated with the typically more complex structures of biological products, as well as the processes by which such products are manufactured, must not be overlooked (see section V.B.1). However, with respect to deemed BLAs that previously, as former NDAs, referenced a DMF for DS/DSI/DP information at the time of the transition, FDA considered the intent underlying the BPCI Act and, as elaborated in the proposed rule, took into account the following considerations that are specific to such deemed BLAs: (1) these applications have already been approved, and the applicants have marketed the product, in certain instances for decades, without overt safety concerns; (2) the deemed BLAs that incorporate by reference DS/DSI/DP information comprise only a small subset of all BLAs and reference a very small number of DMFs; and (3) many of these BLA applicants have accumulated knowledge about the products and have been able to implement appropriate control strategies based on this product knowledge. In addition, prohibiting these deemed BLAs from continuing to incorporate by reference DS/DSI/DP information in these DMFs might have the effect of halting or curtailing production of these products, resulting in drug shortages. FDA interprets the applicable statutory provisions such that the transition was not meant to interrupt access to these products. Therefore, on balance, FDA believes that public health is best served by allowing the small number of deemed BLAs to continue referencing DS/DSI/DP information contained in DMFs on which they relied at the time of transition.

(Comment 14) One comment acknowledges that the general concern about fragmentation of DS/DSI/DP information associated with the use of DMFs is lessened for deemed BLAs by the existence of generally longstanding relationships between the deemed-BLA applicants and the DMF holders because the applicants may have accumulated knowledge about the quality of the DS/DSI/DP supplied by the DMF holder over an extended period. The comment agrees that this accumulated knowledge allows a deemed BLA applicant 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. The comment questions how this approach would change if the contents of the DMF change or the holder of the DMF changes.

(Response 14) FDA does not consider that a change to the holder of the DMF or a change in previously referenced DS/DSI/DP information in the context of a DMF is inconsistent with the rationale for permitting deemed BLAs that previously referenced a master file for DS/DSI/DP information to continue referencing the DMF for the same type of information. The generally longstanding relationships between the deemed BLA applicant and the DMF holder, the knowledge accumulated by the deemed BLA applicant, and the knowledge accumulated by the DMF holder collectively provide some assurance about the quality of a product. When changes are made to a DMF, these assurances should continue to apply in most cases. In addition, the comparability studies required to demonstrate the safety, purity, and potency of post-change and pre-change material should provide further assurance of quality.

When the DMF remains the same but the DMF holder changes, the deemed BLA applicant's product and process knowledge still remains; the deemed BLA applicant will also have designed and implemented a control strategy that is independent of the identity of the holder of the DMF. These measures collectively should provide continued assurance of quality under such circumstances. Therefore, it is appropriate to permit deemed BLAs to continue to incorporate by reference the same type of DS/DSI/DP information contained in a DMF after a change in the content of the DMF or the holder of the DMF.

(Comment 15) One comment asserts that FDA's rationale for allowing deemed BLAs to continue incorporating by reference information on DS/DSI/DP contained in DMFs is insufficient because it is based on a small subset of the deemed BLAs and a very small number of DMFs.

(Response 15) This comment appears to misunderstand the set of deemed BLAs on which FDA's rationale is based. It is true that FDA's approach to deemed BLAs and their use of DMFs for DS/DSI/DP information applies to a small number of applications and DMFs. Deemed BLAs are a small subset of all BLAs, and deemed BLAs that reference a master file for DS/DSI/DP information are, in turn, a subset of all deemed BLAs. However, FDA's risk-based assessment of deemed BLAs' continued referencing of DMFs for DS/DSI/DP information is based on a consideration of the entire set of deemed BLAs that reference DMFs for such information, and it is only those deemed BLAs that will be able to continue referencing DS/DSI/DP information in a DMF. In other words, FDA considered the entire set of applications and DMFs that will be affected by final § 601.2(g)(2).

As elaborated in the preamble to the proposed rule, FDA considered the length of time these products have been marketed without being withdrawn or removed for reasons of safety or effectiveness; the acceptable quality of drug substances provided over decades through this incorporation by reference to DMFs; and the impact of disallowing use of DMFs for these deemed BLAs, which has the potential to curtail or halt production of some of these products, resulting in drug shortages with considerable negative impacts on public health. Based on these reasons, and the fact that there are a small number of deemed BLAs and a small number of master files referenced by these applications, the Agency has determined that it serves the public health best to permit these deemed BLAs to continue incorporating by reference the DS/DSI/DP information contained in this small set of master files.

(Comment 16) One comment proposes that a biosimilar product that references a deemed BLA that incorporates by reference DS/DSI/DP information contained in a master file should also be permitted to incorporate by reference

the same information to assist in demonstrating biosimilarity.

(Response 16) FDA recognizes that an applicant might submit a BLA for a biosimilar or interchangeable biosimilar product to a reference product that is approved in a deemed BLA and is permitted under the exception in final § 601.2(g)(2) to continue incorporating by reference DS/DSI/DP information contained in a DMF. However, for the reasons outlined below, FDA declines to amend the proposed rule to also except such BLAs for biosimilar or interchangeable biosimilar products from final § 601.2(g)(1).

