Alliance for Pharmacy Compounding

Compounding the Joy of Living®

Submitted via Regulations.gov February 4, 2026

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

Pursuant to 21 CFR § 10.30, the undersigned submits this petition under U.S.C.S. § 353a (Section 503A of the Food, Drug, and Cosmetic Act (FD&C Act)), 21 U.S.C.S. § 353b (Section 503B of the FD&C Act), 21 U.S.C.S. § 355 (Section 505 of the FD&C Act), and Section 351 of the Public Health Service Act (PHS Act), to request that the Commissioner of Food and Drugs take administrative actions set forth below regarding the classification and regulation of desiccated thyroid extract (DTE) products.

A. Action Requested

On behalf of the Alliance for Pharmacy Compounding, which represents both 503A state-licensed compounding pharmacies and 503B FDA-registered outsourcing facilities nationwide, we respectfully request that FDA:

1. **Reverse its decision to classify desiccated thyroid extract (DTE) as a biological product** under the PHS Act.
2. **Clarify that the August 6, 2025 "Notice to Industry"[1] does not constitute an across-the-board ban on compounding animal-derived thyroid (ADT) preparations for individual patients pursuant to valid prescriptions.**
3. **Affirm that natural thyroid products should, if approved, proceed through the drug approval pathway under section 505 of the FD&C Act** rather than the biologics pathway under section 351 of the PHS Act.
4. **Engage pharmacy and prescriber stakeholders** in developing a science-based framework for ADT compounding that ensures quality while preserving patient access.

[1] See FDA's Animal-derived thyroid products notice to industry, dated August 6, 2025 (https://www.fda.gov/media/188081/download), attached as **Exhibit A**, hereto.

5. **Adopt a risk-based enforcement approach** to ADT compounding that targets demonstrable safety, quality, or misbranding concerns rather than imposing a categorical prohibition.

B. Statement of Grounds

1. Background and FDA Action

In 2022, FDA reclassified desiccated thyroid extract (DTE) products, which contain thyroglobulin, a protein naturally present in animal thyroid tissue, as biological products under the PHS Act.[2] FDA based this decision on its 2020 final rule defining "protein" at 21 CFR § 600.3 as any alpha amino acid polymer with a defined sequence greater than 40 amino acids, concluding that because DTE necessarily contains thyroglobulin, it falls within the statutory definition of a biological product.[3] Following that reclassification, FDA determined that DTE products must be marketed through an approved Biologics License Application (BLA) under section 351 of the PHS Act,[4] a significantly more burdensome pathway than the traditional drug approval process. Notably, there are no FDA-approved BLAs for animal-derived thyroid products, meaning all such products are now considered unapproved biologics.

On August 6, 2025, FDA issued a "Notice to Industry" in connection with its partial grant and denial of AbbVie's 2024 citizen petition (Docket No. FDA-2024-P-1715), reiterating this position and signaling enforcement action against unapproved ADT products.[5]

2. Concerns with FDA's Process

APC is concerned with both the process and the substance of this determination. The decision to apply the definition of "protein" to DTE was made through internal interpretation, rather than through notice-and-comment rulemaking specific to DTE or ADT products. As a result, pharmacists, prescribers, and patients have had no meaningful opportunity to provide input on the clinical, market, and access implications. Given the widespread use of these therapies and the lack of complete FDA-approved alternatives, such a sweeping policy warrants public engagement. Moreover, the recent resignation of CDER Director George Tidmarsh amidst "serious concerns about his personal conduct" provides further grounds for questioning the basis of the FDA's internal decision to reclassify DTE as a biologic and eliminate patient access to ADT without following the required notice-and-comment rulemaking process.

3. Scientific and Legal Issues

In ADT products, thyroglobulin is not the active ingredient; it is an inactive component of the porcine or bovine thyroid tissue from which the active thyroid hormones (T4 and T3) are derived. FDA's own guidance acknowledges that a drug product containing a protein only as an inactive ingredient (e.g., human serum albumin) is not considered a "protein" for purposes of biologic

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[2] See FDA's letter to NABP, dated September 16, 2022 (https://join.a4pc.org/hubfs/PDFs/MEMO-EO-FDA-Letter-re-DTE5.pdf), attached as **Exhibit B**, hereto.

[3] See Definition of the Term "Biological Product", Docket No. FDA-2018-N-2732 (https://www.fda.gov/media/135421/download?attachment), attached as **Exhibit C**, hereto.

[4] See Exhibit B.

[5] See Exhibit A.

classification.[6] By asserting that the presence of thyroglobulin alone makes DTE a biologic, FDA has departed from its prior guidance without clear justification.

4. Implications for Compounding and Patient Care

FDA's Notice further suggests that compounded ADT products are ineligible for exemptions under sections 503A and 503B of the FD&C Act. APC strongly disagrees. Many patients cannot tolerate synthetic levothyroxine products, and prescribers rely on compounded ADT formulations to meet these patients' clinical needs. FDA itself has previously stated it does not intend to substitute its judgment for that of prescribing practitioners. The FD&C Act contemplates compounding from bulk substances when clinical need exists and when such substances meet statutory criteria, including the existence of a USP monograph, which ADT has.[7] A categorical prohibition against ADT compounding is inconsistent with congressional intent and would harm patients who rely on these therapies.

5. Commercial Dynamics

We also note that AbbVie, which holds approved thyroid hormone products, has an economic interest in eliminating compounded ADT. While manufacturers are entitled to protect their approved products, FDA's enforcement policy should prioritize patient access and safety, not the competitive interests of a single company. Enforcement should be targeted to products with demonstrable safety, quality, or misbranding issues rather than sweeping across compliant compounders.

C. Environmental Impact

Pursuant to 21 CFR §25.30(h) and § 25.31(h), this petition qualifies for a categorical exclusion; it requests administrative action and does not increase the use of any substance in the environment.

D. Economic Impact

Economic impact information will be provided upon request by the Commissioner.

E. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: August 6, 2025. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: N/A. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

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[6] See The "Deemed To Be a License" Provision of the BPCI Act, Questions and Answers, Guidance for Industry, dated March 2020 (https://www.fda.gov/media/135838/download), attached as **Exhibit D**, hereto.

[7] See Pharmacopeia Online: Thyroid (http://www.uspbpep.com/usp29/v29240/usp29nf24s0_m83400.html), attached as **Exhibit E**, hereto.

Respectfully submitted,

Scott Brunner, CAE
Chief Executive Officer
Alliance for Pharmacy Compounding
100 Daingerfield Road Suite 100
Alexandria, VA 22314

EXHIBIT A

VIA EMAIL

August 6, 2025

NAME
FIRM
ADDRESS
EMAIL

RE: _____

Dear Manufacturers, Importers, and Distributors of Animal-Derived Thyroid Products:

The Food and Drug Administration (FDA or we) intends to take action against marketed unapproved animal-derived thyroid (ADT) products (sometimes described as desiccated thyroid extract (DTE) products). ADT products require an approved biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act in order to be legally marketed in the U.S. (42 U.S.C. 262(a)(1)). There are no FDA-approved BLAs for the ADT products currently on the market.

As described in more detail below, FDA intends to take action against marketed unapproved ADT products. To provide notice to manufacturers, importers, and distributors, we are issuing this letter. This notice also serves to promote compliance with FDA's premarket approval requirements. In addition, the timing further discussed below is intended to provide patients currently using these products sufficient time to work with their healthcare providers to transition to an FDA-approved thyroid hormone replacement product.

BACKGROUND

Overt hypothyroidism, a condition of decreased thyroid hormone production from the thyroid gland, affects approximately 2% of the adult population in the U.S.[1] Thyroid hormone replacement products treat hypothyroidism by replacing the hormones that patients need to

[1] Wyne KL et al, 2022, Hypothyroidism Prevalence in the United States: A Retrospective Study Combining National Health and Nutrition Examination Survey and Claims Data, 2009–2019, J Endocr Soc, 7(1): bvac172.

maintain normal circulating thyroid hormone levels and thereby prevent or improve symptoms of hypothyroidism, such as fatigue, weight gain, constipation, cold intolerance, or depressed mood, among others. In general, thyroid hormone replacement products have a narrow therapeutic index, meaning that tight dose regulation is needed to maintain circulating thyroid hormone levels within a narrow therapeutic range.[2]

ADT products were the first pharmacological treatments developed for replacement or supplemental therapy in patients with hypothyroidism and have been in use for this purpose since the late 19th century.[3,4] ADT is a naturally derived mixture from animal thyroid glands. Initially, these products were derived from bovine (cow), ovine (sheep), or porcine (pig) thyroid glands, but currently most ADT products are porcine-derived thyroid extracts.

ADTs are no longer the predominant source of thyroid hormone replacement. Synthetic liothyronine sodium (LT3 or synthetic liothyronine) and synthetic levothyroxine sodium (LT4 or synthetic levothyroxine) became commercially available following FDA approval in 1956 and 2002, respectively.[5,6] These synthetic products provide an approved safe and effective alternative to ADT products for treatment of hypothyroidism. In 2024, approximately 94% of the 24 million patients receiving thyroid hormone replacement were prescribed synthetic levothyroxine sodium, while only 6% (1.5 million patients) received unapproved ADT products.[7] FDA is unaware of any studies demonstrating the safety and effectiveness of ADT products, meaning the benefits and risks of treatment with ADT products have not been adequately assessed.

Certain safety and effectiveness concerns about unapproved ADT products guided current recommendations by professional medical societies and shifted prescribing practices. These concerns include inconsistent potencies from batch to batch of the unapproved ADT products, the

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[2] FDA, Guidance for Industry: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing (December 2000). FDA guidances are available on the FDA guidance web page. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] FDA, Older Therapies Aren't Necessarily Better for Thyroid Hormone Replacement, https://www.fda.gov/consumers/consumer-updates/older-therapies-arent-necessarily-better-thyroid-hormone-replacement.

[4] Connelly KJ, Park JJ, and LaFranchi SH, 2022, History of the Thyroid, Horm Res Paediatr, 95(6): 546-556.

[5] NDA 010379. Drugs@FDA: FDA-Approved Drugs; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=010379.

[6] NDA 021402. Drugs@FDA: FDA-Approved Drugs; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021402.

[7] Symphony Health. Metys. Data extracted February 2025. Percentages shares may sum to more than 100 percent due to patients who may have received more than one product category in a calendar year.

potential for viral contamination due to the animal source, and supraphysiological levels of the thyroid hormone triiodothyronine (T3) provided by the ADT products, which may result in symptoms of hyperthyroidism.[8,9,10,11,12,3,13]

LEGAL AND REGULATORY HISTORY

ADT products meet the definition of a "biological product" in section 351(i)(1) of the PHS Act (42 U.S.C. 262(i)(1)) because ADT (the drug substance) is a "protein" or because it is "analogous" to a protein. FDA's regulations define "protein" to mean "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size" (21 C.F.R. 600.3(h)(6)). ADT is derived from animal (usually porcine) thyroid glands and is a naturally derived mixture that necessarily contains thyroglobulin, an alpha amino acid polymer with a specific defined sequence consisting of 2,770 amino acids. In animal thyroid preparations such as porcine-derived ADT, the thyroid hormones T3 and thyroxine (T4) are incorporated into the thyroglobulin by peptide bonds, and ADT also may contain free T3 and free T4.[14] Following oral administration of an ADT tablet, for example, the proteolytic enzymes of the gastrointestinal tract release iodothyronines and iodotyrosines (including T3 and T4) from the thyroglobulin.[10] ADT that is composed primarily of protein components (e.g., thyroglobulin) is a "biological product" because it falls within the Agency's interpretation of the statutory term "protein" (see 21 C.F.R. 600.3(h)(6)).

Alternately, ADT is "analogous" to a protein, and, thus, a "biological product" because it includes an identified biological product component (i.e., thyroglobulin) that is necessary for the activity of the product and contributes to achieving the intended therapeutic effect and also may include identified non-biological product components (e.g., free T3 and free T4) that can contribute to the product's activity.

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[8] Jackson IM and Cobb WE, Why does anyone still use desiccated thyroid USP?, 1978 Am J Med 64(2): 284-288.
[9] Penny R and Frasier SD, 1980, Elevated serum concentrations of triiodothyronine in hypothyroid patients. Values for patients receiving USP thyroid, Am J Dis Child. 134(1): 16-18.
[10] LeBoff MS et al, 1982, Bioavailability of thyroid hormones from oral replacement preparations, Metabolism 31(9): 900-905.
[11] Lev-Ran A, 1983, Part-of-the-day hypertriiodothyroninemia caused by desiccated thyroid, JAMA 250(20): 2790-2791.
[12] MI Surks et al, 1972, A new radioimmunoassay for plasma L-triiodothyronine: measurements in thyroid disease and in patients maintained on hormonal replacement, J Clin Invest. 51(12): 3104-3113.
[13] Jonklaas J et al, 2014, Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement, Thyroid 24(12): 1670-1751.
[14] Idrees T et al, 2020, Liothyronine and Desiccated Thyroid Extract in the Treatment of Hypothyroidism, Thyroid 30(10): 1399-1413.

Although the majority of therapeutic biological products have been licensed under the PHS Act, some protein products historically had been approved under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act. On March 23, 2010, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) clarified the statutory authority under which certain products would be regulated by amending the definition of a "biological product" in section 351(i) of the PHS Act to include a "protein" (and products "analogous" to a protein) and describing procedures for submission of a marketing application for certain biological products. As of March 23, 2020, all sponsors seeking approval of a biological product that previously could have been submitted under section 505 of the FD&C Act, including ADT products, must submit a marketing application (i.e., a BLA) under section 351 of the PHS Act.

ADT products marketed without a biologics license under the PHS Act are unapproved biological products. This includes ADT products that are prepared by a licensed pharmacist in a state-licensed pharmacy or a federal facility, a licensed physician, or an outsourcing facility. Biological products subject to licensure under section 351 of the PHS Act are not eligible for the exemptions for compounded drugs under sections 503A and 503B of the FD&C Act, nor is there an exemption under section 351 of the PHS Act from the requirement to have an approved BLA.[15]

SAFETY, EFFECTIVENESS, AND QUALITY CONCERNS WITH UNAPPROVED ADT PRODUCTS

Unlike approved biological products, unapproved ADT products currently on the market have not undergone FDA's premarket evaluation, which involves, among other things, an assessment of manufacturing processes and controls, evaluation of labeling, and examination of ADT supplier suitability. Unapproved ADT products have presented issues with potency, content uniformity, labeling, and impurities identified through inspections, sampling, and patient complaints. These products pose unique risks compared to synthetic thyroid drug products because they are derived from animal thyroid glands, potentially containing process-related impurities, elemental impurities, and ADT-unique impurities (e.g., organic iodine and inorganic iodide) and contaminants (e.g.,

[15] For additional discussion of FDA policies pertaining to the mixing, diluting, and repackaging of approved biological products, see FDA's Guidance for Industry: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (January 2018). This guidance is currently available at https://www.fda.gov/media/90986/download. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

viruses and other objectionable microbes). The potency and bioavailability of unapproved ADT products can be highly variable both between batches and within batches, creating uncertainty about the quantity of active hormones delivered, which is particularly concerning given the narrow therapeutic index for thyroid replacement therapies where minor dose changes can lead to serious adverse effects.

