How To Obtain a Covered Product Authorization

Guidance for Industry

DRAFT GUIDANCE

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

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I. INTRODUCTION

This guidance describes how eligible product developers can obtain a Covered Product Authorization (CPA) from FDA under the law widely known as the CREATES Act (referred to herein as CREATES or the CREATES Act). The CREATES Act provides a pathway for eligible product developers to obtain access to the product samples they need to fulfill testing and other regulatory requirements to support their applications. As described in further detail below, to make use of this pathway, an eligible product developer seeking to develop a product subject to a Risk Evaluation and Mitigation Strategies (REMS) with elements to assure safe use (ETASU) must obtain from the Agency a Covered Product Authorization (see 21 U.S.C. 355-2(b)(2)). This guidance replaces the December 2014 draft guidance for industry *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD.* The December 2014 guidance has been withdrawn.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

In December of 2019, the CREATES Act was enacted as part of the Further Consolidated Appropriations Act of 2020.[2] As noted above, CREATES makes available a pathway for

[1] This guidance has been prepared by the Office of Regulatory Policy, the Office of Generic Drugs, and the Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] See P.L. 116-94 (*Further Consolidated Appropriations Act*, 2020, enacting Division N, Title I, Subtitle F, Section 610—Actions for Delays of Generic Drugs and Biosimilar Biological Products (Dec. 20, 2019)). The provisions of this law related to access to product samples were codified at 21 U.S.C. 355-2 and 355-1(l).

developers of potential drug and biological products to obtain samples[3] of brand products[4] that they need to support their applications. CREATES establishes a private right of action that allows eligible product developers[5] to sue brand companies that refuse to sell them product samples needed to support their applications. If the product developer prevails, the court will order the sale of samples, will award attorneys' fees and litigation costs to the product developer, and may impose a monetary penalty on the brand company.

If a product developer is not able to obtain samples of the brand product that they need to support their application from the brand company on a voluntary basis and seeks to use the pathway made available by CREATES, they must take a number of specific steps (outlined in the law) before the brand company will be required to sell them product samples under CREATES. One of these steps – if the brand product for which samples are sought is subject to a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU)[6] – is that the product developer must first obtain a Covered Product Authorization (CPA) from FDA (21 U.S.C. 355-2(b)(2)).[7] CREATES does not require this step for products that are not subject to REMS with ETASU. This guidance describes how an eligible product developer can obtain a CPA from FDA.

A. Relevant Product Types

1. Generic Drug Products

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), which established the current abbreviated new drug application (ANDA) approval process for generic drugs. To obtain approval to market a generic drug, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the proposed generic drug product, but instead may rely on the Agency's previous finding of safety and effectiveness for the reference listed drug (RLD). To do so, an ANDA applicant generally

[3] As used in this guidance, the terms "samples" and "product samples" refer to an amount of a "covered product" as defined by 21 U.S.C. 355-2(a)(2) that the eligible product developer determines allows it to conduct testing to support certain types of applications and fulfill any regulatory requirements relating to approval of such applications.

[4] As used in this guidance, the term "brand product" refers to the statutory term "covered product" as defined by U.S.C. 355-2(a)(2), which include drugs approved under section 505(c) or (j) of the Federal Food, Drug and Cosmetic Act or biological products licensed under section 351(a) or (k) of the Public Health Service Act. In addition, the term "brand company," as used in this guidance, refers to the statutory term "license holder," as defined by 21 USC 355-2(a)(5).

[5] See definitions in section III.A. Note that this guidance also refers to eligible product developers as product developers.

[6] FDA's online listing of approved REMS is available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Product developers should check this listing to confirm that the product for which they seek a CPA is covered by a REMS with ETASU before submitting a CPA request.

[7] Note that requesting or obtaining a CPA from FDA is not a legal requirement to obtain samples of a covered product, and the process described in this guidance is voluntary and applies only to those who seek to avail themselves of the CREATES pathway to obtain such samples. CREATES also provides a pathway for obtaining samples of covered products that are not subject to REMS with ETASU. 21 U.S.C. 355-2.

must demonstrate, among other things, that the proposed generic drug product (1) has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and (with certain exceptions) labeling as the reference listed drug (RLD), and (2) is bioequivalent to the RLD (see section 505(j)(2)(A) of the FD&C Act). Bioequivalence is generally demonstrated via studies in which the proposed generic product is compared to the RLD.