Consistent with FDA's longstanding practice for BLAs, and as codified in final § 601.2(g)(1), a BLA may not reference a master file for DS/DSI/DP information because a BLA applicant needs to demonstrate knowledge of and direct control over the manufacture of the drug product, which includes manufacture of the drug substance and drug substance intermediate. For reasons discussed above, FDA believes that the public health is best served by allowing a small number of deemed BLAs—those that, in former approved applications under section 505 of the FD&C Act, relied on DMFs for DS/DSI/DP information—to continue referencing that information after being deemed a BLA. However, these reasons, such as avoiding disruptions in existing supply chains for products with deemed BLAs, do not apply to new BLAs, including BLAs for products that are biosimilar to or biosimilar and interchangeable with reference products in such deemed BLAs. We continue to consider that an approach which draws a clear distinction between deemed BLAs and other BLAs with regard to the referencing of master files for DS/DSI/DP information is the most appropriate.

FDA notes that the lack of ability to reference a master file for DS/DSI/DP information should not preclude the development of a biosimilar or interchangeable biosimilar product to a reference product in a deemed BLA that is permitted to continue incorporating by reference DS/DSI/DP information from a DMF. For example, an application for licensure as a biosimilar typically will include data derived from comparative analytical studies between the proposed biosimilar and the reference product, which should be feasible even if the biosimilar or interchangeable biosimilar product application does not reference DS/DSI/DP information that is incorporated by reference by the deemed BLA for the reference product. Moreover, data derived from comparative clinical studies, among other things, often will be included as part of a demonstration of biosimilarity. In general, a biosimilar applicant should be able to conduct such studies regardless of whether the biosimilar applicant can reference the same DMF for DS/DSI/DP information as the reference product.

Furthermore, an applicant for a biosimilar or interchangeable biosimilar product that is not permitted to incorporate DS/DSI/DP information by reference to the DMF is not required to manufacture the DS/DSI/DP; as noted above and in the preamble to the proposed rule, alternatives are available, including the use of cooperative manufacturing arrangements that ensure that the licensee for the final product assumes responsibility for compliance with the applicable product and establishment standards.

Overall, we do not believe that an applicant for a proposed biosimilar or interchangeable biosimilar product would face a barrier to generating the data necessary to demonstrate the biosimilarity or interchangeability of its proposed product to a reference product that incorporates by reference DS/DSI/DP information in a DMF, even if the biosimilar applicant is not permitted to incorporate by reference that same DS/DSI/DP information. Therefore, FDA declines to modify this provision as suggested.

We note that the Agency has taken steps to help create a more competitive market for biological products, including encouraging the development of biosimilar products, and is working to implement additional measures to maximize clarity and efficiency in biosimilar development.[9] The Agency invites prospective applicants who seek advice relating to the development and review of a biosimilar or interchangeable biosimilar product, including advice on the feasibility of licensure under section 351(k) of the PHS Act for a particular product, to contact the Agency. For Center for Drug Evaluation and Research (CDER)-regulated products, you may contact CDER-Biologics Biosimilars Inquiries at *CDER-BiologicsBiosimilarsInquiries@fda.hhs.gov;* for Center for Biologics Evaluation and Research (CBER)-regulated products, you may contact CBER at *industry.biologics@fda.hhs.gov.*

3. Final § 601.2(g)(4) (Proposed § 601.2(i))

Final § 601.2(g)(4) (proposed § 601.2(i)) codifies the Agency's practice of permitting BLAs to incorporate by reference information other than DS/DSI/DP information contained in master files, including in DMFs. Comments that address this proposed provision did not object to FDA's overall approach or the underlying rationale, and some focused on operational aspects of the provision. Therefore, we are finalizing § 601.2(g)(4) without substantive changes. Because this provision applies to a BLA regardless of submission type, we have removed the reference to amendments and supplements.

(Comment 17) Three comments request clarification or codification of the type of data and information that constitutes information other than DS/DSI/DP information that is contained in master files and can be leveraged by BLAs.

(Response 17) In the preamble to the proposed rule, we provided examples of the kinds of information that are not DS/DSI/DP information, including excipients, stabilizers, penetrants, container closure, and other materials. However, we decline to codify in this rule an exhaustive list of the specific types of information that are not DS/DSI/DP information and that can be included in a master file and incorporated by reference by a BLA. A potential applicant may seek additional guidance from the relevant review division if the applicant is unsure whether it is appropriate to incorporate by reference a particular type of information contained in a master file.

(Comment 18) One comment requests that FDA codify the tests and analyses that should be performed by the applicant when data or information is being incorporated by reference by the BLA.

(Response 18) FDA declines to codify the tests and analyses that the applicant should perform because these depend on, among other things, the nature of the data and information contained in the master file and incorporated by reference.

(Comment 19) One comment requests that FDA clarify whether proposed § 601.2(i) applies to master files held by contract manufacturing organizations (CMOs). The comment reasons that sponsors developing biological products frequently incorporate into BLAs information other than DS/DSI/DP (*e.g.,* for a fill or incorporation of a device, such as an autoinjector) by referencing a master file held by a CMO.

(Response 19) FDA clarifies that this final rule applies to all master files containing information that is being considered for incorporation by reference by a BLA, regardless of the ownership of the master file. Therefore, BLAs may incorporate by reference information (other than DS/DSI/DP

[9] See ''Biosimilars Action Plan: Balancing Innovation and Competition,'' pgs. 5–7 (Ref. 4).

information) that is contained in master files held by CMOs.

(Comment 20) One comment requests that FDA update the proposed rule to explicitly state that Type V DMFs can be used for certain non-product-specific equipment and facility information, including sterilization validation information, to support multiple NDAs/BLAs.