Since late 2017, FDA inspections of ADT manufacturers, ADT product manufacturers, and ADT product distributors have identified significant current good manufacturing practice (CGMP) violations, resulting in warning letters, an import alert, and recalls due to issues including, but not limited to: inadequate quality unit oversight, lack of stability data to support labeled expiration dates, failure to investigate out-of-specification results, and manufacturing processes not operating in a state of control. FDA is aware of over 500 adverse event reports associated with ADT products from 1968 through February 2025, with a substantial increase between 2019-2020 that may have been related to several voluntary recalls of subpotent or superpotent ADT products.

Additionally, unapproved ADT products have inconsistent labeling that does not comply with regulatory standards, with some products including the non-metric unit of measurement of “grain” and using different measurements for one "grain" (ranging from 60 mg to 65 mg), creating confusion and potential dosing errors that FDA premarket review could prevent.

RISK-BASED PATIENT TRANSITION PERIOD

FDA understands that a significant number of patients currently take unapproved ADT products. We believe it will require up to 12 months to safely transition patients to an FDA-approved thyroid hormone replacement product. FDA intends to provide adequate time to transition patients to an FDA-approved thyroid hormone replacement product before initiating action against manufacturers, distributors, and importers of ADT and unapproved ADT products intended for commercial distribution. During this time, FDA will continue to apply a risk-based enforcement policy.[16]

It is your responsibility to ensure that your firm complies with all applicable requirements of

[16] See 85 FR 75331 (Nov. 25, 2020) and 86 FR 28605, 28608 (May 27, 2021) (“FDA will continue to exercise its existing general approach to prioritizing regulatory and enforcement action [for marketed unapproved new drugs], which involves risk-based prioritization in light of all the facts of a given circumstance.”).

federal law and FDA regulations. Within 30 working days from the date of receipt, please acknowledge receipt of this letter by emailing FDAADVISORY@fda.hhs.gov. Please include your firm name and the unique identifier "_____" in the subject line of the email.

Sincerely,

U.S. Food and Drug Administration

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
www.fda.gov

EXHIBIT B

NABP
National Association of Boards of Pharmacy

847/391-4406
Fax: 847/375-1114

1600 Feehanville Dr
Mount Prospect, IL 60056
help@nabp.pharmacy

TO: EXECUTIVE OFFICERS – STATE BOARDS OF PHARMACY

FROM: Lemrey "Al" Carter, Executive Director/Secretary

DATE: September 22, 2022

RE: FDA Letter Regarding Desiccated Thyroid Extract Preparations

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The Food and Drug Administration (FDA) has become aware of desiccated thyroid extract (DTE) that appears to have been prepared by state-licensed pharmacies being offered to patients. FDA has issued the attached letter to NABP and asked that it be shared with our member boards.

States that wish to provide information to FDA should submit the information by email to the following mailbox: compounding@fda.hhs.gov.

Attachment

cc: NABP Executive Committee

U.S. FOOD & DRUG ADMINISTRATION

September 16, 2022

Lemrey "Al" Carter, MS, PharmD, RPh
Executive Director/Secretary
National Association of Boards of Pharmacy
1600 Feehanville Dr
Mount Prospect, IL 60056
acarter@NABP.pharmacy

Dear Dr. Carter:

The purpose of this letter is to bring to the attention of the National Association of Boards of Pharmacy (NABP) that the Food and Drug Administration (FDA) is aware of desiccated thyroid extract (DTE) that appears to have been prepared by state-licensed pharmacies being offered to patients. These products can put patients at harm. We encourage you to share this information with your members.

There are two types of thyroid replacement therapies: (1) synthetic therapies containing only levothyroxine or liothyronine; and (2) therapies made from DTE, which is produced from dried ground animal thyroid glands. DTE is sold in the United States as Armour Thyroid, NP Thyroid, Nature-Throid, and Natural Thyroid, among other names.

While synthetic thyroid replacement therapies containing only levothyroxine or liothyronine are drugs subject to approval under the Federal Food, Drug, and Cosmetic Act (FD&C Act), therapies containing DTE are biological products subject to licensure under section 351 of the Public Health Service Act (PHS Act).

DTE products meet the definition of a "biological product" under section 351(i) of the PHS Act (21 U.S.C. § 262(i)). Under that definition, a "biological product" is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, *protein, or analogous product*, . . . applicable to the prevention, treatment, or cure of a disease or condition in human beings." 21 U.S.C. § 262(i)(1) (emphasis added). FDA's regulations define the term "protein" in the statutory definition of "biological product" to mean "any alpha amino acid polymer with a specific, defined sequence that is *greater* than 40 amino acids in size" (see 21 CFR 600.3(h)(6); see also 85 FR 10057). DTE meets the definition of a biological product because it is a "protein" or "analogous" to a protein. DTE is derived from animal thyroid glands (usually porcine, meaning from a pig) and necessarily contains thyroglobulin, an alpha amino acid polymer with a specific defined sequence, consisting of 2,770 amino acids.

Section 351(a)(1) of the PHS Act prohibits the introduction into interstate commerce of any biological product unless "a biologics license . . . is in effect for the biological product." Biological products subject to licensure under section 351 of the PHS Act are not eligible for the exemptions for compounded drug products under sections 503A and 503B of the FD&C Act.

FDA has not approved any biologics license applications (BLAs) for DTE products. Some biological products, including thyroglobulin products, had historically been approved under section 505 of the FD&C Act (21 U.S.C. § 355). However, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) required that as of March 23, 2020, all sponsors seeking approval of a biological product that previously could have been submitted under section 505 of the FD&C Act (21 U.S.C. § 355) must submit a BLA under section 351 of the PHS Act (42 U.S.C. § 262).

In addition, unlicensed DTE products have not been reviewed by the FDA to ensure safety, purity, and potency, and therefore may present issues with respect to quality and dosing, among other things. For example, tablets made from the same batches may not always have the same hormone levels. Inconsistent dosage can have serious consequences for patients; too much medication can cause bad side effects, and too little can be ineffective. As a reminder, FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drug products, because these compounders are not licensed by FDA and generally do not register their facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint. Recently, FDA has received complaints related to the safety, purity, and potency of unlicensed DTE products that appear to have been prepared by state-licensed pharmacies.

We advise that you encourage state boards of pharmacy to submit to FDA any concerns or questions involving the preparation of biological products, including DTE, outside the scope of an approved BLA. States that wish to provide this information to FDA should submit the information by email to the following mailbox: compounding@fda.hhs.gov.

We are also sending this letter to the Federation of State Medical Boards to facilitate communication among associations with shared goals regarding these matters.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

We look forward to continuing to work with you on matters related to human drug compounding. If you have additional questions, please contact the Office of Compounding Quality and Compliance at compounding@fda.hhs.gov.

Sincerely,

Shannon Glueck, PharmD
Branch Chief
Branch 4
Division of Compounding II
Office of Compounding Quality and Compliance
Office of Compliance
Center for Drug Evaluation and Research

EXHIBIT C

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Definition of the Term "Biological Product"

Docket No. FDA-2018-N-2732

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

Economics Staff
Office of Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

Table of Contents

I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." This final rule is a significant regulatory action under sec. 3(f) of E.O. 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that will 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 an assessment of anticipated costs and benefits, 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 $154 million, using the most current (2018) 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.

B. Summary of Costs and Benefits

This final rule codifies the Food and Drug Administration's (FDA or Agency) interpretation of the statutory term "protein" that the Agency previously described in guidance (Ref. 1). This final rule does not finalize the FDA's interpretation of "chemically synthesized polypeptide" because section 605 of the Further Consolidated Appropriations Act, 2020 (Public Law 116-94) (FCA Act) removed the parenthetical "(except any chemically synthesized polypeptide)" from the category of "protein" in the definition of "biological product" in section 351(i) of the Public Health Service Act (PHS Act). Formalizing this interpretation will reduce regulatory uncertainty introduced by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) and section 605 of the FCA Act. Specifically, the rule clarifies the criteria for whether certain products will be regulated as drugs or biological products. The "bright-line" approach under the rule will reduce the amount of time and resources spent by FDA staff and industry in support of making such determinations.

In this regulatory impact analysis, we identify the products most likely to require a case-by-case determination under the baseline scenario. Under the rule, these determinations will be made by FDA according to the bright line standard outlined in the final rule. We calculate the cost savings from the amount of time saved by both the FDA and industry by avoiding a case-by-case determination. We also calculate the incremental costs to industry that are the result of reading and understanding the rule.

The primary estimate of the benefits in 2018 dollars annualized over 10 years is $395,000 using a 7% discount rate and $348,000 using a 3% discount rate. We also calculate ranges of benefits of $357,000 to $411,000 and $316,000 to $363,000, respectively. The estimated annualized costs range from $14,000 to $17,000, with a primary estimate of $15,000 using a 7% discount rate over a 10-year horizon. For a 3% discount rate, we estimate a range of $12,000 to $16,000, with a primary estimate of $14,000. These figures are shown in Table 1 below.

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

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $/year	$395,000	$357,000	$411,000	2018	7%	10	Cost savings to FDA and industry to avoid case-by-case review of applications.
		$348,000	$316,000	$363,000	2018	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized $/year	$15,000	$14,000	$17,000	2018	7%	10	Costs of reading the rule
		$14,000	$12,000	$16,000	2018	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government:							
	Small Business:							
	Wages:							
	Growth:							

In line with Executive Order (EO) 13771, in Table 2 we estimate present and annualized values of costs and cost savings over an infinite time horizon. With a 7 percent discount rate, discounted relative to year 2016, the estimated annualized net cost-savings equal $163,000 in 2016 dollars over an infinite horizon. Based on these cost savings, this final rule is considered a deregulatory action under EO 13771.

Table 2. EO 13771 Summary Table (in 2016 Dollars, Over an Infinite Time Horizon)

	Primary Estimate (7%)
Present Value of Costs	$88,000
Present Value of Cost Savings	$2,421,000
Present Value of Net Costs	($2,334,000)
Annualized Costs	$6,000
Annualized Cost Savings	$170,000
Annualized Net Costs	($163,000)

C. Summary of Changes

In 2018, we published the proposed rule "Definition of the Term Biological Product" (83 FR 63817). Accompanying the proposed rule was a comprehensive preliminary regulatory impact analysis on which we requested public comments (Ref. 2). We received no comments regarding this analysis. Compared to the preliminary analysis, the final regulatory impact analysis makes a substantive change to reflect the subsequent enactment of the FCA Act and several technical changes. First, we no longer exclude "any chemically synthesized polypeptide" from the category of "protein" in our analysis of the effects of the rule because the final rule reflects the revised statutory definition of "biological product" following the enactment of the FCA Act. Second, we now analyze the monetized effects of the rule for calendar years 2020 through 2029. Third, we updated several inputs into our cost and cost savings model with more recent industry wage figures. Fourth, we incorporated the most recent data available on approved drug products, including an updated list of products affected by the BPCI Act that are the focus of the final rule.

II. Final Regulatory Impact Analysis

A. Background

The BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (ACA) on March 23, 2010. The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. The statute defines "biosimilarity" to mean that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product. The statute defines "interchangeability" to mean that the biological product has been shown to be biosimilar and meet additional requirements, and may be substituted for the reference product without the intervention of the prescribing health care provider. The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984, which established abbreviated pathways for the approval of drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

In addition to creating an abbreviated pathway for licensure of biological products, the BPCI Act also amended the definition of a "biological product" to include a "protein (except any chemically synthesized polypeptide)." The FCA Act further amended the statutory definition of "biological product" to remove the parenthetical "(except any chemically synthesized polypeptide)" from the category of "protein." By including the category of "protein," the BPCI Act clarified the statutory authority under which protein products that are currently regulated as drugs under section 505 of the FD&C Act are to be regulated. The BPCI Act requires that new marketing applications for biological products, which previously would have been submitted under section 505 of the FD&C Act, must be submitted under section 351 of the PHS Act, with certain exceptions. The BPCI Act also includes a provision to transition approved applications for such products that fall under the revised definition of a biological product on March 23, 2020. On this date, applications for biological products that are approved under section 505 of the FD&C Act will no longer exist as New Drug Applications (NDAs) and will be deemed to be (and replaced by) approved Biologics License Applications (BLAs). Additionally, an application for a protein product that has been submitted under section 505 of the FD&C Act and is pending on March 23, 2020, will not be approved under the FD&C Act (unless the application falls within the exception described in section 607 of the FCA Act). Such an application may, for example, be withdrawn and resubmitted under section 351(a) or 351(k) of the PHS Act, as appropriate (Ref. 3).

B. Market Failure Requiring Federal Regulatory Action

This regulatory action is not intended to address a market failure *per se*. The regulation is intended to reduce regulatory confusion introduced into the existing regulatory system related to the statutory introduction of a new undefined regulatory term. Specifically, by introducing the undefined scientific term "protein" in the statutory definition of "biological product," Congress introduced uncertainty into the regulatory process. Without additional regulatory action by the FDA to clarify the term "protein" in this definition, manufacturers and the FDA would have needed to spend time and

resources to determine whether individual products are to be regulated as drugs under section 505 of the FD&C Act or as biological products under section 351 of the PHS Act. As such, the confusion surrounding the amended definition of a "biological product" in the PHS Act, as amended by the BPCI Act, and as subsequently amended by section 605 of the FCA Act, added a new regulatory burden to drug and biological product manufacturers and the FDA which this rule seeks to address.

C. Purpose of the Rule

The rule directly addresses the uncertainty introduced into the regulatory process by the BPCI Act and section 605 of the FCA Act by interpreting the term "protein." The rule codifies the interpretation of the statutory term "protein" that FDA previously described in guidance (Ref. 1). Specifically, the rule interprets "protein" to mean "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size."

This interpretation will reduce the burden on drug and biological product manufacturers and the FDA by instituting a bright-line standard for classifying existing products and new product applications, providing regulatory clarity, and reducing the time spent on such determinations.