2. 505(b)(2) Products

Section 505(b)(2) of the FD&C Act represents another abbreviated approval pathway added by the Hatch-Waxman Amendments. As background, a "stand-alone new drug application (NDA)" submitted under section 505(b)(1) contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use (see 21 U.S.C. 355(b)(1), (c)). A "505(b)(2) application," meanwhile, is an NDA that also contains full reports of investigations of safety and effectiveness, but for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)). A 505(b)(2) application may be submitted to seek approval for, among other things, a new chemical entity, or for a change to an approved drug that would not be permitted under section 505(j). A 505(b)(2) application should include, among other things, an identification of those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference. If the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug, or on literature derived from studies of a listed drug or drugs, a 505(b)(2) application should also include, among other things, a bioavailability/bioequivalence study comparing the proposed product to the listed drug or drugs and studies necessary to support any change or modification from the listed drug or drugs, if any.

3. Biosimilar Products

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amended the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Public Law 111–148)). Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for the licensure of a proposed biosimilar or a proposed interchangeable biosimilar. An application submitted under section 351(k) must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product[8] based upon data derived from analytical studies, animal studies, and a clinical study or studies (see section 351(k)(2)(A)(i)(I) of the PHS Act). FDA has the discretion to determine that an element is unnecessary in a 351(k) application. In addition, FDA expects that applications for interchangeable biosimilars generally will include data from a "switching study" or studies, meaning a clinical study or studies used to determine the impact of alternating or switching

[8] Under section 351(i)(4) of the PHS Act, the term "reference product" means the single biological product licensed under section 351(a) of that Act, against which a biological product is evaluated in a 351(k) application.

between the proposed interchangeable product and the reference product, in one or more appropriate conditions of use.[9]

B. Need for Brand Product Samples to Support Product Applications

To conduct the studies and testing described above to support their applications, ANDA, 505(b)(2) and biosimilar product applicants typically need access to some amount of the brand product. Other testing (such as that necessary to establish the appropriate dissolution specifications for a proposed product) and/or regulatory requirements (such as those relating to the retention of reserve samples) may require an applicant to obtain additional supplies of the brand product to support their applications. The amount of product needed will depend on, among other things, the scientific requirements of such studies and testing, including, where appropriate, the number of lots necessary to provide adequate information regarding brand product variability, and on applicable regulatory requirements.

Often, product developers are able to obtain these product samples needed to support their application through normal distribution channels (e.g., via wholesalers). Sometimes, however, samples of the brand product are not available through normal distribution channels. A product may not be available through standard distribution channels because the brand company limits its distribution (for example, by selling it through a central or small group of pharmacies) on its own initiative. In other cases, a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU) might impact the way the product is distributed.

A REMS is a required risk management plan that uses tools beyond the prescribing information to ensure that the benefits of a drug outweigh its risks (section 505-1 of the FD&C Act). FDA may require a REMS with ETASU when such elements are necessary to mitigate specific serious risks associated with a particular drug (section 505-1(f) of the FD&C Act). ETASU may include, for example, requirements that health care providers who prescribe or administer the drug have particular training or are specially certified, that patients using the drug be monitored and/or enrolled in a registry, that pharmacies, practitioners, or health care settings that dispense the drug be specially certified, that the drug be dispensed to patients with evidence or other documentation of safe use conditions, or that the drug be dispensed to patients only in certain health care settings. A REMS with ETASU might impact the way a product is distributed if, for example, only a limited number of pharmacies are willing and/or able to meet the specific pharmacy certification requirements in a REMS.

Once such distribution limitations are in place (whether they are voluntarily imposed or related to REMS requirements) FDA understands that some product developers have encountered difficulty obtaining product samples from brand companies because brand companies have (1) refused to sell the product directly to developers (or imposed terms on the sale that developers found burdensome or impossible to comply with), or (2) placed limitations on the ability of pharmacies or wholesalers to sell samples to the companies for development purposes. As a

[9] See guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fdaguidance-documents.

result, protracted and/or unsuccessful efforts to obtain brand product samples slowed, prevented, or deterred development of competing versions of these products.