(Response 20) Final § 601.2(g)(4) codifies that BLAs may incorporate by reference information other than DS/DSI/DP information contained in master files. Information in Type V DMFs, like information in all master files, may be incorporated by reference by multiple applications, provided that the information is not DS/DSI/DP information. We do not consider it necessary to explicitly reference Type V DMFs in the codified language.

(Comment 21) One comment requests that FDA qualify proposed § 601.2(i) by adding that nothing in proposed § 601.2(g) limits or alters a license holder's ability to modify a product under § 601.12, nor is it intended to expand or reduce the changes allowed to a deemed BLA that incorporates by reference information contained in master files.

(Response 21) FDA declines to change proposed § 601.2(i) (final § 601.2(g)(4)) as the comment requests. As stated in the preamble to the proposed rule, this codification of current practice is not intended to alter an applicant's existing ability to modify a product under § 601.12. We further stated in the preamble to the proposed rule that 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.

4. Combination Products Approved in BLAs

The Agency recognized in the preamble for the proposed rule that there are combination products approved in BLAs. Although the proposed rule did not focus on combination products in BLAs, in the preamble, we stated our position that the rationale for the treatment of BLAs for biological products also applies to the biological product constituent part(s) of combination products licensed under the PHS Act (*i.e.,* BLAs should not be permitted to incorporate by reference DS/DSI/DP information contained in master files for a biological product constituent part of a combination product for the same reasons that BLAs for biological products should not be permitted to do so).[10] Additionally, the Agency specifically requested comments on whether BLAs should be permitted to incorporate by reference DS/DSI/DP information for any non-biological product constituent part of a combination product.

We received several comments disagreeing with our position that, since BLAs for biological products cannot incorporate by reference DS/DSI/DP information contained in a master file, then BLAs should also not be permitted to incorporate by reference such information for a biological product constituent part of a combination product. We also received comments both in support and not in support of permitting BLAs to incorporate by reference DS/DSI/DP information for the non-biological product constituent part(s) of a combination product. We did not receive any comments discussing whether BLAs should be able to reference master files for information other than DS/DSI/DP information for either the biological or non-biological product constituent parts of a combination product.

Based on our consideration of the comments regarding BLAs' incorporation by reference of information contained in master files for constituent parts of combination products, we are addressing combination products approved as BLAs under section 351 of the PHS Act in the final rule.

*a. BLAs referencing a master file for DS/DSI/DP information for a biological product constituent part of a combination product: final § 601.2(g)(1) (proposed § 601.2(g)).* We received several comments disagreeing with our position that BLAs will not be permitted to incorporate by reference DS/DSI/DP information contained in a master file for a biological product constituent part of a combination product.

(Comment 22) The comments disagreeing with FDA's proposal regarding biological product constituent parts of a combination product refer to the reasons that the commenters disagree with the Agency's rationale for not permitting BLAs generally to reference master files for DS/DSI/DP information but do not provide a reason for their disagreement that is specific to a biological product constituent part of a combination product.

(Response 22) The comments do not provide any reason why a BLA should be permitted to reference a master file for DS/DSI/DP information for a biological product constituent part of a combination product. Instead, the comments refer to the arguments they provide for why BLAs more generally should be permitted to incorporate by reference DS/DSI/DP information. In section V.B.1 of this preamble, we explain why we disagree with that position. None of the comments suggest that there is anything unique about a biological product constituent part of a combination product that warrants not extending the approach for BLAs to a biological product constituent part of a combination product in a BLA. Accordingly, we have modified final § 601.2(g)(1) to state that, except as provided, a BLA may not incorporate by reference DS/DSI/DP information contained in a master file, including for a biological product constituent part of a combination product.

*b. BLAs referencing a master file for information other than DS/DSI/DP information for a constituent part of a combination product: final § 601.2(g)(4) (proposed § 601.2(i)).* With regard to the referencing of a master file for information other than DS/DSI/DP information, we did not receive any comments objecting to BLAs' referencing this information for either a biological product constituent part or a non-biological product constituent part of a combination product. Therefore, FDA has decided that these BLAs, like all other BLAs, may incorporate by reference information other than DS/DSI/DP information contained in master files (see section V.B.3). Accordingly, final § 601.2(g)(4) covers the incorporation by reference of information contained in master files that is not DS/DSI/DP information by all BLAs, regardless of whether such information is incorporated by reference for the product or for a constituent part of a combination product.

*c. BLAs referencing a master file for DS/DSI/DP information for a non-biological product constituent part of a combination product: final § 601.2(g)(3) (new).* As discussed above, in the preamble of the proposed rule, the Agency specifically requested comments on whether applications for combination products submitted in BLAs should be permitted to incorporate by reference DS/DSI/DP information for any non-biological product constituent part of a combination product. FDA received numerous comments on this topic. Most

[10] The Agency intends to continue to take a consistent approach to biological product constituent parts of combination product applications subject to regulation under other (non-BLA) marketing applications (*i.e.,* non-BLA marketing applications for combination products should not be permitted to incorporate by reference DS/DSI/DP information contained in master files for biological product constituent parts).

of the comments support permitting BLAs to reference master files for DS/DSI/DP information with respect to the non-biological product constituent part(s) of a combination product, while a few comments are against such an approach. The comments we received helped inform our decision to clarify in this final rule that a BLA may incorporate by reference DS/DSI/DP information contained in any master file for any non-biological product constituent part of a combination product.