D. Baseline Conditions

OMB's Circular A-4 offers guidance to Federal agencies on the development of regulatory analysis. A first step in developing the analysis is to "[i]dentify a baseline. Benefits and costs are defined in comparison with a clearly stated alternative. This normally will be a 'no action' baseline: what the world will be like if the rule is not adopted." In our primary analysis, we adopt a baseline that we believe reflects the best forecast of the world without the rule. We also analyze the effects of the rule relative to a pre-statutory baseline, which allows us to explore more of the effects of the BPCI Act than the primary baseline. In this Section, we describe the two baselines. In the Sensitivity Analysis (Section III) of the regulatory impact analysis, we explore implications of this alternative pre-BPCI Act baseline.

a. Primary Baseline

The November 2019 version of the FDA's Orange Book contains 5,050 approved NDAs (Ref. 4). From these, the FDA has identified a list of 91 approved applications for products that FDA classifies as proteins under the interpretation described in Agency guidance (Ref. 1) and will be deemed BLAs on March 23, 2020, under the BPCI Act "transition" provision ("transition list"). The transition list also includes 4 approved applications that subsequently were administratively closed and do not appear in the Orange Book but are related to other approved applications on the transition list, for a total of 95 products that will transition from NDA to BLA.

Among the 95 applications on the transition list, 25 have been discontinued according to the FDA Orange Book (Ref. 4). Four applications are NDAs that were submitted for a new indication or claim for a product reviewed under a different NDA (the "parent" NDA) and subsequently were administratively closed. These NDAs do not appear in the Orange Book because they were administratively closed (submissions are made to the "parent" NDA, which also appears on the transition list), but are included here for completeness. To give a sense of the market size of the affected products, we matched the remaining 66 non-discontinued products[1] with IQVIA sales data.[2] We estimate that for the 12-month period from December 2018 to November 2019, the total combined revenue was approximately $38.0 billion dollars, or an average of $576 million per product.

Without a regulation that codifies FDA's interpretation of the term "protein," as described in this rule, drug and biological product manufacturers may be more likely to challenge Agency classification decisions made on a product-by-product basis. Under this baseline scenario, the Agency expects that the 95 existing approved NDAs will transition to BLAs. We also forecast an additional 3 new approved applications per year will fall into the same size category as the 95 products described above. This is approximately equal to the average annual number of approvals of existing NDA products in this size category over both the last 5 years, and over the last 20 years, that will be transitioning to BLAs. However, without the rule, we anticipate these applications will need a case-by-case analysis to determine whether the product is a drug product or a biological product.

We note that FDA received a comment recommending that the Agency reconsider the case-by-case approach for evaluating whether a proposed product is composed of amino acid chains that are associated with each other in a manner found in nature based on the commenter's view that this approach is inconsistent with the bright line standard that FDA has otherwise adopted. In response to this comment to the rule, FDA recognizes that the application of the fact-specific, case-by-case analysis for proposed products composed of amino acid chains that are associated with each other in a manner not found in nature does not provide the same level of certainty that is provided by the bright-line rule. FDA does not expect to receive applications for many proposed products requiring such an a determination; however, to the extent that the agency will need to perform such analyses, these would be necessary under both the baseline and rule, and do not represent effects of the rule. FDA also received one comment requesting that FDA clarify its approach to assessing the appropriate application type for combination products, including peptide-protein combination products. However, this request is outside the scope of the rulemaking. This rulemaking applies to the evaluation of whether a product contains a biological product constituent part. The determination of the appropriate application type for a combination product that contains a biological product constituent part is a separate assessment conducted pursuant to different regulatory processes.

[1] One of these products is covered by two applications, one of which has been administratively closed. Therefore, these 66 non-discontinued products are covered by 67 applications in total.

[2] Sales history is dynamic and reflects the present view of the database at the time the information is provided. IQVIA, National Sales Perspective™, Calendar Year 2016, data extracted January 2020.

As a result of the BPCI Act's requirement to deem approved NDAs for biological products to be BLAs, affected products will be subject to requirements under the PHS Act that may differ in some respects from those under the FD&C Act. For example, in some instances, holders of deemed BLAs may be required to report or provide different information than was required under the FD&C Act. However, FDA expects that holders of an approved NDA for a biological product that is deemed to be a BLA will experience minimal disruption due to these differences in the applicable requirements.

Another effect of the BPCI Act is that certain products approved in NDAs and certain proposed products that seek licensure in a 351(a) BLA could see changes to their potential periods of exclusivity, and associated delays in approval of competitor products. Any unexpired period of 5-year or 3-year exclusivity associated with a product approved in an NDA will cease to have any effect when the NDA is deemed to be a BLA because FDA will not file or approve any application for a biological product under the FD&C Act after March 23, 2020. In contrast to products in approved NDAs that are deemed to be BLAs, proposed products falling under the amended statutory definition of a biological product and submitted under section 351(a) of the PHS Act could potentially receive a longer exclusivity period following approval. Biological products that are first licensed under section 351(a) of the PHS Act may be eligible to receive a 12-year period of exclusivity, whereas products approved in an NDA may be eligible to receive a 5-year period and, in some cases, one or more 3-year period(s) of exclusivity.

As noted before, our baseline forecasts 3 new applications per year that could potentially receive 12 years of exclusivity instead of 5- or 3-year exclusivity. If such applications are eligible for this longer period of exclusivity, it could potentially lead to a lengthened period of higher pricing for the affected products. After this exclusivity period expires, products may face additional competition due to the new abbreviated approval pathway for biological products included in the BPCI Act. FDA expects that the rule will not significantly affect which biological products will be eligible for 12 years of exclusivity under the PHS Act (compared to the baseline) because the size threshold for a product to be classified as a "biological product" will remain the same as described in guidance. Although FDA's interpretation no longer excludes "any chemically synthesized polypeptide" from the statutory category of "protein," we do not expect this to result in a significant increase in biological products that will be eligible for 12 years of exclusivity under the PHS Act (compared to the baseline). Therefore, in our primary estimate of benefits and costs, we do not forecast and quantify how these provisions of the BPCI Act will affect competition.

b. Alternative Baseline

While we believe the primary baseline described above reflects the best forecast of the world without the rule, we have identified a secondary baseline that allows us to explore more of the effects of the BPCI Act's amendment to the statutory definition of "biological product" and clarification of the statutory authority under which protein products that are currently regulated as drugs under section 505 of the FD&C Act are to be regulated ("BPCI Act statutory changes"). Under this alternative baseline, we assume

that no products will transition from NDA to BLA. The Sensitivity Analysis (Section III) calculates the effects of the BPCI Act statutory changes and subsequent statutory changes made by the FCA Act against this alternative baseline scenario.

E. Benefits of the Rule

Under the rule, FDA will make determinations for each of the affected products based on the size of the molecule using the "bright-line" standard. Since the FDA already collects this information during the application review process, only minimal staff time will be required to classify all existing products under the proposed definition as a drug product or a biological product. Compared to the primary baseline scenario of case-by-case determinations for each of the affected products, we identify and monetize potential cost savings under the rule from this streamlined review process.

For our primary estimate, we expect that the 95 products on the transition list and 3 additional products per year will require the FDA to determine the classification of each product on a case-by-case basis with input from industry. Based on the FDA's experience with a single product, we estimate that such a determination will take at least 114 hours by FDA staff and 78 hours by industry for each product. These estimates are such that the resulting cost-savings estimates are likely understated. For our lower-bound estimate of cost savings, we assume that no time will have been spent for the 25 discontinued products and 4 administratively closed applications for industry only under the baseline scenario. For our upper-bound estimate of cost savings, based on FDA's experience, we approximate 5 additional products near the size threshold under the rule will require a case-by-case determination.

To calculate the cost savings of the rule, we multiply the FDA staff hours by a loaded wage of $135.39 per hour. For industry, we apply estimates from the Bureau of Labor Statistics (BLS) of the mean wage for a medical scientist working in the pharmaceutical and medicine manufacturing industry as grouped by the North American Industry Classification System (NAICS) (Ref. 5). We double the wage estimate of $62.77 to $125.52 to account for overhead and multiply this to the number of hours spent by industry. Using these hour and wage estimates, we estimate that each case-by-case review avoided under the rule will generate about $15,000 in cost savings to the FDA and $10,000 to industry.

We assume that these determinations will take place in 2020 for existing products, and during the submission year for determinations about future product submissions. This results in an initial cost savings of about $1.51 million in 2020 to FDA and $0.96 million to industry, with estimate ranges of $1.51 million to $1.59 million and $0.70 million to $1.0 million, respectively. Combining these estimates yields total cost savings in 2020 of $2.47 million, or between $2.19 million and $2.60 million. In future years, the FDA will experience cost savings of $46,000 and industry of $29,000, for a total of about $76,000. Table 3 reports the cost savings to FDA and industry by year, as well as the present discounted value (PDV) and annualized value of these cost savings. The PDV and annualized values cover a 10-year time horizon using a 3% and 7% discount rate.

Table 3. Cost Savings to FDA and Industry Over a 10-year Time Horizon

Year	FDA			Industry			Total		
	Primary	Low	High	Primary	Low	High	Primary	Low	High
2020	$1,512,532	$1,512,532	$1,589,702	$959,628	$675,656	$1,008,588	$2,472,160	$2,188,188	$2,598,290
2021	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2022	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2023	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2024	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2025	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2026	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2027	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2028	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2029	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
PDV, 3%	$1,818,490	$1,818,490	$1,893,412	$1,153,743	$878,043	$1,201,278	$2,972,233	$2,696,532	$3,094,690
PDV, 7%	$1,695,514	$1,695,514	$1,767,636	$1,075,721	$810,327	$1,121,479	$2,771,235	$2,505,841	$2,889,114
Annualized, 3%	$213,182	$213,182	$221,966	$135,254	$102,933	$140,826	$348,436	$316,116	$362,792
Annualized, 7%	$241,403	$241,403	$251,672	$153,158	$115,372	$159,673	$394,562	$356,775	$411,345

F. Costs of the Rule

We assume that all firms that manufacture drug products will need to read this rule. The rule contains about 6,500 words. If the average adult reads between 200 and 250 words per minute, we estimate that it will take approximately 0.5 hours to read the rule at the midpoint of 225 words per minute. Using data from the FDA Orange Book (Ref. 4), we count that there are 1,637 firms that manufacture drug products. We assume that the person reading the rule at each firm is a legal professional and obtain data on the pharmaceutical and medicine manufacturing industry-specific mean hourly wage from the BLS (Ref. 5). Doubling this wage to account for overhead, we assume that the individuals reading the rule earn a mean fully loaded hourly wage of $163.66. Multiplying the number of firms by the time to read the rule, and then multiplying that product by the mean fully loaded hourly wage, we estimate that the total cost to read the rule will be about $129,000 using 2018 wage figures. We also estimate a lower-bound of $116,000 and an upper-bound of $145,000, corresponding to faster and slower reading speeds. This will be a one-time cost that occurs in the first year.

G. Net Benefits of the Rule

To calculate the net benefits of the rule, we subtract the costs of reading the rule identified in Section F from the cost savings to the FDA and industry calculated in Section E. Table 4 displays these figures yearly and reports the PDV and annualized values in 2018 dollars using both a 3 percent and 7 percent discount rate.

Table 4. Net Benefits of the Rule Over a 10-year Time Horizon

Year	FDA			Industry			Total		
	Primary	Low	High	Primary	Low	High	Primary	Low	High
2020	$1,512,532	$1,512,532	$1,589,702	$830,633	$530,538	$892,493	$2,343,165	$2,043,070	$2,482,195
2021	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2022	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2023	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2024	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2025	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2026	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2027	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2028	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2029	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
PDV, 3%	$1,818,490	$1,818,490	$1,893,412	$1,028,506	$737,151	$1,088,564	$2,846,995	$2,555,640	$2,981,976
PDV, 7%	$1,695,514	$1,695,514	$1,767,636	$955,166	$674,702	$1,012,979	$2,650,680	$2,370,216	$2,780,614
Annualized, 3%	$213,182	$213,182	$221,966	$120,572	$86,417	$127,613	$333,755	$299,599	$349,579
Annualized, 7%	$241,403	$241,403	$251,672	$135,994	$96,062	$144,225	$377,397	$337,466	$395,897

H. Analysis of Regulatory Alternatives to the Rule

For purposes of this analysis, in addition to the proposed interpretation described above, FDA considered and analyzed two regulatory alternatives to the rule. Under the first alternative approach, rather than a single size cutoff, this option would apply an algorithm based on certain limits to isolate the size ranges over which there seems to be some scientific agreement about whether a molecule is a peptide or a protein. Under this option, molecules of 40 amino acids or less in size would be considered peptides, and those of 100 amino acids or more in size would be considered proteins. Molecules within the range of uncertainty would be analyzed case-by-case based on structural or functional characteristics.

Under this algorithm-based approach, products approved under an NDA with 40 or fewer amino acids would continue to be regulated as drug products. Products approved under an NDA with 100 or more amino acids would transition and be regulated as biological products. Under this policy option, 32 of the 95 applications would require a case-by-case review, similar to the process described in the baseline scenario. Initial cost savings under this option would come from the existing 63 applications that transition without a costly review by FDA and industry.

Under the primary baseline, we forecasted 3 new applications per year will require a determination by the FDA. Under the algorithmic approach, we predict that about 1 application per year would fall into the range of uncertainty and about 2 applications per year could be sorted as a drug or biological product by the size threshold alone. This figure assumes that the share of products with at least 100 amino acids remains constant at around 66%.

Table 5 presents the benefits in the form of cost savings to FDA and Industry under this algorithm alternative. The estimated cost savings under this proposal are lower than those described in the analysis of the rule. We do not estimate the costs of reading this policy proposal, because we do not have the word count of such a policy; however, we expect that these costs are likely to be similar in magnitude to the costs of reading the rule.

Table 5. Benefits to FDA and Industry Under the Algorithm Alternative Over a 10-year Time Horizon

Year	FDA			Industry			Total		
	Primary	Low	High	Primary	Low	High	Primary	Low	High
2020	$1,003,048	$1,003,048	$1,054,223	$636,385	$448,067	$668,853	$1,639,432	$1,451,114	$1,723,077
2021	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2022	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2023	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2024	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2025	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2026	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2027	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2028	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2029	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
Proposed Rule									
PDV, 3%	$1,818,490	$1,818,490	$1,893,412	$1,153,743	$878,043	$1,201,278	$2,972,233	$2,696,532	$3,094,690
PDV, 7%	$1,695,514	$1,695,514	$1,767,636	$1,075,721	$810,327	$1,121,479	$2,771,235	$2,505,841	$2,889,114
Annualized, 3%	$213,182	$213,182	$221,966	$135,254	$102,933	$140,826	$348,436	$316,116	$362,792
Annualized, 7%	$241,403	$241,403	$251,672	$153,158	$115,372	$159,673	$394,562	$356,775	$411,345
Alternative									
PDV, 3%	$1,205,946	$1,205,946	$1,255,631	$765,114	$582,281	$796,637	$1,971,060	$1,788,227	$2,052,268
PDV, 7%	$1,124,394	$1,124,394	$1,172,222	$713,373	$537,375	$743,717	$1,837,767	$1,661,769	$1,915,939
Annualized, 3%	$141,374	$141,374	$147,198	$89,695	$68,261	$93,390	$231,068	$209,635	$240,588
Annualized, 7%	$160,088	$160,088	$166,898	$101,568	$76,510	$105,889	$261,657	$236,598	$272,787
Difference									
PDV, 3%	$612,544	$612,544	$637,781	$388,629	$295,762	$404,641	$1,001,173	$908,306	$1,042,422
PDV, 7%	$571,121	$571,121	$595,414	$362,348	$272,952	$377,761	$933,469	$844,073	$973,175
Annualized, 3%	$71,809	$71,809	$74,767	$45,559	$34,672	$47,436	$117,368	$106,481	$122,204
Annualized, 7%	$81,315	$81,315	$84,774	$51,590	$38,862	$53,785	$132,905	$120,177	$138,558

As a second alternative, we consider a different bright-line standard that FDA considers to be an alternate scientifically supported approach, based on the Agency's evaluation of the scientific literature. Under this option, the statutory term "protein" would be interpreted to mean any alpha amino acid polymer with a specific, defined sequence that is greater than 50 amino acids in size. Accordingly, products approved under an NDA with 50 or fewer amino acids would be considered "peptides" and continue to be regulated as drug products.