III. PASSAGE OF THE CREATES ACT

In December of 2019, CREATES was enacted to address these issues by providing a pathway for developers of ANDA, 505(b)(2), and biosimilar products to obtain needed product samples to support their applications. CREATES established a private right of action that allows an eligible product developer to bring suit in an appropriate U.S. district court alleging that the license holder (i.e., the brand company) has declined to provide them with sufficient quantities of the covered product on commercially reasonable, market-based terms.

A. Key Terms in CREATES

The law defines the terms used above as follows:[10]

Eligible product developer:
"a person that seeks to develop a product for approval pursuant to an application for approval under subsection (b)(2) or (j) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or for licensing pursuant to an application under section 351(k) of the Public Health Service Act (42 U.S.C. 262(k))"

License holder:
"the holder of an application approved under subsection (c) or (j) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or the holder of a license under subsection (a) or (k) of section 351 of the Public Health Service Act (42 U.S.C. 262) for a covered product"

Sufficient quantities:
"an amount of a covered product that the eligible product developer determines allows it to— (A) conduct testing to support an application under— (i) subsection (b)(2) or (j) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355); or (ii) section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)); and (B) fulfill any regulatory requirements relating to approval of such an application"

Covered product:
"(i) any drug approved under subsection (c) or (j) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or biological product licensed under subsection (a) or (k) of section 351 of the Public Health Service Act (42 U.S.C. 262);
(ii) any combination of a drug or biological product described in clause (i); or
(iii) when reasonably necessary to support approval of an application under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), or section 351 of the Public Health Service Act (42 U.S.C. 262), as applicable, or otherwise meet the

[10] 21 U.S.C. 355-2(a).

requirements for approval under either such section, any product, including any device, that is marketed or intended for use with such a drug or biological product."

The term covered product "does not include any drug or biological product that appears on the drug shortage list in effect under section 506E of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356e), unless—

(i) the drug or biological product has been on the drug shortage list in effect under such section 506E continuously for more than 6 months; or

(ii) the Secretary determines that inclusion of the drug or biological product as a covered product is likely to contribute to alleviating or preventing a shortage."

Commercially reasonable, market-based terms:

"(A) a nondiscriminatory price for the sale of the covered product at or below, but not greater than, the most recent wholesale acquisition cost for the drug, as defined in section 1847A(c)(6)(B) of the Social Security Act (42 U.S.C. 1395w–3a(c)(6)(B));

(B) a schedule for delivery that results in the transfer of the covered product to the eligible product developer consistent with the timing under [subsection (b)(2)(A)(iv) of CREATES]; and

(C) no additional conditions are imposed on the sale of the covered product"

B. Covered Product Authorizations Under CREATES

To prevail in the private right of action established by CREATES, the eligible product developer must prove that it has taken a number of specific steps. It must show, among other things, that it submitted a written request to the license holder to purchase sufficient quantities of the covered product, and that the request (1) was sent to a named corporate officer of the license holder, (2) was made by certified/registered mail with return receipt requested, (3) specified an individual point of contact and a means for written and electronic communication with them, and (4) provided a delivery address for samples.[11] The eligible product developer must also prove that the license holder did not deliver sufficient quantities of the covered product on commercially reasonable, market-based terms within 31 days of receiving the request (for non-REMS ETASU products) or (for REMS ETASU products) within 31 days of receiving either the request OR a copy of the Covered Product Authorization (CPA), whichever is later.[12]

The CPA is a document obtained by the eligible product developer from FDA. CREATES provides that "[a]n eligible product developer may submit to [FDA] a written request for the eligible product developer to be authorized to obtain sufficient quantities of an individual covered product subject to a REMS with ETASU."[13] The law requires that FDA must respond to this request within 120 days.[14]

[11] 21 U.S.C. 355-2(b)(2)(A)(iii).
[12] 21 U.S.C. 355-2(b)(2)(A)(iv).
[13] 21 U.S.C. 355-2(b)(2)(B).
[14] Id.

CPAs are only available for products that are subject to a REMS with ETASU. To prevail in the private right of action established by CREATES, an eligible product developer seeking samples of a product that is *not* subject to a REMS with ETASU does not need to obtain a CPA.