(Comment 23) Several comments support codifying in the final rule that BLAs are permitted to incorporate by reference DS/DSI/DP information contained in master files for the non-biological product constituent parts of combination products, but the comments do not provide a rationale. Another comment reasons that DMFs for drug products have been relied on for decades and enabling continued referencing of DS/DSI/DP information for the non-biological product constituent part(s) of a combination product in a BLA will allow further development of ''superior treatments.'' An additional comment suggests that permitting BLAs to reference a master file for DS/DSI/DP information for the non-biological product constituent part(s) of a combination product would enable biological product and small molecule manufacturers to collaborate more efficiently. Finally, one comment analogizes that, because a BLA would be permitted to incorporate any information from the device master file system for a medical device constituent part of a combination product, BLAs should also be able to reference DMFs for DS/DSI/DP information for drug constituent parts.

(Response 23) We agree that BLAs should be permitted to reference master files for DS/DSI/DP information with respect to the non-biological product constituent part(s) of combination products. As we explained in the preamble to the proposed rule, historically, the Agency has, as a scientific matter, expected applicants to submit information about DS/DSI/DP directly to the BLA for a biological product, rather than have the BLA incorporate it by reference to a master file. However, as a scientific matter, a similar expectation would not apply to applications for non-biological products regulated under the FD&C Act, which are permitted to incorporate by reference DS/DSI/DP information contained in a master file.

Much of the rationale for why a BLA is not permitted to reference a master file for DS/DSI/DP information does not apply in the case of a non-biological product constituent part of a combination product in a BLA. As we explained in the preamble to the proposed rule, the risk associated with the manufacture of biological products is generally significantly higher than that associated with the manufacture of products regulated under NDAs, which are often less complex.[11] 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, which makes them less amenable to characterization than small molecule chemical entities. While these considerations apply to biological product constituent parts of combination products, they generally do not apply to non-biological product constituent parts, which are often relatively simple, homogenous, and fully characterizable by extensive analytical testing. As such, the need for direct knowledge and control in the manufacturing of a non-biological product constituent part is generally mitigated by the ability to define the non-biological constituent part through analytical testing, and the risk associated with such manufacturing is generally lower than that associated with the manufacture of the biological product constituent part.

As two comments suggest, such an approach is consistent with how a non-biological product constituent part of a combination product, such as a drug constituent part, would be treated if it were a standalone product regulated under the FD&C Act. Additionally, we agree with the comment that permitting such referencing of information for non-biological product constituent part(s) could foster innovation by enabling more efficient collaboration between the manufacturer of the non-biological product constituent part and the manufacturer of the final product submitted in a BLA.

Accordingly, final § 601.2(g)(3) permits BLAs to incorporate by reference DS/DSI/DP information contained in a master file for the non-biological product constituent part(s) of a combination product.

(Comment 24) One comment does not support allowing BLAs to incorporate by reference DS/DSI/DP information for the non-biological product constituent part(s) of a combination product. The comment contends that the lack of knowledge and control over a drug constituent part for which a master file is referenced for DS/DSI/DP information introduces risk when that drug constituent part is combined with a biological product constituent part.

(Response 24) We understand that permitting a BLA to reference a master file for DS/DSI/DP information for a non-biological product constituent part, such as a drug constituent part, that is then combined with a biological product constituent part may introduce additional risk for the final combination product. However, the Agency considers it generally practical for the BLA applicant to confirm the DS/DSI/DP quality characteristics of the non-biological product constituent part through testing. This feasibility of testing and characterizing the non-biological product constituent part generally enables the BLA applicant to implement a robust control strategy for the final combination product that can mitigate the risks to quality arising from the applicant's lack of access to the DS/DSI/DP information for the non-biological product constituent part. Furthermore, the applicant would still be expected at the time of review of the BLA to have sufficient control strategies for the entire combination product, including an appropriate control strategy to mitigate the risk of the applicant not having access to the manufacturing information for the non-biological product constituent part.

(Comment 25) Another comment is concerned with non-biological product constituent parts categorically being permitted to reference a master file for DS/DSI/DP information because special controls may be necessary for drug constituent parts that are cytotoxic in nature, such as in the case of an antibody-drug conjugate combination product licensed in a BLA.

(Response 25) FDA acknowledges that the manufacture of cytotoxic drugs requires special expertise and controls to address the risks associated with the toxic nature of the drug, such as the implementation of special air-handling systems to reduce the risk of exposure to the cytotoxic drug by manufacturing personnel. We point out, however, that such controls to address toxicity-related risks differ from the controls that are discussed elsewhere throughout this rulemaking, which address the risks associated with the generally complex manufacturing of biological products. Permitting a BLA to incorporate by reference DS/DSI/DP information contained in a master file for a cytotoxic drug constituent part of a combination product does not increase the toxicity-related risks associated with either the

[11] As addressed in the preamble to the proposed rule, the Agency recognizes that, in limited circumstances, this may not always be the case.

manufacture of the cytotoxic drug constituent part or the manufacture of the combination product that contains the cytotoxic drug constituent part. Furthermore, the toxicity-related risks associated with the manufacture of a cytotoxic drug constituent part of a combination product licensed in a BLA are unlikely to differ significantly from the toxicity-related risks associated with the manufacture of cytotoxic drug products that are not constituent parts of combination products licensed in BLAs. Therefore, FDA declines to treat cytotoxic drug constituent parts differently from other non-biological product constituent parts and will permit BLAs to incorporate by reference DS/DSI/DP information contained in master files for cytotoxic drug constituent parts of combination products.