Under this alternative, bright-line standard, the Agency expects that 92 of the 95 approved NDAs for biological products would transition to BLAs. However, 3 approved NDA products are composed of between 41 and 50 amino acids. Under this alternative proposal, these 3 products would not meet the definition of a biological product because each of these products would be a peptide (i.e., composed of 50 or fewer amino acids), rather than a protein, and would not transition to BLAs. According to the Orange Book, one of these products has an exclusivity expiration date of July 27, 2021. For this product, this regulatory alternative could delay the time it may face a competitor product. For all three products, not transitioning to a BLA would also prevent potential competitor products from using the 351(k) pathway.

III. Sensitivity Analysis

In our main analysis of the costs and cost savings of this rule, our primary baseline assumes that the interpretation of the statutory term "protein" as reflected in FDA's guidance (Ref. 1) will continue to guide FDA's determinations on a case-by-case basis. Therefore, we attribute the transition of certain products from an NDA to a BLA to the BPCI Act and the FCA Act rather than this rule and expect the final outcome of such case-by-case determination for each individual product will remain unchanged with or without this rule. Under our secondary baseline, we evaluate the effects of the transition itself using a pre-statutory baseline as if the transition will not occur without the BPCI Act statutory changes.

We expect the bulk of the effects of the statutes under this baseline are driven by two, interrelated factors: (1) the differences in the length of available exclusivity periods between NDA and BLA products, and (2) competition from the abbreviated licensure pathway for biological products licensed as biosimilar to or interchangeable with a reference product after the March 23, 2020, transition date, as compared with competition from "follow-on" products approved prior to March 23, 2020 through the pathway described in section 505(b)(2) of the FD&C Act.

Compared to the pre-statutory baseline, the BPCI Act's statutory changes and subsequent statutory changes made by the FCA Act will affect the existing periods of exclusivity for the products on the preliminary transition list, and any exclusivity granted to approved applications for similar products in the future. As described earlier, any unexpired period of 5-year or 3-year exclusivity associated with a product approved as an NDA will cease to have any effect when the NDA is deemed to be a BLA because FDA will not file or approve any application for a biological product under the FD&C Act after March 23, 2020 (unless the application falls within the exception described in section 607 of the FCA Act, which specifies that any such applications remain subject to any unexpired period of exclusivity for a relied-upon listed drug). According to November 2019 Orange Book exclusivity data (Ref. 4), only 7 NDAs on the transition list have exclusivity expiration dates beyond the March 23, 2020 transition date. Of these applications, 3 products have exclusivity expiration dates in late 2020, 2 products have exclusivity that expires in mid-2021, and 1 product has exclusivity that expires in 2022. Though any unexpired exclusivity for these applications and any other NDAs for

biological products approved before the transition date will cease to have any practical effect at the time of the transition, this effect is minimal because the standard review timeframe for a competitor product submitted in a BLA on or after March 23, 2020, generally will extend beyond these unexpired exclusivity expiration dates.

In contrast, in accordance with the BPCI Act's statutory changes, applications for similar products submitted under section 351(a) of the PHS Act before, on, or after the March 23, 2020 transition date will be potentially be eligible to receive a 12-year period of exclusivity. Taken by itself, the extra years of exclusivity afforded to biological products first licensed in a 351(a) BLA relative to the periods of exclusivity available for NDA approvals will likely be seen as an incentive to prioritize development and submission of additional products similar to those on the preliminary transition list. However, because these differences in exclusivity coincide with a switch from potential follow-on product competition to biosimilar or interchangeable product competition, this prediction is less clear cut.

Orange Book (Ref. 1) data show that very few of the applications on the preliminary transition list have unexpired periods of exclusivity; however, competition is currently limited to certain follow-on products approved through the 505(b)(2) pathway and other products in the product class. Historically, applications for follow-on products in this category have been submitted pursuant to section 505(b)(2) of the FD&C Act generally due to past scientific challenges and statutory limitations on the scope of data that can be relied upon in abbreviated new drug applications (ANDAs). There are no currently marketed biological products that were approved through the ANDA pathway. The framework created by section 351(k) of the PHS Act provides a pathway under which increased competition has the potential to emerge.

In addition to the advantages of regulatory certainty with respect to the approval pathway for these products, the 351(k) pathway also creates new possibilities for the product development of biosimilar and interchangeable products, where sponsors can leverage FDA's finding of safety and effectiveness for the reference product to support approval of follow-on products. In this context, there may be a reduced need for multiple large clinical outcomes studies as part of biosimilar product development, which can significantly lower development costs. We therefore assume that it may be possible that the statutory requirements for obtaining a license under the 351(k) pathway for a biosimilar product or an interchangeable product will lead to greater competition (compared with follow-on products approved through the 505(b)(2) pathway) for the types of applications that will transition under the rule. We note that it would be difficult to evaluate any additional administrative burden that may be associated with the regulation of some of these products as biological products under section 351 of the PHS Act as compared to section 505 of the FD&C Act, in part because the relative administrative burden associated with one pathway versus another may vary by product. However, in the aggregate, FDA expects that any additional administrative burden that may be associated with regulation of products as biological products under the PHS Act as compared to the FD&C Act would be outweighed by the benefits associated with the

availability of the 351(k) pathway, which provides a clear path to market for follow-on biological products, including products that may be substitutable at the pharmacy level.

To quantify how competition may differ for these products, it is necessary to identify the probability and timing of one or more biosimilar or interchangeable competitors and the difference in price following competition. Evidence on these factors is scarce, so we attempt to use the best information available for inputs and estimates.

With respect to pricing, we note an earlier study of the biosimilar pathway as a whole by the Congressional Budget Office (Ref. 6). They predicted the following: “that during the first year of competition, the sales-weighted market average discount on FOBs relative to brand-name innovator drugs would be about 20 percent, reaching 25 percent in the most competitive markets. By the fourth year of competition, we anticipate that the sales-weighted average discount of the FOB relative to the brand-name price would reach about 40 percent.” In a press release, former FDA Commissioner Scott Gottlieb referenced an FDA finding “that entry of a single biosimilar product in non-U.S. OECD markets lowers prices relative to the reference product by 30 percent; markets with three to four biosimilar entrants have prices 35 to 43 percent lower than their reference biologics” (Ref. 7). These estimates are consistent with a recent report published by the RAND Corporation (Ref. 8) describing a literature review “that assumptions on biosimilar price relative to original price ranged from 10 to 51 percent (mean 27 percent).” These figures, when combined with estimates of biosimilar market shares, result in estimated “cost savings as a share of total biologic spending rang[ing] from 0.2 to 10.5 percent (mean 3.1 percent).” We adopt these estimates as our predicted cost savings for products potentially facing biosimilar competition following the transition date.

We note that the RAND report, in its own estimates of cost savings from biosimilars, makes an additional assumption about products that represent the largest revenue in the transition list: "We expect the biosimilar market for insulins and human growth hormones—where there are already multiple competing products—to look different than the market for other biologics," and further assumed that these products would see "one-half the biosimilar penetration and price discounts of other markets." While we do not adopt a comparable assumption in our primary estimate of total cost savings, and note that there may be reason to believe competition from biosimilar or interchangeable versions of many transition products may provide substantial cost savings relative to competition in the current market, this approach is well within the range of uncertainty that we do estimate.

To generate a dollar value of total cost savings, we need to define a baseline forecast for total expenditures on the affected products. As described earlier, we estimate that the products on the transition list accounted for $38 billion dollars, which is about $576 million per product. Noting that differences in incentives from additional years of potential exclusivity and from the newly available pathway for biosimilar or interchangeable products may have meaningful impacts on this estimate, we adopt an earlier forecast of 3 additional products approved per year that are currently regulated as

drugs under the baseline and will be regulated as biological products under the BPCI Act statutory changes and subsequent statutory changes made by the FCA Act. In years beyond 2019, we assume that, under the baseline scenario, revenues of existing products will grow at an annual 7% rate, which is consistent with the RAND study's approach. For the additional 3 products approved per year, we impute sales revenue equal to the average sales revenue of existing products.

After calculating the annual revenue for each existing and projected product, we multiply these by the estimated cost savings for products that are potentially subject to biosimilar competition and have no unexpired exclusivity. For example, in the year 2020, we expect there to be the products that are the subject of the 95 applications on the transition list, plus 3 additional applications approved in 2020. We assume that all additional applications approved in 2020 will occur after the transition date of March 23, 2020. Under this forecast, there will be 98 products, of which 95 will have no unexpired exclusivity potentially facing biosimilar competition and 3 products that will potentially have 12 years of exclusivity. We therefore expect 97% of these products will receive discounts in the magnitudes described above in 2020. Under our forecast, the total number of products will continue to grow by 3 per year. This means that, beginning in 2032, the number of products without exclusivity will increase by up to 3 per year, reflecting a 12-year delay before biosimilar competition for products approved after 2020. We note that exclusivity is not the only factor that can limit competition in a particular market.

In 2020, the projected spending under the alternative baseline is about $51.4 billion. We estimate that the BPCI Act statutory changes and subsequent statutory changes made by the FCA Act will generate between $100 million and $5.2 billion in savings relative to this baseline in 2020, with a primary estimate of $1.5 billion. Table 6 reflects our estimated savings for the first ten years and reports the presented discounted value and annualized figures over the same time horizon using a 3% and 7% discount rate.

Table 6. Reduced Expenditures on Affected Products Relative to Alternative Baseline ($ Million)

Year	Products	Baseline Expenditures	Products without Exclusivity	% of Products	Reduced Expenditures		
					Low	Primary	High
2020	98	$51,448	95	97%	$100	$1,546	$5,237
2021	95	$56,734	95	94%	$107	$1,654	$5,603
2022	98	$62,509	95	91%	$114	$1,770	$5,995
2023	101	$68,814	95	89%	$122	$1,894	$6,415
2024	104	$75,695	95	86%	$131	$2,027	$6,864
2025	107	$83,203	95	84%	$140	$2,168	$7,345
2026	110	$91,391	95	82%	$150	$2,320	$7,859
2027	113	$100,317	95	80%	$160	$2,483	$8,409
2028	116	$110,045	95	78%	$171	$2,656	$8,998
2029	119	$120,644	95	76%	$183	$2,842	$9,627
PDV, 3%		$684,359			$1,156	$17,924	$60,712
PDV, 7%		$547,056			$932	$14,449	$48,941
Annualized, 3%		$80,228			$136	$2,101	$7,117
Annualized, 7%		$77,888			$133	$2,057	$6,968

The expenditure reductions relative to the alternative baseline described above will only occur if firms invest in developing biosimilar products, which is expensive. In a broader review of the economics of biosimilars, Blackstone and Joseph (Ref. 9) cite "a cost of between $100 million and $250 million" to develop a biosimilar, and also note that these products involve high manufacturing costs. If these figures are accurate, and all 91 products available for biosimilar competition see one additional biosimilar entrant, this will come at the cost of between $9.0 billion and $22.5 billion just on product development. Similarly, when products approved after the transition date begin to lose exclusivity in 2032, this could result in costs of $300 million to $750 million per year if one biosimilar is developed for each of the 3 forecasted biological products with expiring exclusivity. It is possible that some of these biological products may not face biosimilar competition even after the expiration of exclusivity, suggesting that these costs may be overestimates. On the other hand, it is also possible that products with higher revenues will eventually compete with more than one biosimilar. Additionally, these only reflect the cost of developing a biosimilar and do not reflect the recurring costs of manufacturing these products.

We also note that firms will not be expected to make investments in developing biosimilars unless they are able to recover the costs of development, manufacturing, and marketing of these products. Therefore, firms considering developing biosimilars will likely make such decisions based on predictions about market share and product markups. Table 6 also presents the present discounted value and annualized values of total expenditures on the affected products over a 10-year time horizon, which are likely to be relevant factors to entry. The estimates of cost savings following biosimilar competition reflect important distributional effects, however we are not able to fully measure the net social benefits. Instead, these represent a transfer of income from the

manufacturer of the reference product to patients and other purchasers. Additionally, some of the sales revenue from the reference product will instead flow to the biosimilar competitor or competitors. If lower prices result in greater access to products and higher market quantities, this will reduce the deadweight loss associated with monopoly pricing, which will result in greater total surplus. We have not estimated the welfare effects of these potential increases in utilization.

In addition to the effects of the exclusivity periods and abbreviated licensure pathways described above, the FDA also has experienced different costs in reviewing NDA and BLA applications (Ref. 10). Finally, we note that biological products are subject to certain provisions of both the FD&C Act and the PHS Act, and there are some differences in the regulatory requirements for biological products, which we do not attempt to monetize.

We have identified several additional factors that could affect the estimates in this section. First, we note that there is no pathway under the PHS Act that directly corresponds to the 505(b)(2) pathway under the FD&C Act. Since several of the products on the transition list were approved through this pathway, this suggests that the forecasted number of new products per year could be overstated. Additionally, if this pathway is currently resulting in competition and price reductions, then our primary estimate of cost savings under the rule will also likely be overstated. A second issue is that other factors besides exclusivity can limit competition. Patent protection can also delay marketing of competitor products, regardless of whether the reference product may have received 3 or 5 or 12 years of exclusivity. If patent-related issues were not considered in the timing of biosimilar or interchangeable product entrants or the estimates of market shares of biosimilar products, this would suggest that the resulting primary cost-savings estimates are also overstated.