In addition, the CPA established by CREATES replaces the "Safety Determination Letter" that FDA had been issuing prior to CREATES as described in the withdrawn draft guidance for industry *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD*. The purpose of the Safety Determination Letter was to provide RLD sponsors with written assurance that providing samples to a potential applicant would not be considered a violation of their REMS. The CPA provides the same written assurance. Note that unlike Safety Determination Letters, which FDA sent to the RLD sponsor at the prospective ANDA applicant's request, CREATES provides that the eligible product developer is responsible for providing a copy of the CPA to the applicable license holder.[15]

IV. HOW TO OBTAIN A COVERED PRODUCT AUTHORIZATION FROM FDA

We recommend that interested developers seeking CPAs submit their requests as follows:

- For generic products, submit the request as a controlled correspondence to the CDER NextGen Collaboration Portal[16] (general questions may be submitted to GenericDrugs@fda.hhs.gov).
- For 505(b)(2) products and biological products, submit the request to your pIND file or IND (with a copy to the related marketing application, if there is one). If you do not have a pIND or IND number, request a file number as described at https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number and submit the request to that numbered file. Please also email a copy of your CPA request to ONDCommunications@fda.hhs.gov.

A. Contents of a CPA Request

- Please prominently identify the request as a "REQUEST FOR COVERED PRODUCT AUTHORIZATION." Requests should specify that the product developer is seeking a CPA and the product for which a CPA is being sought.
- If the samples will be used for purposes of development and testing that involve human clinical trials, requests should be accompanied by study protocols, informed consent documents, and informational materials for testing demonstrating that safety protections comparable to those in the REMS for the brand product will be provided for in the study or studies for which samples are sought.
- If the samples will be used for purposes of development and testing that does not involve any testing in humans, the request should state that the samples will not be

[15] 21 U.S.C. 355-2(b)(2)(A)(i).

[16] For more information, see guidance for industry, *Controlled Correspondence Related to Generic Drug Development* (Dec. 2020).

used for testing in humans. If you receive a CPA for development and testing that does not involve testing in humans and your development plan subsequently changes such that product samples are needed for human clinical trials, you should obtain a new CPA for these purposes.[17]

- If you seek a CPA for a product that is on the drug shortage list in effect under section 506E of the Federal Food, Drug & Cosmetic Act ("in shortage"), please specify in your request that the product is on the drug shortage list.[18]

CREATES does not impose limitations on the number of times an eligible product developer may request samples pursuant to a particular CPA or on the number of requests an eligible product developer may make for product samples to support their application.

B. FDA Review

- The Agency will review any draft protocol(s), informed consent document(s), and informational materials submitted. As the Agency processes your request for a CPA, we may ask for additional information via an information request.
- If the Agency determines that the protocols, informed consent documents, and informational materials for testing contain safety protections comparable to those provided by the applicable REMS with ETASU, FDA will issue a CPA letter within 120 days of the date of submission.[19]
- If the drug is in shortage, FDA will determine whether (1) it has been in shortage continuously for more than six months, or (2) its inclusion as a covered product is likely to contribute to alleviating or preventing a shortage. If the answer to either is yes, the Agency will issue a CPA to the requester, assuming the requester has met the remaining requirements for obtaining a CPA. If not, the drug would not be considered a covered product under CREATES, and the CPA request will be rejected.[20] If a CPA request is rejected on this basis, FDA recommends that the eligible product developer continue to monitor FDA's drug shortage list and consider submitting a new CPA after the product is either no longer in shortage or has been in shortage continuously for more than six months.
- If FDA cannot determine from the protocols, informed consent documents, and informational materials for testing submitted with your CPA request that safety protections comparable to those provided by the applicable REMS with ETASU will be provided, and the deficiencies in the materials submitted are more significant than can be resolved via an information request, your CPA request will be rejected and the reasons for rejection specified in the response. The Agency intends to process any resubmission on a new 120-day clock.

[17] See 21 U.S.C. § 355-2(b)(2)(B)(ii).
[18] For more information, see https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages.
[19] 21 U.S.C. 355-2(b)(2)(B)(ii).
[20] Id.; 21 U.S.C. 355-2(a)(2)(B).