(Comment 26) One comment expresses concern that the BLA applicant would have a greater burden to establish a quality assurance program to mitigate the risk if the BLA incorporates by reference DS/DSI/DP information contained in a master file for the non-biological product constituent part of a combination product and this would be costlier and more complex than if the BLA is not permitted to rely on a master file for such information for the non-biological product constituent part.

(Response 26) To the extent that there is concern that an applicant would find it costlier and more complex to establish a quality assurance program to mitigate the risk associated with the use of a master file for DS/DSI/DP information for the non-biological product constituent part of a combination product than it would be to directly include such information in the BLA, we point out that FDA is not mandating the use of master files under such circumstances.

5. Final § 601.2(g)(5) (Proposed § 601.2(j))

FDA proposed in § 601.2(j) of the proposed rule that INDs for products that would be subject to licensure under the PHS Act not be restricted from incorporating by reference any information, including DS/DSI/DP information, contained in a master file, including a DMF submitted under § 314.420 (21 CFR 314.420). Several comments support the proposed approach. However, a few comments disagree and recommend that, as is the case for BLAs, an IND for a product that would be subject to licensure under the PHS Act not be permitted to incorporate by reference DS/DSI/DP information.

(Comment 27) One comment disagrees with FDA's proposed approach of permitting INDs for products that would be subject to licensure under the PHS Act to incorporate by reference DS/DSI/DP information contained in a master file. The comment contends that the approach is unreasonable because, while exposure to the biological product is limited during the IND stage, the IND should still ensure that clinical trial subjects are not exposed to what the comment considers unreasonable harm should the IND incorporate by reference DS/DSI/DP information contained in a master file.

(Response 27) FDA agrees that it is important to ensure that clinical trial subjects are not exposed to an unreasonable risk of harm but disagrees with the comment's assessment of FDA's approach.

During early preclinical development for a new product, the primary goal of FDA and sponsors is to ensure that the product is reasonably safe for initial use in humans and to determine whether the test product exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

Clinical trials permit the assessment of the safety and efficacy of investigational products from early drug development through the approval process and beyond. To ensure that clinical trial subjects are not exposed to unreasonable risk of harm, FDA has issued numerous regulations governing human subject protection and the conduct of clinical trials, including regulations regarding informed consent (part 50 (21 CFR part 50)) and institutional review boards, which also participate in the oversight of clinical trials (21 CFR part 56).

All subjects in clinical trials under an IND receive appropriate informed consent that discusses the known benefits and risks. With limited exceptions, investigators must obtain the informed consent of subjects (or their legally authorized representatives) in clinical trials under IND (§ 50.20). In seeking informed consent, certain information is provided to subjects, including a description of reasonably foreseeable risks and a description of benefits that may reasonably be expected (§ 50.25).

Furthermore, safety monitoring is not static and continues to apply as product development progresses. IND regulations in part 312 (21 CFR part 312) set forth safeguards that are designed to ensure such safety. Sponsors are expected to continue to ensure the safety of subjects and, as new safety information is identified, to take appropriate steps, which may include incorporating additional safety monitoring and updating the informed consent form. FDA has authority to place an investigation on clinical hold (§ 312.42) if it finds that human subjects are or would be exposed to an unreasonable and significant risk of illness or injury. IND regulations at § 312.56 state that a sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects must discontinue those investigations that present the risk.

As explained above and in the preamble to the proposed rule, exposure to the investigational product is limited at the IND stage because the product is only administered to subjects enrolled in clinical trials, which are typically carried out in controlled settings. The controlled nature of a clinical trial allows for close safety monitoring of these subjects, rapid identification of any safety issues that may arise, and implementation of corresponding mitigation strategies.

For these reasons, FDA considers that the existing safeguards available in the IND process are sufficient to ensure that subjects participating in clinical trials, including those for products that would ultimately be regulated under BLAs and for which the INDs incorporate by reference DS/DS/DP information contained in master files, are not exposed to unreasonable risk of harm.

(Comment 28) Another comment expresses concern that the sponsor of an IND for a product that would be subject to licensure under the PHS Act that incorporates DS/DSI/DP information by reference to a master file may not be able to develop the necessary knowledge and control over the manufacturing process when product development reaches the BLA stage. Therefore, the comment suggests setting a deadline during the development stage by which time the sponsor needs to demonstrate knowledge and control over the manufacturing process and can no longer incorporate by reference DS/DSI/DP information from a master file.

(Response 28) FDA notes that a deadline to develop the requisite knowledge and direct control is not necessary because the submission of the BLA effectively serves as a deadline. As

noted in the preamble to the proposed rule, it has been FDA's practice to permit INDs for products that would be subject to licensure under the PHS Act to incorporate by reference DS/DSI/DP information contained in a master file. By later stages of development, however, FDA requires the sponsors to have knowledge of and direct control over the manufacturing process, and to be able to submit DS/DSI/DP information directly to the BLA. A sponsor can plan its product development to ensure that, at the time the BLA is submitted, the sponsor is able to meet these requirements.

(Comment 29) Several comments agree with the Agency's proposed approach with respect to INDs for products that would be subject to licensure under the PHS Act and the referencing of master files for information including DS/DSI/DP information. One comment suggests that allowing the referencing of DS/DSI/DP information at the IND stage could promote product development and proposes that this benefit be explicitly included in the corresponding codified section. Another comment advises that permitting INDs for products that would be subject to licensure under the PHS Act to reference master files for DS/DSI/DP information ensures that previous knowledge is leveraged.