Finally, we again note that following publication of the preliminary analysis, the statute was modified to no longer exclude "any chemically synthesized polypeptide" from the category of “protein” in the statutory definition of "biological product," and FDA revised the final rule accordingly. Removing this exception now allows for potential competition if a developer were to chemically synthesize a protein product (e.g., a follow-on insulin) because the developer would now be able to seek licensure of such product and bring it to market through the abbreviated biosimilar or interchangeable pathway, which would be less resource-intensive than submitting a new drug application. We are unable to quantify the effects of removing this exception on competition because we do not know how many such products may be developed.

IV. Final Small Entity Analysis

The Regulatory Flexibility Act requires us to analyze regulatory options that will minimize any significant impact of a rule on small entities when “the agency publishes a general notice of rulemaking” (5 U.S.C. § 601(2)). We have analyzed this rule under the Regulatory Flexibility Act and propose to certify that, because we expect that the only cost of this rule is the opportunity cost to read and understand the rule, which is estimated

to be about $79 for a typical firm, this rule will not have a significant economic impact on a substantial number of small entities.

Under the current Small Business Size Standards published by the U.S. Small Business Administration (Ref. 11), pharmaceutical and medicine manufacturing (NAICS code 325400) firms qualify as small businesses if they employ fewer than 1,000 employees. This threshold is higher for certain sub-industries, such as pharmaceutical preparation manufacturing (NAICS code 325412), for which the SBA applies a 1,250-employee cut-off. According to the most recent Statistics of U.S. Business (Ref. 12), 1,615 of 1,775 firms classified in the pharmaceutical and medicine manufacturing industry employed fewer than 500 workers (Ref. 5). We observe that at least 91% of firms in this sector qualify as small businesses, which is understated due to data limitations.

Although most of the firms that are affected by this rule will be considered small businesses, these costs are limited to the time burden of reading the rule. As discussed earlier, we predict that this could be done by a legal professional in about 0.5 hours, earning a loaded hourly wage of about $164. Our primary estimate is that each small business will incur $79 in time costs associated with reading the rule. We also estimate a lower bound of $71 and upper bound of $89, which corresponds to faster or slower reading paces. This range of costs will likely not have a significant economic impact on a substantial number of small entities.

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EXHIBIT D

The "Deemed To Be a License" Provision of the BPCI Act

Questions and Answers Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2020
Procedural

The "Deemed To Be a License" Provision of the BPCI Act

Questions and Answers Guidance for Industry

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March 2020
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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

The "Deemed To Be a License" Provision of the BPCI Act Questions and Answers Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to provide answers to common questions about FDA's implementation of the "transition" provision of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) under which an application for a biological product approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) as of March 23, 2020, will be deemed to be a license for the biological product under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) on March 23, 2020 (the transition date).[2] This guidance also describes FDA's compliance policy for the labeling of biological products that are the subject of deemed biologics license applications (BLAs). This guidance is intended to facilitate planning for the transition date and provide further clarity regarding the Agency's implementation of this statutory provision.

Although the majority of therapeutic biological products have been licensed under section 351 of the PHS Act, some protein products historically have been approved under section 505 of the FD&C Act. On March 23, 2010, the BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (Public Law 111-148). The BPCI Act clarified the statutory authority under which certain protein products will be regulated by amending the definition of a "biological product" in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)," and describing procedures for submission of a marketing application for certain "biological products." Section 605 of the Further Consolidated Appropriations Act, 2020, further amended the definition of a "biological product" in section 351(i) of the PHS Act

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at FDA.

[2] Section 607 of the Further Consolidated Appropriations Act, 2020 (Public Law 116-94), amended section 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).

to remove the parenthetical "(except any chemically synthesized polypeptide)" from the statutory category of "protein."[3]

The BPCI Act requires that a marketing application for a biological product (that previously could have been submitted under section 505 of the FD&C Act) must be submitted under section 351 of the PHS Act; this requirement is subject to certain exceptions during a 10-year transition period ending on March 23, 2020 (see section 7002(e)(1)-(3) and (e)(5) of the BPCI Act). On March 23, 2020 (i.e., the transition date), an approved application for a biological product under section 505 of the FD&C Act shall be deemed to be a license for the biological product under section 351 of the PHS Act (see section 7002(e)(4)(A) of the BPCI Act; see also section 7002(e)(4)(B) of the BPCI Act).[4]

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

II. BACKGROUND

A. BPCI Act

The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the BPCI Act). The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (commonly referred to as the "Hatch-Waxman Amendments"), which established abbreviated pathways for the approval of drug products under section 505(b)(2) and 505(j) of the FD&C Act. An abbreviated licensure pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the generally larger, and typically more complex, structure of biological products, as well as the processes by which such products are manufactured. Most biological products are produced in a living system, such as a microorganism or plant or animal cells, whereas small molecule drugs are typically manufactured through chemical synthesis.

Section 351(k) of the PHS Act, added by the BPCI Act, sets forth, among other things, the requirements for an application for a proposed biosimilar product and an application or a

[3] As amended by the BPCI Act and the Further Consolidated Appropriations Act, 2020, a "biological product" is defined, in relevant part, as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings" (see section 351(i) of the PHS Act).

[4] Section 607 of the Further Consolidated Appropriations Act, 2020, redesignated section 7002(e)(4) of the BPCI Act as section 7002(e)(4)(A) and added the title "In General" to the new subparagraph. Conforming revisions have been made throughout this guidance to refer to the new subparagraph.

supplement for a proposed interchangeable product. Section 351(i) defines "biosimilarity" to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (section 351(i)(2) of the PHS Act). A 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act). To meet the standard for "interchangeability," an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider (see section 351(i)(3) of the PHS Act).

B. Transition Period for Certain Biological Products

Section 7002(e) of the BPCI Act provides that a marketing application for a biological product (that previously could have been submitted under section 505 of the FD&C Act) ***must*** be submitted under section 351 of the PHS Act, subject to the following exception during the transition period described below.

An application for a biological product ***may*** be submitted under section 505 of the FD&C Act not later than March 23, 2020, if the biological product is in a product class[5] for which a biological product in such product class was approved under section 505 of the FD&C Act not later than March 23, 2010.

However, an application for a biological product ***may not*** be submitted under section 505 of the FD&C Act if there is another biological product approved under section 351(a) of the PHS Act that could be a "reference product"[6] if such application were submitted under section 351(k) of the PHS Act.

[5] FDA has interpreted the statutory term *product class* for purposes of determining whether an application for a biological product may be submitted under section 505 of the FD&C Act during the transition period (see FDA's guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (December 2018) (Biosimilars Q&A Guidance), at Q. II.2). 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/regulatory-information/search-fda-guidance-documents.

[6] The term *reference product* means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in an application submitted under section 351(k) (see section 351(i)(4) of the PHS Act).

An approved application for a biological product under section 505 of the FD&C Act shall be deemed to be a license for a biological product under section 351 of the PHS Act (a "deemed BLA") on March 23, 2020 (see section 7002(e)(4)(A) of the BPCI Act; see also section 7002(e)(4)(B) of the BPCI Act). For additional information about FDA's interpretation of this "transition" provision, please refer to FDA's guidance for industry *Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (December 2018) (Transition Policy Final Guidance).

III. QUESTIONS AND ANSWERS

A. Identification of Products Subject to the Transition Provision

Q1. What products are affected by the transition provision? How will the holder of an approved new drug application (NDA) for a biological product know if it will be affected by the transition provision?

The "deemed to be a license" provision in section 7002(e)(4)(A) of the BPCI Act (also known as the transition provision) will apply on March 23, 2020, to each approved application for a biological product under section 505 of the FD&C Act.[7] The BPCI Act and Further Consolidated Appropriations Act, 2020, amended the definition of a "biological product" in section 351(i) of the PHS Act to include a "protein."

FDA has previously stated its interpretation of the statutory term "protein" in the amended statutory definition of "biological product."[8] As explained in FDA's final rule entitled "Definition of the Term 'Biological Product'" (Biological Product Definition Final Rule), FDA interprets the term "protein" to mean any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of

[7] General references in this guidance to "applications" submitted or approved under section 505 of the FD&C Act also may include ANDAs, to the extent applicable. An ANDA generally must contain information to demonstrate, among other things, that the proposed generic drug has the same active ingredient(s), conditions of use, dosage form, route of administration, strength, and (with certain permissible differences) labeling as the reference listed drug (section 505(j)(2)(A) of the FD&C Act). Given the complexity of protein molecules and limitations of current analytical methods, it may be difficult for manufacturers of proposed protein products to demonstrate that the active ingredient in their proposed product is the same as the active ingredient in an already approved product, and thus ANDAs are not a focus of this guidance. There are no currently marketed biological products that were approved through the ANDA pathway.

[8] See, e.g., 80 FR 24259, April 30, 2015 (announcing the availability of a guidance for industry entitled "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," available at www.regulations.gov (Docket No. FDA-2011-D-0611)). FDA also described its interpretation of the term "chemically synthesized polypeptide" in the statutory definition of "biological product" as amended by the BPCI Act in this guidance and in a proposed rule entitled "Definition of the Term 'Biological Product'" (83 FR 63817, December 12, 2018). However, this interpretation is no longer necessary to our interpretation of the statutory term "biological product," given that the parenthetical exception for "any chemically synthesized polypeptide" subsequently was removed from the category of "protein" (see section 605 of the Further Consolidated Appropriations Act, 2020).

the amino acid polymer for purposes of this interpretation will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence.[9] FDA interprets the statutory definition of "biological product" such that any amino acid polymer composed of 40 or fewer amino acids (i.e., a "peptide") is outside the scope of the term "protein." A "peptide" is not a "biological product" and will continue to be regulated as a drug under the FD&C Act unless the peptide otherwise meets the statutory definition of a "biological product" (e.g., a peptide vaccine) (see Q. II.1 in FDA's draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)* (December 2018) (Biosimilars Q&A Draft Guidance)). Moreover, a drug product that contains a protein only as an inactive ingredient (e.g., a drug product formulated with human serum albumin as an inactive ingredient) is not considered to be a "protein" for purposes of the statutory definition of "biological product" and the transition provision of the BPCI Act.

The prescription or over-the-counter status of a biological product with an approved application under section 505 of the FD&C Act will not change when the approved application is deemed to be a license for the biological product under section 351 of the PHS Act on March 23, 2020.

Examples of biological products approved under the FD&C Act are listed in the Appendix to the Transition Policy Final Guidance. To enhance transparency and facilitate planning for the transition date, FDA is posting on the FDA website (https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act) a preliminary list of approved applications for biological products under the FD&C Act (as of December 31, 2019) that will be affected by the transition provision, and FDA intends to periodically update the list before the transition date (see Q3 below). Shortly after the transition date, FDA intends to post a final list of approved applications under the FD&C Act that have been deemed to be licenses under the PHS Act.

Q2. Does the holder of an approved NDA for a biological product on FDA's list need to take any affirmative steps for its NDA to be deemed a BLA?

FDA interprets the transition provision to mean that the holder of an approved application for a biological product does not need to take any affirmative steps for its NDA to be deemed a BLA. Specifically, FDA interprets section 7002(e)(4)(A) of the BPCI Act to mean that an approved application under the FD&C Act for a biological product will be "deemed to be a license" for the biological product on the transition date by operation of the statute.[10]

[9] In the Federal Register of February 21, 2020, FDA issued a final rule that amends its regulation that defines "biological product" to incorporate changes made by the BPCI Act and the Further Consolidated Appropriations Act, 2020, and to provide its interpretation of the statutory term "protein" (85 FR 10057). This rule is effective on March 23, 2020.

[10] Similarly, FDA interprets section 7002(e)(4)(B)(iii) of the BPCI Act to mean that upon approval under the FD&C Act of any application described in section 7002(e)(4)(B)(i) of the BPCI Act, the approved application for the biological product would be "deemed to be a license" for the biological product by operation of the statute. For purposes of this guidance, we focus on the transition of approved NDAs to deemed BLAs pursuant to section 7002(e)(4)(A) of the BPCI Act.

The statute is silent regarding the process for accomplishing the transition of approved NDAs to deemed BLAs. FDA intends to send a letter to such application holders on March 23, 2020, advising that the approved NDA was deemed to be a BLA at 12:00 am Eastern Daylight Time (EDT) on March 23, 2020, and no longer exists as an NDA. (If the NDA is approved on March 23, 2020, the approved NDA will be deemed to be a BLA immediately after approval.) In the letter, FDA also will notify the application holder that it has been issued a license that authorizes the application holder to manufacture the biological product within the meaning of section 351 of the PHS Act and to introduce the biological product or deliver the biological product for introduction into interstate commerce (see Q6 below). The letter also will remind application holders that they will need to ensure that the listing information for the biological product is updated in FDA's electronic Drug Registration and Listing System (eDRLS) between March 23, 2020, and June 30, 2020, to reflect a change in the prefix of the application number (from "NDA" to "BLA") (see 21 CFR 207.57(b)). FDA notes that the deeming of an approved NDA to be a BLA and the corresponding update of the eDRLS listing information for the biological product to change the prefix for the application number will not result in the need for a new National Drug Code (NDC) number with a new product code. Accordingly, in the absence of other changes made by the application holder that would require a new NDC number, biological products approved under the FD&C Act will retain their current NDC number after the NDA is deemed to be a BLA. This will provide consistency for manufacturers and for the databases and pharmacy systems that track drug and biological products.

To enhance transparency and facilitate planning for the transition date, FDA is posting on the FDA website a preliminary list of approved applications for biological products under the FD&C Act (as of December 31, 2019) that will be affected by the transition provision, and FDA intends to periodically update the list before the transition date (see Q1 above). Biological products approved in NDAs that are deemed to be BLAs will be removed from FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) on March 23, 2020, and will be listed in FDA's *Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations* (the Purple Book) and the *CDER Therapeutic Biologics Products* list on or shortly after the March 23, 2020, transition date.

Q3. Who should an application holder contact if it believes that its approved NDA should or should not be included on FDA's preliminary list of approved applications for biological products that will be affected by the transition provision?

If an application holder or other person reviews, on FDA's website, the preliminary list of approved applications for biological products under the FD&C Act that will be affected by the transition provision and believes that an approved NDA should be added to the list or should not be included on the list, the application holder or other person should submit a comment to the public docket established for this guidance and the preliminary list. For information on submission of comments to the public docket, please refer to the Federal Register (FR) Notice of Availability of this guidance.

Q4. How will FDA notify the sponsor of a proposed biological product who seeks to obtain approval under section 505 of the FD&C Act that the planned application would need to be approved under the FD&C Act on or before March 23, 2020?