(Response 29) We agree that not limiting the ability of INDs for products that would be subject to licensure under the PHS Act to reference a master file for DS/DSI/DP information may facilitate product development. As we explained in the preamble of the proposed rule, and as discussed above, without this option a sponsor might not choose to make the significant investment to manufacture the necessary DS/DSI/DP for a product at this early stage of development. However, we do not think it is necessary to add an explicit reference to the benefit of promoting product development to the codified language.

6. Other Issues Raised by Commenters

(Comment 30) One comment suggests that it would be helpful if the Agency defined the term ''drug substance intermediate,'' especially in reference to combination products.

(Response 30) FDA is not defining the term ''drug substance intermediate'' in this rule because such a definition would have implications beyond the scope of this rule. FDA will consider whether to provide a definition in rulemaking that has a broader scope since the term is used throughout the BLA regulations.[12]

(Comment 31) One comment requests that FDA outline any plans for publication of guidances that more clearly articulate the Agency's current thinking on specific kinds of master files (*e.g.,* those containing information on autoinjectors, on fillers, or those owned by CMOs) that may be referenced in BLAs, to enable appropriate referencing of relevant master files, thereby promoting improved compliance and reducing the risk of delays in application reviews.

(Response 31) FDA will take this suggestion under consideration with respect to the development of future guidances. FDA annually publishes nonbinding lists of new and revised draft guidance documents that it plans to publish in the upcoming calendar year. In addition, a potential applicant may also seek additional guidance from the relevant review division if the applicant is unsure whether it is appropriate to incorporate by reference a particular type of information contained in a master file.

(Comment 32) One comment encourages FDA to undertake modifications to internal processes and training of staff and revise the DMF guidance to implement this rule. Specifically, the comment requests that FDA: (1) update its internal training procedures and relevant procedural documents to ensure that Agency reviewers consistently implement and apply proposed § 601.2(i) during application assessment; (2) update the DMF guidance to improve the format and layout of a DMF to avoid duplicating the content of DMFs across multiple applications and supplements; (3) explore potential technological solutions to permit cross-linking between BLAs and DMFs; and (4) incorporate the feedback provided in this comment into the revised draft guidance ''Drug Master Files'' (Ref. 5).

(Response 32) FDA agrees that consistency in the implementation of final § 601.2(g)(4) (proposed § 601.2(i)) is important. As with any regulation, FDA will work to ensure correct and consistent implementation of this rule.

Regarding the DMF guidance, we note that the revised draft guidance was issued on October 21, 2019, and reflects additional information to assist sponsors in improving the format of DMFs. Comments to guidance documents may be submitted at any time.

Regarding technological solutions to permit cross-referencing between BLAs and DMFs, FDA believes that its recent efforts in the area of electronic submissions of DMFs may address some of the concerns.[13] [14]

(Comment 33) One comment requests that there should also be provisions established that would notify applicants referencing a DMF when that DMF has been altered (without disclosing proprietary information). The comment notes that such notification would be beneficial to regulators and applicants who would be aware of any changes made by the DMF holder that may improve quality or safety of the final product.

(Response 33) The purpose of this rule is to clarify when BLAs and INDs for products subject to licensure under the PHS Act can use master files. The operation of a DMF, which is addressed under § 314.420, falls outside the scope of this rule; accordingly, FDA declines to address this issue in this rule.

(Comment 34) One comment observes that, if a DMF were reviewed prior to submission of an NDA or abbreviated new drug application (ANDA), it would allow companies, especially less established ones, to avoid any issues with referencing an incomplete DMF for their NDA or ANDA filing. Additionally, the comment suggests that FDA should consider eliminating assessment fees to encourage smaller biotech and pharmaceutical companies to develop biosimilars.

(Response 34) FDA declines to make changes to this final rule that would address these suggestions because the process for incorporating by reference information contained in master files, the timing of such referencing, and the fees related to assessment of DMFs are outside the scope of this rule.

(Comment 35) One comment notes, without suggesting any changes, that in the description of the proposed rule for proposed paragraph § 601.2(h), FDA should include information on the impact of the transition of an NDA to a BLA on exclusivity of the product.

(Response 35) Exclusivity considerations are outside the scope of this rule. We note that FDA has issued guidance that, in part, addresses FDA's

[12] FDA notes that an applicant may seek guidance from the relevant review division at the Agency if the applicant is unsure whether information in a master file constitutes DS/DSI/DP information in the context of a particular BLA.

[13] See the revised draft guidance for industry ''Drug Master Files'' (Ref. 5).

[14] See the guidance for industry ''Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications'' (Ref. 6) for relevant discussion of FDA's current thinking on electronic submissions.

current thinking about its interpretation of section 7002(e) of the BPCI Act and exclusivity.[15]

(Comment 36) One comment requests that FDA approve stem cells as an alternative to surgery that can be covered by insurance; another comment relates to ''pandemic flu'' and acquired immunity.

(Response 36) These topics are outside the scope of this rule.

## VI. Effective/Compliance Date

This final rule is effective 30 days after the date of publication in the **Federal Register**.

## VII. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601–612), the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801, Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4).

Executive Orders 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers 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). Rules are ''significant'' under Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they ''have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of the Office of Information and Regulatory Affairs (OIRA) for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities.'' OIRA has determined that this final rule is not a significant regulatory action under Executive Order 12866 Section 3(f)(1).

Because this rule is not likely to result in an annual effect on the economy of $100 million or more or meets other criteria specified in the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act, OIRA has determined that this rule does not fall within the scope of 5 U.S.C. 804(2).

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule does not impose new regulatory burden on small entities, other than administrative costs of reading and understanding the rule, we certify that the final 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 estimates of anticipated impacts, before issuing ''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 $177 million, using the most current (2022) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

Allowing deemed BLAs for biological products to continue referencing DMFs for DS/DSI/DP information will generate net cost-saving benefits for the private and government sectors. Furthermore, the final rule will provide certainty, promote continuity, and help avoid potential disruptions in the supply of certain biological products that were approved in applications under section 505 of the FD&C Act and deemed, pursuant to section 7004(e) of the BPCI Act, to be licenses for the biological products under section 351 of the PHS Act.

By allowing certain BLAs to continue referencing a DMF for DS/DSI/DP information, FDA avoids imposing a potential new regulatory burden. Affected entities will incur minimal costs to read and understand the rule. FDA estimates that over 10 years at a discount rate of 7 percent, the final rule will generate annualized net cost savings ranging from $0.40 million to $5.19 million with a primary estimate of $2.80 million; at a discount rate of 3 percent, the final rule will generate annualized net cost savings ranging from $0.37 million to $5.17 million with a primary estimate of $2.77 million. Table 1 summarizes our estimate of the annualized costs and the annualized cost-saving benefits of the final rule.

TABLE 1—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE FINAL RULE

[Millions in 2022 dollars]

| Category | Primary estimate | Low estimate | High estimate | Units | | | Notes |
|---|---|---|---|---|---|---|---|
| | | | | Year dollars | Discount rate (%) | Period covered (years) | |
| Benefits: | | | | | | | |
| Annualized Monetized $millions/year | $2.81 | $0.41 | $5.20 | 2022 | 7 | 10 | Cost savings. |
| | $2.78 | $0.38 | $5.18 | 2022 | 3 | 10 | Cost savings. |
| Costs: | | | | | | | |
| Annualized Quantified | | | | | 7 | | |
| | | | | | 3 | | |
| Qualitative | | | | | | | |
| Annualized Monetized $millions/year | $0.01 | $0.01 | $0.01 | 2022 | 7 | 10 | |
| | $0.01 | $0.01 | $0.01 | 2022 | 3 | 10 | |
| Annualized Quantified | | | | | 7 | | |
| | | | | | 3 | | |
| Qualitative | | | | | | | |
| Transfers: | | | | | | | |
| Federal Annualized Monetized $millions/year | | | | | 7 | | |
| | | | | | 3 | | |
| From/To | From: | | | To: | | | |

[15] See the guidance for industry ''Interpretation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009'' (Ref.1).

TABLE 1—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE FINAL RULE—Continued
[Millions in 2022 dollars]

| Category | Primary estimate | Low estimate | High estimate | Units | | | Notes |
|---|---|---|---|---|---|---|---|
| | | | | Year dollars | Discount rate (%) | Period covered (years) | |
| Other Annualized Monetized $millions/year | | | | | 7<br>3 | | |
| From/To | From: | | | To: | | | |
| Effects: | | | | | | | |
| State, Local, or Tribal Government: None.<br>Small Business: None.<br>Wages: None.<br>Growth: None. | | | | | | | |

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. The full analysis of economic impacts is available in the docket for this final rule (Ref. 7) and at *https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria*.

## 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 final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

## X. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the 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 rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that have substantial direct effects 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. Accordingly, we conclude that the rule does not contain policies that have tribal implications as defined in the Executive Order and, consequently, a tribal summary impact statement is not required.

## XII. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m. Monday through Friday; they are also available electronically at *https://www.regulations.gov/*. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

1. FDA, Guidance for Industry, ''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/media/119272/download*. Accessed May 12, 2023.

2. FDA, Guidance for Industry, ''Cooperative Manufacturing Arrangements for Licensed Biologics,'' November 2008. Available at *https://www.fda.gov/media/70712/download*. Accessed May 12, 2023.

3. FDA, Guidance for Industry and FDA Staff, ''Bundling Multiple Devices or Multiple Indications in a Single Submission,'' June 2007. Available at *https://www.fda.gov/media/73500/download*. Accessed May 12, 2023.

4. FDA, ''Biosimilars Action Plan: Balancing Innovation and Competition,'' July 2018. Available at *https://www.fda.gov/media/114574/download*. Accessed May 12, 2023.

5. FDA, Draft Guidance for Industry, ''Drug Master Files (Rev.1),'' October 2019. Available at *https://www.fda.gov/media/131861/download*. Accessed May 12, 2023.

6. FDA, Guidance for Industry, ''Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Rev. 7),'' February 2020. Available at *https://www.fda.gov/media/135373/download*. Accessed May 12, 2023.

7. Final Regulatory Impact Analysis, ''Biologics License Applications and Master Files.''

## List of Subjects in 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, 21 CFR part 601 is 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, as amended by sec. 607, Division N, Pub. L. 116–94, 133 Stat. 3127.

■ 2. In § 601.2, add paragraph (g) to read as follows:

### § 601.2 Applications for biologics licenses; procedures for filing.

* * * * *

(g) *Master files*—(1) *Biologics license applications under section 351 of the Public Health Service Act not permitted to incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a master file.* Except as provided in paragraphs (g)(2) and (3) of this section, a biologics license application 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, for the product, including for a biological product constituent part of a combination product.