FDA provided notice to sponsors of proposed biological products intended for submission in an application under section 505 of the FD&C Act that they will be affected by the transition provision through the Biosimilars Q&A Guidance, as well as through FDA's draft guidance for industry *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (March 2016) (Transition Policy Draft Guidance) and the Biosimilars Q&A Draft Guidance. In the Biosimilars Q&A Guidance, FDA initially stated its interpretation of the statutory term "protein" in the amended definition of "biological product" (see Q1 above and Biological Product Definition Final Rule). In the Transition Policy Final Guidance, FDA provides recommendations to sponsors of proposed protein products intended for submission in an application that may not receive final approval under section 505 of the FD&C Act on or before March 23, 2020, to facilitate alignment of product development plans with FDA's interpretation of section 7002(e) of the BPCI Act.[11] FDA recommends that sponsors of development programs for proposed protein products evaluate whether a planned submission under section 505 of the FD&C Act would allow adequate time for approval of the application prior to March 23, 2020, considering, among other things, whether the submission may require a second cycle of review and, for certain types of applications, whether unexpired patents or exclusivity may delay final approval. If a sponsor is unsure whether its proposed product may receive approval under the FD&C Act by March 23, 2020, the sponsor should consider submitting a BLA under section 351(a) or 351(k) of the PHS Act instead. For additional information, please see the Transition Policy Final Guidance.

B. Applications for Biological Products Submitted Under Section 505 of the FD&C Act on or Before the Transition Date

Q5. When will the holder of an approved NDA for a biological product receive the application number that will be used for its deemed BLA?

FDA intends to assign the same application number used for the approved NDA to the deemed BLA on the March 23, 2020, transition date. As a hypothetical example, NDA 012345 would be deemed to be BLA 012345 on the transition date. This approach is intended to minimize burden on holders of approved applications for biological products under the FD&C Act who are preparing submissions to their applications around the transition date and to facilitate the administrative conversion of any pending supplements to such applications (see the Transition Policy Final Guidance for additional information regarding such supplements). The use of a predictable application numbering system for deemed BLAs is also expected to facilitate preparation and submission of a 351(k) BLA for a proposed biosimilar or interchangeable

[11] After FDA issued the Transition Policy Final Guidance, the Further Consolidated Appropriations Act, 2020 was enacted. Section 607 of this Act amended section 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).

product that references a product licensed in a deemed 351(a) BLA as a reference product. The FDA letter that notifies the application holder that its approved NDA is deemed to be a BLA on the transition date will include the product's BLA number.

Q6. When will the holder of an approved NDA for a biological product receive the license number that will apply to its deemed BLA(s)?

The FDA letter that notifies the application holder that its approved NDA is deemed to be an approved BLA will include the U.S. license number assigned to the application holder. Each establishment that is listed in the approved NDA as currently involved in the manufacture of the biological product on the transition date will be considered a licensed establishment on that date (see section 7002(e)(4)(A) of the BPCI Act; see also section 7002(e)(4)(B)(iii) of the BPCI Act). FDA does not intend to conduct pre-license inspections of manufacturers of the transitioning biological products because FDA interprets section 7002(e)(4)(A) of the BPCI Act to mean that an approved application under the FD&C Act for the biological product will be "deemed to be a license" on the transition date by operation of the statute.[12] Moreover, the establishments will have been inspected in connection with the previously approved NDAs under the FD&C Act (see Q16 below for information on establishment inspections related to certain supplements to a deemed 351(a) BLA).

FDA issues only one U.S. license number per BLA holder, regardless of the number of licensed biological products manufactured by that BLA holder under separate BLAs. Accordingly, if an NDA holder is also a BLA holder and has been assigned a U.S. license number for another biological product, the NDA holder will not be issued a different U.S. license number when its approved NDA for a biological product is deemed to be a BLA on the transition date.

Section 351(a)(1)(B)(ii) of the PHS Act requires that each package of a biological product is plainly marked with, among other things, the applicable license number of the manufacturer of the biological product in order for the biological product to be introduced or delivered for introduction into interstate commerce. To minimize possible disruption in the distribution of biological products in the United States and to minimize burden on holders of deemed BLAs, FDA intends to adopt a compliance policy for the labeling of biological products that are the subject of deemed BLAs (see Q14 and section IV below for additional information on the compliance policy for labeling of biological products in deemed BLAs).

Q7. Will an approved NDA for a biological product be deemed to be a 351(a) BLA or a 351(k) BLA?

FDA interprets the transition provision, along with the applicable provisions of the FD&C Act and the PHS Act, to mean that an approved NDA, including an application submitted through the pathway described by section 505(b)(2) of the FD&C Act (505(b)(2) application), will be deemed to be a 351(a) BLA on the transition date.

Section 7002(e) of the BPCI Act is directed primarily to the submission of an application for a biological product during the transition period ending on March 23, 2020, and does not explicitly

[12] See also footnote 10 in the response to Q2.

state whether an approved NDA will be deemed to be a 351(a) BLA or a 351(k) BLA. The Agency's interpretation that an approved NDA submitted under section 505(b)(1) of the FD&C Act will be deemed to be a 351(a) BLA is based on the shared requirement that both types of applications contain full reports of investigations of safety and effectiveness (or, for a 351(a) BLA, safety, purity, and potency). We expect that the measures FDA has taken to minimize differences in the review and approval of products in marketing applications submitted under section 351(a) of the PHS Act and section 505(b)(1) of the FD&C Act will facilitate implementation of the statutory provision under which an approved NDA will be deemed to be a BLA.

The Agency's interpretation that an approved 505(b)(2) application will be deemed to be a 351(a) BLA reflects the shared requirement that both types of applications contain full reports of investigations of safety and effectiveness (or, for a 351(a) BLA, safety, purity, and potency).[13] This approach also reflects the Agency's view that it is more appropriate to regulate a biological product approved through the 505(b)(2) pathway that may be intended to differ in certain respects (e.g., different strength, dosage form, or route of administration or approved conditions of use) from a previously approved product under the statutory and regulatory framework for 351(a) BLAs, as such differences are not permitted under the statutory framework for 351(k) BLAs. Moreover, FDA's approval of a 505(b)(2) application reflects the Agency's evaluation of the data against a different statutory standard than a determination of biosimilarity or interchangeability under section 351(k) of the PHS Act.

Q8. Will an approved NDA for a biological product that has been discontinued from marketing be deemed to be a BLA?

Section 7002(e)(4) states that an "approved application for a biological product under section 505 of the [FD&C Act]" will be deemed to be a BLA on the transition date. Accordingly, FDA interprets the statute to mean that an approved NDA for a biological product that has been discontinued from marketing, but for which FDA has not withdrawn approval of the application, will be deemed to be a BLA on the transition date. The holder of an NDA for a discontinued product must comply with applicable statutory and regulatory requirements for its application before the transition date, and after its application is deemed to be a BLA. These requirements include, for example, postmarketing reporting of adverse drug experiences and, if appropriate, the submission of proposed revisions to product labeling. If the holder of a deemed BLA for a biological product that has been discontinued from marketing seeks to reintroduce the product to the market, the BLA holder should consult with the relevant FDA review division before submitting a supplement to the deemed BLA, to discuss any data and information that may be needed.

[13] A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., FDA's finding of safety and/or effectiveness for a listed drug or published literature).

Q9. How will the transition on March 23, 2020, affect the annual program fee for an approved NDA for a biological product?

Under section 736(a)(2) of the FD&C Act, a person named as the applicant in a human drug application (which refers to an NDA or a 351(a) BLA, subject to applicable statutory exceptions) is assessed an annual prescription drug program fee. A prescription drug program fee is assessed each fiscal year for each prescription drug product identified in a human drug application approved as of October 1 of the fiscal year, with certain exceptions described by statute. For more information about the prescription drug program fee, consult the FDA guidance for industry *Assessing User Fees Under the Prescription Drug User Fee Amendments of 2017* (May 2018).

In general, sponsors of biological products for which annual prescription drug program fees are assessed prior to the transition, and that are deemed to be licensed under section 351(a) of the PHS Act on the transition date, will continue to be assessed prescription drug program fees for such products after the transition, subject to applicable statutory requirements and exceptions.

Q10. If an applicant withdraws an NDA that is tentatively approved on or before the transition date, or otherwise pending with FDA, and submits an application for the same product under section 351(a) of the PHS Act, will an additional PDUFA application fee be assessed?

An applicant (or the applicant's licensee, assignee, or successor) will not be charged a Prescription Drug User Fee Act (PDUFA) application fee for the submission of an application under section 351(a) of the PHS Act if all of the following circumstances are satisfied (see section 736(a)(1)(C) of the FD&C Act):

- The applicant previously submitted an NDA for the same product and paid the associated PDUFA application fee for the NDA.
- The NDA was accepted for filing. (Note that an NDA for a biological product will not be accepted for filing after the transition date.)
- The NDA was not approved[14] or was withdrawn (without a waiver).

For questions regarding user fees, please contact the User Fee Staff at CDERCollections@fda.hhs.gov or 301-796-7900.

[14] An NDA that is tentatively approved is not an approved NDA (see 21 CFR 314.105(a)).

Q11. If the applicant withdraws an NDA that is tentatively approved on or before the transition date, or otherwise pending with FDA, and submits an application for the same product under section 351(k) of the PHS Act, will a BsUFA application fee be assessed?

An application for licensure of a biological product under section 351(k) of the PHS Act meets the definition of a "biosimilar biological product application" in section 744G(4) of the FD&C Act, with certain exceptions. Under section 744H(a)(2) of the FD&C Act, a biosimilar biological product application fee is assessed to the applicant at the time of submission of a biosimilar biological product application, unless an exception applies under section 744H(a)(2)(D). Certain applicants may be eligible for a small business waiver of the biosimilar biological product application fee under section 744H(d)(1) of the FD&C Act. If an applicant withdraws an NDA that is tentatively approved or pending on or before the transition date and later submits a biosimilar biological product application under section 351(k) of the PHS Act, the applicant would be assessed a biosimilar biological product application fee for the 351(k) application, unless a small business waiver has been granted or the applicant previously submitted a biosimilar biological product application for the same product and meets the other criteria for the exception described in section 744H(a)(2)(D) of the FD&C Act. For more information about the biosimilar biological product application fee, consult the FDA guidance for industry *Assessing User Fees Under the Biosimilar User Fee Amendments of 2017* (June 2018).

Q12. Will approved NDAs that are deemed to be BLAs remain within the same review office/division in CDER? Will pending NDAs that are withdrawn and submitted as BLAs be reviewed within the same CDER review office/division?

In general, approved NDAs that are deemed to be BLAs will remain within the same review office/division within CDER's Office of New Drugs (OND) after the transition date, subject to any reassignments related to any reorganization of CDER's OND. Similarly, pending NDAs that are withdrawn and submitted as BLAs will be reviewed within the same OND review office/division.

With respect to the product quality assessment, review responsibilities within CDER's Office of Pharmaceutical Quality (OPQ) for products composed of amino acid polymers are in the process of being assigned or reassigned based on certain characteristics of the molecule, rather than the regulatory pathway, with the expectation that the reassignments will be completed by the transition date. Accordingly, on the transition date, we generally expect to maintain the assigned OPQ review offices for approved NDAs that are deemed BLAs, as well as pending NDAs that are withdrawn and submitted as BLAs.

C. Statutory and Regulatory Requirements for BLAs

Q13. Will the holder of a deemed 351(a) BLA be subject to requirements under the PHS Act and FDA regulations for BLAs that are different from requirements for NDAs? If so, when will the requirements apply to deemed BLAs?

The holder of a deemed 351(a) BLA will be subject to applicable requirements under the PHS Act and FDA regulations and, as provided in section 351(j) of the PHS Act, also will be subject to requirements under the FD&C Act that apply to BLAs. In general, FDA anticipates that a holder of an NDA for a biological product that is being deemed a 351(a) BLA will experience minimal disruption due to differences in requirements under the FD&C Act and PHS Act. FDA has taken measures to minimize differences in the review and approval of products required to have licensed BLAs under section 351(a) of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FD&C Act (see section 123(f) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115)). However, there are certain statutory and regulatory requirements for biological products regulated under the PHS Act that differ from requirements for drug products regulated under the FD&C Act. FDA is committed to working with application holders to minimize any potential burden.

Labeling requirements for deemed BLAs, including certain differences between the requirements in the PHS Act and FD&C Act, are further described in Q14 below. The Agency's compliance policy for the labeling of biological products that are the subject of deemed BLAs is described in section IV below.

Biological products that are deemed to be licensed under section 351 of the PHS Act on March 23, 2020, will be subject to chemistry, manufacturing, and controls (CMC) requirements applicable to products regulated under the PHS Act beginning on March 23, 2020.[15] Holders of deemed BLAs should be aware that there are certain CMC-related requirements that differ between the PHS Act and FD&C Act. However, as further described in Q15 below, the burden related to these statutory and regulatory differences is expected to be minor.

Q14. Will the holder of a deemed BLA need to update the product labeling to conform to labeling requirements for BLAs?

The holder of a deemed BLA will be required to revise the product labeling (e.g., container labels, carton labeling, and prescribing information) so that biological products introduced or delivered for introduction into interstate commerce on or after March 23, 2020, conform to labeling requirements for biological products regulated under section 351 of the PHS Act. However, FDA acknowledges that holders of deemed BLAs may need time to revise their labeling to conform to such requirements and may not be able to make these revisions until receiving the information provided in the letter sent from FDA on the transition date. Accordingly, based on our understanding that holders of deemed BLAs may need time to

[15] Similarly, any biological product that is deemed to be licensed under section 351 of the PHS Act after March 23, 2020, pursuant to section 7002(e)(4)(B)(iii) of the BPCI Act will be subject to CMC requirements applicable to products regulated under the PHS Act beginning on the date on which the approved NDA for the biological product is deemed to be a BLA for the biological product.

conform their products' labeling to BLA labeling requirements, FDA generally does not intend to object to the labeling of biological products marketed under a deemed BLA with labeling that does not conform to certain labeling requirements until March 23, 2025, provided that the labeling at issue complies with all other applicable labeling requirements (see section IV below for information about the Agency's compliance policy). FDA recommends, in order to facilitate the implementation of the proposed revisions within that timeframe, that the holder of the deemed BLA submit a prior approval supplement (PAS) with proposed revised product labeling between March 23, 2020 (when the approved application under section 505 of the FD&C Act for the biological product is deemed to be a BLA), and March 23, 2022.[16]

Most labeling requirements for container labels, carton labeling, and prescribing information are the same for biological products currently regulated under the FD&C Act as they are for biological products regulated under the PHS Act. However, there are certain labeling requirements under the PHS Act and regulations for BLAs that differ from requirements under the FD&C Act and regulations for NDAs.