(2) *Former approved applications deemed to be licenses for biological products pursuant to section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009.* An application for a biological product that:

(i) Is a former approved application under section 505 of the Federal Food, Drug, and Cosmetic Act that, pursuant to section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009, has been deemed to be a license for the biological product under section 351 of the Public Health Service Act; and

(ii) At the time it was so deemed, 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. Amendments and supplements to such applications may also continue to incorporate by reference the information contained in that drug master file.

(3) *Non-biological product constituent parts of combination products regulated under biologics license applications under section 351 of the Public Health Service Act.* A biologics license application under section 351 of the Public Health Service Act may incorporate by reference drug substance, drug substance intermediate, and/or drug product information contained in a master file, including a drug master file submitted under § 314.420 of this chapter, for any non-biological product constituent part of a combination product.

(4) *Biologics license applications under section 351 of the Public Health Service Act permitted to incorporate by reference information contained in a master file that is not drug substance, drug substance intermediate, or drug product information.* Nothing in paragraph (g)(1) of this section limits or restricts a biologics license application 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.

(5) *Investigational new drug applications.* Nothing in paragraph (g)(1) of this section limits or restricts an investigational new drug application for a product that would be subject to licensure under section 351 of the Public Health Service Act 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: January 30, 2024.

**Robert M. Califf,**

*Commissioner of Food and Drugs.*

[FR Doc. 2024–02741 Filed 2–9–24; 8:45 am]

**BILLING CODE 4164–01–P**

## DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

### 24 CFR Part 1006

**[Docket No. FR–6273–F–02]**

**RIN 2577–AD13**

## Implementing Rental Housing Assistance for the Native Hawaiian Housing Block Grant Program

**AGENCY:** Office of the Assistant Secretary for Public and Indian Housing, HUD.

**ACTION:** Final rule.

**SUMMARY:** This rule amends HUD's regulations covering rental housing assistance for the Native Hawaiian Housing Block Grant (NHHBG) program, consistent with the Native American Housing Assistance and Self-Determination Act of 1996 (NAHASDA). The amendments clarify and improve consistency with NAHASDA's statutory requirements and HUD's Indian Housing Block Grant (IHBG) program regulations. This rule would also help to make affordable housing opportunities, in the form of NHHBG-assisted rental housing, more available to eligible Native Hawaiian families.

**DATES:** Effective March 13, 2024.

**FOR FURTHER INFORMATION CONTACT:** Claudine Allen, Lead Native Hawaiian Program Specialist, Office of Native American Programs, HUD Honolulu Field Office, 1003 Bishop Street, Suite 2100, Honolulu, HI 96813; telephone number 808–457–4674 (this is not a toll-free number). HUD welcomes and is prepared to receive calls from individuals who are deaf or hard of hearing, as well as from individuals with speech and communication disabilities. To learn more about how to make an accessible telephone call, please visit *https://www.fcc.gov/consumers/guides/telecommunications-relay-service-trs.*

**SUPPLEMENTARY INFORMATION:**

### I. Background

*Statutory Authority for the Native Hawaiian Housing Block Grant program*

Section 513 of the Hawaiian Homelands Homeownership Act of 2000 (HHH Act),[1] Public Law 106–569, amended the Native American Housing Assistance and Self-Determination Act of 1996 (25 U.S.C. 4101 *et seq.*) (NAHASDA) by adding to it a new ''Title VIII—Housing Assistance for Native Hawaiians.'' Title VIII of NAHASDA established the Native Hawaiian Housing Block Grant (NHHBG) program to provide block grant assistance for affordable housing for eligible Native Hawaiians, including rental assistance.[2]

The NHHBG program must primarily benefit low-income Native Hawaiian families who are eligible to reside on the Hawaiian Home Lands. 25 U.S.C. 4222(a); 25 U.S.C. 4228(a)(2)(A). These families experience more significant housing challenges compared to Native Hawaiian households overall, including other Hawaii residents and Native Hawaiians already residing on the Hawaiian Home Lands.

*Interim Rule*

On June 13, 2002, HUD published an interim rule (''interim rule'') adding new regulations at 24 CFR part 1006 to implement the NHHBG program. 67 FR 40773. HUD modeled the NHHBG regulations after the Indian Housing Block Grant (IHBG) regulations implemented at 24 CFR part 1000 because NAHASDA authorizes and applies overlapping requirements to both programs.[3]

[1] The HHH Act was enacted as both Title II of the Omnibus Indian Advancement Act (Pub. L. 106–568, 114 Stat. 2868, approved December 27, 2000) and Subtitle B of Title V of the American Homeownership and Economic Opportunity Act of 2000 (Pub. L. 106–569, 114 Stat. 2944, approved December 27, 2000).

[2] Section 513 of the HHH Act adds sections 801 through 824 of NAHASDA's Title VIII, which authorize this NHHBG program. 25 U.S.C. 4221 *et seq.* Although NAHASDA may be referenced throughout this rule, NHHBG serves Native Hawaiians specifically.

[3] 67 FR 40773; *see* Native American Housing Assistance and Self-Determination Act of 1996 [hereinafter NAHASDA] sections 810–811, 25 U.S.C. 4229–30. There are also differences between the statutory authorities governing the IHBG and NHHBG programs. In 2008, the Native American Housing Assistance and Self-Determination Reauthorization Act of 2008 (Pub. L. 110–411) (NAHASDA Reauthorization Act), made several changes to, *inter alia,* statutory requirements governing HUD's IHBG program, and implemented statutory changes to NAHASDA made by several

Continued