The PHS Act requires that each "package" of a biological product is plainly marked with, among other things, "the proper name of the biological product contained in the package" and "the name, address, and applicable license number of the manufacturer of the biological product" in order for the biological product to be introduced or delivered for introduction into interstate commerce (see section 351(a)(1)(B) of the PHS Act; 21 CFR 610.61, 610.63, 610.64 and 201.1(m)). The "package" means the "immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package" (21 CFR 600.3(cc)). The "manufacturer" of a biological product regulated under the PHS Act that needs to be identified on each package is the BLA holder (see 21 CFR 600.3(t)(definition of *manufacturer*); see also 21 CFR 610.63 (labeling requirements for divided manufacturing responsibility)).[17]

The holder of the deemed BLA will need to revise product labeling to ensure that the biological products are labeled with the proper name of the biological product, the name and address of the manufacturer (if the required information on the manufacturer is not already provided), and the license number, and that the labeling otherwise conforms to the labeling requirements for biological products regulated under section 351 of the PHS Act (see section IV below for information about the Agency's compliance policy). The FDA letter that notifies the application holder that its approved NDA is deemed to be a BLA on the transition date will provide the U.S.

[16] Depending on the circumstances, submission of a PAS may be required to make the BLA-specific labeling revisions for certain deemed BLAs (see 21 CFR 601.12(f)(1)). However, to facilitate efficient and appropriate revisions to container labels, carton labeling, and prescribing information, FDA recommends submitting a PAS even when doing so would not be required.

[17] This definition differs in certain respects from the use of the term *manufacturer* in the context of a drug product regulated under the FD&C Act (see, e.g., 21 CFR 201.1(b)). The name and address of the distributor of a biological product may appear on the labeling provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the phrases listed in 21 CFR 610.64 (e.g., "Manufactured by [BLA holder] for [Distributor]"). FDA notes that a BLA holder is not required to list a contract manufacturer on the labeling because contract facilities are considered to be under the control of the BLA holder.

license number assigned to the application holder. The license authorizes the application holder to manufacture the biological product within the meaning of section 351 of the PHS Act and to introduce the biological product or deliver the biological product for introduction into interstate commerce. FDA will designate the *proper name* of the biological product in the license (see 21 CFR 600.3(k) and Q21 below).

There are additional requirements for the container labels and carton labeling for a biological product regulated under section 351 of the PHS Act (see 21 CFR 610.60 and 21 CFR 610.61; see also 21 CFR 610.62 for requirements applicable to biological products that do not fall within the specified categories of biological products described in 21 CFR 601.2 ("non-specified biological products")). In the table below, we provide an overview of key changes[18] from NDA labeling requirements for container labels and carton labeling that will apply to biological products in deemed BLAs.

[18] Additional labeling requirements not summarized in this chart are described in the text that follows.

Table. Selected Requirements for Container Labels and Carton Labeling for Biological Products

Labeling Information	Change From NDA Labeling Requirements That Will Apply to Biological Products in Deemed BLAs
	New Required Information
Proper Name	Container labels and carton labeling must include the *proper name* of the biological product designated by FDA in the license (see 21 CFR 610.60(a)(1) and 610.61(a)). For non-specified biological products (e.g., pancrelipase, urofollitropin), the regulations provide more specific requirements for the position and prominence of the proper name, and the legibility of information on the package and container label (see 21 CFR 610.62).
Manufacturer Name, Address, and License Number	The name and address of the manufacturer (i.e., the BLA holder) must appear on container labels and carton labeling in the format specified by the regulations (see 21 CFR 610.60(a)(2) and 610.61(b); see 21 CFR 600.3(t) for the definition of *manufacturer* and 21 CFR 610.63 for labeling requirements for divided manufacturing responsibility). • For containers capable of bearing only a partial label, only the proper name, the lot number or other lot identification, and the name of the manufacturer is required (see 21 CFR 610.60(c)); we also recommend including the strength and expiration date. • The name and address of the distributor of the biological product may appear in addition to the name and address of the manufacturer. The qualifying phrases used for a distributor are the same for drug and biological products (compare 21 CFR 201.1(h)(5) with 21 CFR 610.64). Container labels and carton labeling must also include the license number of the manufacturer of the biological product (see 21 CFR 610.60(a)(2) and 610.61(b)).
	Required Information That May Currently Appear in Approved Labeling
Preservative	Carton labeling must include the name of the preservative used (which already appears in the statement of ingredients on the carton of biological products approved under the FD&C Act) and its concentration (see 21 CFR 610.61(e)). If no preservative is used and the absence of a preservative is a safety factor, the words "no preservative" must appear on the carton labeling (see 21 CFR 610.61(e)).
Potency Statement	Carton labeling must include the minimum potency of product expressed in terms of official standard of potency (compare 21 CFR 610.61(r) with 21 CFR 201.51(a)). If potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency" must appear on the carton labeling (see 21 CFR 610.61(r)).
Source of the Product When a Factor in Safe Administration	Carton labeling must include the source of the product when a factor in safe administration, such as products made from sources that may be allergenic (see 21 CFR 610.61(p)).

Certain requirements for container labels and carton labeling (see, e.g., 21 CFR 610.60(a)(5) and (c), and 21 CFR 610.61(j)) can be addressed by including a statement that refers to the prescribing information and by including the required information in the prescribing information (see, e.g., 21 CFR 610.61(l), (n), and (q)).

There also are certain differences in the content of prescribing information for biological products regulated under the PHS Act. The key differences for the prescribing information for a biological product regulated under the PHS Act are that the labeling must include the proper name of the biological product, including any appropriate descriptors (see 21 CFR 201.57(a)(2)), and the manufacturer name, address, and license number (see 21 CFR 610.60(a)(2) and 610.61(b)). Conforming revisions also would need to be made to FDA-approved patient

labeling. In addition, for biological products that are required to meet the content and format requirements of the Physician Labeling Rule (PLR) as described in 21 CFR 201.56(d) and 201.57, the year used for the Initial U.S. Approval included in the Highlights of Prescribing Information (Highlights) differs for a biological product under the FD&C Act (i.e., the year of initial U.S. approval of the new molecular entity) and the PHS Act (i.e., the year of initial U.S. approval of the new biological product). Accordingly, the Initial U.S. Approval in the Highlights may need to be revised to reflect the year in which the first NDA for the biological product(s) described in the labeling was initially approved.

The date of initial approval of the NDA (and not the date on which the NDA is deemed to be a BLA) and the date(s) of approval of efficacy supplement(s) will continue to govern the applicability of the labeling content and format requirements described by 21 CFR 201.56(d) and 201.57. For NDAs that are not required to have labeling in PLR format, application holders may consider voluntarily converting the labeling to PLR format because the PLR format represents a more useful and modern approach for communicating information on the safe and effective use of products and makes prescribing information more accessible for use with electronic prescribing tools and other electronic information resources.

The holder of a deemed BLA for a biological product should submit all proposed revisions to product labeling necessary to conform to labeling requirements for biological products regulated under section 351 of the PHS Act (i.e., container labels, carton labeling, prescribing information, and patient labeling) together in the same PAS. To facilitate identification of the type of submission for the Agency, the applicant should mark clearly on the cover letter, "Deemed BLA Labeling Revisions."

Q15. Are there different requirements related to CMC that will apply to a biological product in a deemed 351(a) BLA?

Certain CMC requirements and recommendations applicable to biological products regulated under the PHS Act may differ in some respects from CMC requirements and recommendations applicable to biological products regulated under the FD&C Act. However, FDA expects that in many instances the practical implications of such differences on holders of deemed BLAs will be minimal because the CMC requirements under both the PHS Act and the FD&C Act address many of the same types of CMC considerations for ensuring quality biological products. For example, FDA anticipates that most biological products subject to the transition provision, upon being deemed BLAs, will meet the related general BLA requirements (e.g., potency, sterility, purity, and identity) under the PHS Act based on the products having been previously approved under the FD&C Act.

The holders of deemed BLAs may be required to report or provide different information than is required for biological products under the FD&C Act. In the sections below, we highlight such requirements, namely lot release, biological product distribution reports, notification of manufacturing problems involving distributed products, and establishment standards for "non-specified biological products."

Additionally, as with all biological products, FDA may recommend changes to the control strategy throughout the product life cycle to modernize control strategies, to address product-specific issues, and to help ensure that biological products remain safe, pure, and potent for their approved conditions of use. Furthermore, as with all biological products, these changes may be recommended as a result of postapproval or surveillance inspections, which are independent of a submission and generally expected to be similar for a biological product whether approved in an NDA prior to the transition date or licensed in a BLA. For inspections related to CMC supplements see Q16 below.

FDA is committed to working with application holders to minimize any potential burden, and encourages application holders with any CMC-related questions to contact OPQ/Office of Program and Regulatory Operations (OPRO) at CDER-OPQ-Inquiries@fda.hhs.gov.

1. Lot Release

FDA may require that a BLA holder submit samples and CMC data for each lot of product for FDA review and release (see 21 CFR 610.2). However, FDA generally does not anticipate that lot release requirements will apply for biological products approved in NDAs that are deemed to be BLAs.

In 1995, FDA announced the elimination of lot-by-lot release for licensed well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products (see the 1995 *Federal Register* notice "Interim Definition and Elimination of Lot-by-Lot Release For Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products; Notice," (60 FR 63048, December 8, 1995)). FDA subsequently amended 21 CFR 601.2 to specify, instead of the term "well characterized biotechnology product," the categories of products to which lot-by-lot release would not be necessary (see "Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products," 61 FR 24227, May 14, 1996). Most of the biological products subject to the transition provision will meet the description of products for which lot-by-lot release is not required. Furthermore, for biological products that do not fall into the categories specified in 21 CFR 601.2, FDA generally does not anticipate that lot-by-lot release will be needed. As stated in the December 1995 *Federal Register* notice:

> [O]nce a company has demonstrated its ability to consistently produce acceptable lots, and has procedures in place that will prevent the release of lots that do not meet release specifications, it is not necessary for FDA to verify that each manufactured lot is acceptable for release.[19]

FDA generally considers application holders for biological products subject to the transition provision as having demonstrated the "ability to consistently produce acceptable lots" and as having "procedures in place that will prevent the release of lots that do not meet release specifications" based on product history.

[19] See 60 FR 63048, December 8, 1995.

2. Product Distribution Reports

FDA anticipates that all biological product application holders will have adequate records of the product distributed to the market. Although the frequency and content of distribution reporting required for products regulated under the FD&C Act and PHS Act differ, FDA expects these differences will present minimal burden to holders of deemed BLAs.

Application holders of biological products affected by the transition provision should be aware that 21 CFR 600.81, which covers product distribution reporting for licensed BLAs, requires submission of more granular distribution data than is required for approved NDAs under 21 CFR 314.81. However, FDA anticipates that affected application holders will generally already have the distribution information specified in 21 CFR 600.81. Additionally, 21 CFR 600.81 requires reporting every 6 months, in contrast to annual reporting. However, holders of deemed BLAs may request at any time, including within the first 6 months of being deemed a BLA, a waiver to provide product distribution reports annually (e.g., to align with the timing of the holder's Annual Report) rather than every 6 months (21 CFR 600.90). The requirements for a waiver request are described in 21 CFR 600.90.

3. Notification of Manufacturing Problems Involving Distributed Products

Regardless of whether a biological product has been approved under the FD&C Act or licensed under the PHS Act, application holders are required to report certain events that have the potential to affect the safety, purity, or potency of a distributed product. Under the FD&C Act, reporting of such events is through a field alert report (FAR) (see 21 CFR 314.81(b)(1)), while under the PHS Act, reporting is through a biological product deviation report (BPDR) (see 21 CFR 600.14). FDA expects the change in reporting between FAR and BPDR will present minimal burden to holders of deemed BLAs.

In particular, we note that under 21 CFR 600.14, application holders for biological products approved under the FD&C Act will be required, once the product is deemed to be licensed under a BLA, to report on events with the potential to affect the safety, purity, or potency of a distributed product by submission of BPDRs to CDER. Additionally, the BPDR is to be submitted as soon as possible but within 45 calendar days of acquiring information reasonably suggesting that a reportable event has occurred (rather than within 3 calendar days as is required in the case of a FAR). Finally, for any initial FAR submitted by the holder of an approved NDA for a biological product before March 23, 2020, the corresponding follow-up report is to be submitted as a BPDR if submitted on or after March 23, 2020.

4. Establishment Standards for "Non-Specified Biological Products"

Biological products that do not fall within the specified categories of biological products described in 21 CFR 601.2 ("non-specified biological products") are subject to certain additional CMC-related requirements under the PHS Act when seeking marketing approval in a BLA or BLA supplement (see establishment standards described in 21 CFR 600.10, 600.11, 600.12 and 600.13). These requirements differ in some respects from establishment standards under the FD&C Act; however, FDA expects the practical implications for transition biological products to

be minimal. As a preliminary matter, we note that an approved NDA for a biological product will be deemed to be a license (i.e., an approved BLA) for the biological product by operation of the BPCI Act. Accordingly, certain premarket approval requirements may not be applicable unless the application holder seeks approval of a supplement to the deemed BLA and the requirement applies to the supplement (see Q16 below). Moreover, as provided in 21 CFR 601.2, the additional requirements described above are not applicable to the "specified categories" of biological products described in that section of the regulations, and many transition biological products will fall within those identified categories of biological products, for which such additional requirements would not be applicable.

Q16. What is required for CMC changes submitted in a PAS or changes being effected supplements submitted to deemed 351(a) BLAs?

FDA requires applicants or application holders of biological products—whether approved under the FD&C Act or licensed under the PHS Act—to notify FDA about each change in the conditions established in an approved application. The types of reporting categories for biological products generally are the same for an NDA (see 21 CFR 314.70) and for a BLA (see 21 CFR 601.12), and in both cases, the applicant or application holder is expected to demonstrate that the postchange product continues to be of acceptable quality as it may relate to the safety or effectiveness of the product. Overall, the nature and type of data required to support such a demonstration has historically been similar for biological products approved under the FD&C Act or licensed under the PHS Act.

However, there are limited differences with respect to the type, timing, and evaluation of certain data in submissions, and verification of these data during the review cycle and inspection varies. For example, validation data would be required to be submitted in BLA supplements to support certain postapproval changes (21 CFR 601.12). In another example, for biological products that do not fall within the specified categories of biological products described in 21 CFR 601.2 ("non-specified biological products"), compliance with the establishment standards set forth under 21 CFR 600.10, 600.11, 600.12, and 600.13 may be required for a BLA supplement to support certain postapproval changes (e.g., addition of a new facility).

Application holders that intend to propose manufacturing changes are encouraged to contact OPQ/OPRO at CDER-OPQ-Inquiries@fda.hhs.gov. FDA is committed to working with application holders to minimize any potential burden.

1. Data Necessary to Support a Process or Manufacturing Site Change

Supplements to applications for biological products subject to the transition provision that remain under review after the transition date, including supplements submitted prior to the transition date, must comply with 21 CFR 601.12 and other applicable regulations. Applicants should also consult relevant guidances for biological products. A supplement submitted to a deemed BLA to support process or manufacturing site changes must contain, for the lots manufactured using the postchange process, manufacturing process validation data (see 21 CFR 601.12). Specifically, process validation for a BLA should be performed at commercial manufacturing scale, prior to submission of a supplement. Process validation information should

be included in the supplement as this may affect submission and implementation timelines of the changes for commercial distribution.

A supplement requesting approval of a proposed change to the manufacturing site for a biological product also must assess the effects of the change and contain sufficient information to support the safety, purity, and potency of material manufactured with the change (21 CFR 601.12(a)(2); compare 21 CFR 314.70). In assessing the effects of the change, information demonstrating comparability of the pre and postchange material should also be submitted, consistent with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (June 2005) and the recommendations below.

- Comparability data.
    - The type and amount of data needed to support a comparability exercise depends on the extent of the changes and the potential risk to product quality. A robust control strategy for drug substance and drug product is critical in generating comparability data. For example, a potency assay that is accurate, precise, and reliable will facilitate the review of manufacturing changes. In some cases, in addition to the typical battery of release tests, extended characterization may be necessary for comparison, in particular for process changes that may affect purity, potency, or safety of the product.
- Batch analysis data.
- Appropriate stability data.
    - Generally, limited real-time stability data for the postchange product and comparability study results, including stability data under accelerated and stressed storage conditions, are sufficient to leverage existing stability data to support the shelf life of the postchange product.

As with all biological products, FDA may recommend changes to the control strategy throughout the product life cycle to modernize outdated assays, to address product-specific issues, and to help ensure that biological products remain safe, pure, and potent for their approved conditions of use.

2. Facility Inspections Related to Certain Supplements to a Deemed 351(a) BLA

Whether a biological product is regulated under the FD&C Act or the PHS Act, application holders for biological products should be ready for FDA inspections to assure such compliance with the conditions of approval.

After March 23, 2020, supplements submitted to deemed BLAs, including supplements submitted prior to the transition date but with an action date after the transition date, must

comply with the inspection requirements as specified in the relevant regulations in 21 CFR part 600.

In particular, supplements for site changes where facilities are added to the license or supplements for major manufacturing changes may be subject to an inspection. FDA intends to contact the holder of a deemed BLA to schedule any such inspection during the review of the supplement. After March 23, 2020, holders of deemed BLAs that submit a site change or major manufacturing change supplement are advised that, as with the holder of any BLA, they should be ready for an inspection while in operation and manufacturing the product for which the change is requested during the supplement review timeframe.

Q17. Can the application holder for a deemed 351(a) BLA for a biological product originally approved through the 505(b)(2) pathway submit a supplement that relies, in part, on FDA's finding of safety, purity, and potency for another licensed biological product?

Supplements to a deemed 351(a) BLA, like any supplement to any 351(a) BLA, must meet the requirements of section 351(a) of the PHS Act. The holder of a deemed BLA for a biological product originally approved through the 505(b)(2) pathway may not, for example, submit an efficacy supplement to the deemed 351(a) BLA that relies on FDA's finding of safety, purity, and potency for another licensed biological product (e.g., for a newly approved indication or other condition of use for a related biological product).

There might be instances where there is a pending 505(b)(2) efficacy supplement to a stand-alone NDA or a pending 505(b)(2) efficacy supplement to a 505(b)(2) application that would be administratively converted to a pending efficacy supplement to the corresponding deemed 351(a) BLA on the transition date. To obtain approval under section 351(a) of the PHS Act, the applicant may need to amend the administratively converted supplement to provide the scientific data necessary to meet the requirements of section 351(a) of the PHS Act, or a right of reference to such data, for the change proposed in the supplement.

Q18. Can a biological product approved in an NDA that is deemed to be a 351(a) BLA on the transition date subsequently be a "reference product" for a proposed biosimilar or interchangeable product?

A biological product approved in an NDA (including a 505(b)(2) application) that is deemed licensed under section 351(a) of the PHS Act may be a reference product for a 351(k) BLA. The term "reference product" is defined as the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act (see section 351(i)(4) of the PHS Act).

Sponsors may request advice from FDA regarding proposed biosimilar or interchangeable product development programs that identify a biological product approved under section 505 of the FD&C Act as the intended reference product. A sponsor will be able to submit a 351(k) BLA that references the biological product approved under section 505 of the FD&C Act as its reference product after the NDA for the biological product is deemed to be a 351(a) BLA.

Q19. Can an application holder for a biological product that is the subject of a "deemed" 351(a) BLA seek a determination of biosimilarity or interchangeability under section 351(k) of the PHS Act to another biological product licensed under section 351(a) of the PHS Act?

Any person (including an application holder for a biological product that is the subject of a "deemed" 351(a) BLA) may seek to establish the biosimilarity or interchangeability under section 351(k) of the PHS Act of a proposed biosimilar or interchangeable product to another biological product licensed or deemed licensed under section 351(a) of the PHS Act. FDA intends to work with applicants to address scientific or regulatory issues that may arise in the context of these 351(k) development programs, and to provide additional procedural information. Any sponsor or applicant may contact the relevant review division within the Office of New Drugs in FDA's CDER to request advice on a 351(k) development program.

D. Transition of Biological Products from the Orange Book to the Purple Book

Q20. Will any therapeutic equivalence evaluations for biological products previously listed in the Orange Book be reflected in the Purple Book?

No, the Purple Book does not include therapeutic equivalence evaluations as reflected in the Orange Book. The Purple Book identifies, among other things, whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product.

E. Designation of Proper Name

Q21. What will be the proper name for a biological product that has been approved in an NDA that is deemed to be a BLA?

The *proper name* is the nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act (section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k)). FDA does not intend to apply the nonproprietary naming convention (in which the proper name is composed of a core name and a four-letter distinguishing suffix) to biological products that are the subject of an approved application under section 505 of the FD&C Act that is deemed to be a license under section 351(a) of the PHS Act. This is consistent with what was previously communicated in FDA's draft guidance for industry *Nonproprietary Naming of Biological Products: Update* (March 2019).[20]

[20] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

IV. COMPLIANCE POLICY FOR REQUIREMENTS RELATED TO LABELING

To minimize possible disruption to the distribution of biological products that are the subject of the transition provision and to minimize burden on holders of deemed BLAs, FDA generally does not intend to object to the labeling of biological products that are marketed under a deemed BLA with labeling that does not conform to certain labeling requirements for BLAs until March 23, 2025, provided that all other applicable labeling requirements are met. The compliance policy set forth in this guidance would apply only as described below.

FDA generally does not intend to object to the labeling of biological products that are marketed under a deemed BLA and that are introduced or delivered for introduction into interstate commerce between March 23, 2020, and March 22, 2025, where the package is not marked with:

- The proper name of the biological product contained in the package (provided that the current packaging is plainly marked with the established name of the biological product);
- The name and address of the manufacturer of the biological product (provided that the current packaging is plainly marked with the name and place of business of the manufacturer, packer, or distributor as required in 21 CFR 201.1);
- The applicable license number; or
- Other information required by 21 CFR 610.60 through 610.64, for which there is not a corresponding requirement under 21 CFR 201.1.

FDA also generally does not intend to object to the labeling of biological products that are marketed under a deemed BLA and that are introduced or delivered for introduction into interstate commerce between March 23, 2020, and March 22, 2025, where the content and format of labeling required by 21 CFR 201.56, 201.57, 201.80, and/or 208.20, as applicable, does not include the following information:

- The proper name of the biological product, including any appropriate descriptors (provided that the current labeling uses the established name of the biological product);
- The name and address of the manufacturer of the biological product (provided that the current labeling includes the name and place of business of the manufacturer, packer, or distributor as required by 21 CFR 201.1);
- The applicable license number; or
- For biological products with approved labeling in the format described by 21 CFR 201.56(d) and 201.57 (PLR format), the year of Initial U.S. Approval of the new biological product (provided that the current labeling includes the year of Initial U.S. Approval of the new molecular entity).

FDA notes that the timing of BLA-specific revisions to the prescribing information should be coordinated with the corresponding revisions to the container labels, carton labeling, and any FDA-approved patient labeling for the biological product to ensure consistency among the different types of product labeling.

If the holder of a deemed BLA for a biological product has an administratively converted supplement that includes proposed revisions to product labeling or submits a supplement that includes proposed revisions to product labeling before March 22, 2025 (i.e., the end of the compliance period), and the required BLA-specific labeling revisions to container labels, carton labeling, and prescribing information referenced in this guidance have not already been addressed, such revisions would need to be addressed before the supplement could be approved (see, e.g., 21 CFR 610.60). A changes-being-effected (CBE-0) supplement may be submitted prior to submission of a prior approval supplement that includes the BLA-specific labeling revisions. However, the prior approval supplement would need to be approved before or concurrent with approval of the CBE-0 supplement. Under this approach, holders of deemed BLAs may coordinate BLA-specific labeling updates with their plans for other proposed revisions to product labeling.

After FDA approval of a supplement for the BLA-specific labeling revisions, FDA understands that application holders may need to wait to implement these labeling revisions until their next printing of the labels and labeling. Accordingly, to enable such application holders to exhaust existing inventory, FDA generally does not intend to object to the labeling of biological products that are marketed under a deemed BLA where FDA has already approved a supplement that includes the BLA-specific labeling revisions but the labels and labeling do not include the BLA-specific labeling revisions prior to March 22, 2025.

EXHIBIT E

Thyroid

» Thyroid is the cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by humans.

On hydrolysis it yields not less than 90.0 percent and not more than 110.0 percent each of the labeled amounts of levothyroxine ($C_{15}H_{11}I_4NO_4$) and liothyronine ($C_{15}H_{12}I_3NO_4$), calculated on the dried basis. It is free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. It may contain a suitable diluent such as Lactose, Sodium Chloride, Starch, Sucrose, or Dextrose.

Packaging and storage— Preserve in tight containers.

USP Reference standards ⟨ 11 ⟩ — *USP Levothyroxine RS*. *USP Liothyronine RS*.

Identification— The retention times of the peaks for liothyronine and levothyroxine in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Microbial limits ⟨ 61 ⟩ **—** It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

Loss on drying ⟨ 731 ⟩ **—** Dry it in vacuum at 60° for 4 hours: it loses not more than 6.0% of its weight.

Limit of inorganic iodides—

Extracting solution— Prepare a 1 in 100 solution of sulfuric acid in water.

Reference solution— Dissolve an accurately weighed quantity of potassium iodide in water to obtain a stock solution containing 0.131 mg, equivalent to 0.100 mg of iodide, per mL. Transfer 1.0 mL of this stock solution into a 100-mL volumetric flask, dilute with *Extracting solution* to volume, and mix. Each mL of the *Reference solution* contains 1.0 µg of iodide. [NOTE—Prepare this solution on the day of use.]

Test solution— Transfer 1.00 g, or proportionately less if the iodine content is greater than 0.2%, of Thyroid to a beaker, add 100.0 mL of *Extracting solution*, and sonicate for 5 minutes.

Electrode system— Use an iodide-specific, ion-indicating electrode and a silver-silver chloride reference electrode connected to a pH meter capable of measuring potentials with a minimum reproducibility of ±1 mV (see *pH* ⟨ 791 ⟩).

Procedure— Transfer the *Reference solution* to a beaker containing a magnetic stirring bar. Rinse and dry the electrodes, insert in the solution, stir for 5 minutes or until the reading stabilizes, and read the potential, in mV. Repeat this process using the *Test solution.* The requirements of the test are met if the *Test solution* has a higher potential, in mV, than the *Reference solution:* the limit is 0.01%.

Residual solvents ⟨ 467 ⟩ **:** meets the requirements.
(Official January 1, 2007)

Assay—

Mobile phase— Prepare a degassed and filtered mixture of water, acetonitrile, and phosphoric acid (650:350:5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨ 621 ⟩).

Reducing buffer solution— Freshly prepare a solution in 0.11 M sodium chloride that is 0.04 M with respect to tris(hydroxymethyl)aminomethane and 0.05 M with respect to methimazole. Adjust, if necessary, with 6 N hydrochloric acid or 0.1 N sodium hydroxide to a pH of 8.4 ± 0.05.

Proteolytic enzyme— Freshly prepare a solution containing 15 mg of bacterial protease* in each 5 mL of *Reducing buffer solution*.

Enzyme deactivating solution— Prepare a 1 in 100 mixture of phosphoric acid in acetonitrile.

Standard preparation— [NOTE—Protect solutions from light.] Transfer accurately weighed quantities of about 9 mg of *USP Liothyronine RS* and about 38 mg of *USP Levothyroxine RS* to a 100-mL volumetric flask, add 50 mL of a mixture of water, acetonitrile, and ammonium hydroxide (500:500:1), and swirl to dissolve. Dilute with a mixture of water and acetonitrile (1:1) to volume, and mix (stock solution). On the day of use, pipet 5 mL of the freshly prepared stock solution into a 250-mL volumetric flask, dilute with *Reducing buffer solution* to volume, and mix to obtain a solution having known concentrations of about 1.8 µg of liothyronine per mL and about 7.6 µg of levothyroxine per mL. Pipet 5 mL of this solution into a screw-capped 16- × 125-mm culture tube. Pipet 2 mL of *Enzyme deactivating solution* into the tube, place the cap on the tube, and shake the mixture vigorously.

Assay preparation— Transfer an accurately weighed portion of finely powdered Thyroid, equivalent to about 38 µg of levothyroxine, to a screw-capped 16- × 125-mm culture tube that previously has been flushed with nitrogen. Taking precautions to avoid unnecessary exposure to air, pipet 5 mL of *Proteolytic enzyme* into the tube. Allow nitrogen to flow gently over the mixture for 5 minutes. Place the cap on the tube, mix to disperse the contents, and place in a covered water bath maintained at a temperature of 37 ± 1° for 28 hours. Protect the contents of the tubes from light. Examine occasionally, and mix as necessary to ensure dispersion. At the end of the incubation period, pipet 2 mL of *Enzyme deactivating solution* into the tube, place the cap on the tube, mix vigorously, and centrifuge at about 2000 rpm for 5 minutes. Filter the supernatant through a 0.45-µm porosity filter, discarding the first 1 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨ 621 ⟩)— The liquid chromatograph is equipped with a 230-nm detector and a 4.6- × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factors for the liothyronine and levothyroxine peaks are not more than 1.8, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure— Separately inject equal volumes (about 200 µL) of the *Assay preparation*, and the *Standard preparation,* record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of liothyronine ($C_{15}H_{12}I_3NO_4$) and levothyroxine ($C_{15}H_{11}I_4NO_4$) in the portion of Thyroid taken by the formula:

$$7C(r_U / r_S),$$

in which C is the concentration, in µg per mL, of the corresponding USP Reference Standard in the *Standard preparation,* and r_U and r_S are the peak responses for the corresponding analytes obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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* A suitable grade is available as “Pronase” (Catalog number 53702) from Calbiochem-Behring, P. O. Box 12087, San Diego, CA 92112.

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