Competitive Generic Therapies

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact the Center for Drug Evaluation and Research (CDER) Susan Levine, 240-402-7936.

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

February 2019
Generic Drugs

Competitive Generic Therapies

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U.S. Department of Health and Human Services
Food and Drug Administration
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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The FDA Reauthorization Act of 2017, or FDARA,[2] created a new pathway by which FDA may, at the request of the applicant, designate a drug[3] with "inadequate generic competition"[4] as a competitive generic therapy (CGT).[5] At the request of the applicant, FDA may also expedite the development and review of an abbreviated new drug application (ANDA) for a drug designated as a CGT.

This guidance[6] provides a description of the process that applicants[7] should follow to request designation of a drug as a CGT and the criteria for designating a drug as a CGT. This guidance also includes information on the actions FDA may take to expedite the development and review of ANDAs for drugs designated as CGTs. This guidance also provides information on how FDA implements the statutory provision for a 180-day exclusivity period for certain first approved applicants that submit ANDAs for CGTs.

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

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

[2] Public Law 115-52.

[3] For the purposes of this guidance, the term *drug* is intended to cover any product submitted for approval in an ANDA, including those products meeting the definition of a *combination product* under 21 CFR 3.2.

[4] See section 506H(b)(3), (e)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356h(b)(3), (e)(2)).

[5] The term *generic drug* refers to a drug that is approved pursuant to section 505(j) of the FD&C Act (21 U.S.C. 355(j)). See section 506H(e)(1).

[6] This draft guidance has been issued in accordance with section 803(b)(1) of FDARA.

[7] For the purposes of this guidance, the term *applicant* refers to any person developing a drug intended for submission in an ANDA or any person who submits a drug in an original ANDA.

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

On August 18, 2017, FDARA was signed into law. As part of FDARA, the Generic Drug User Fee Amendments were reauthorized (through Title III of FDARA) to support timely access to high-quality affordable generic medicines. FDARA also created other enhancements associated with generic drugs. Specifically, section 803 of FDARA amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to add section 506H, which established a new process to designate, and expedite the development and review of, certain drugs either intended for submission or submitted in an ANDA and for which there is inadequate generic competition.[8]

FDA recognizes that various factors may influence an applicant's decision to develop a certain generic drug. For instance, some drugs may not attract a high level of interest from generic drug applicants if there is a limited market for those products and/or if the products are more difficult to develop. Nevertheless, these drugs can play an important role in diagnosing, treating, and preventing various types of diseases or conditions, and incentivizing generic competition for these products can help ensure patients have access to the medicines they need. The provisions associated with CGTs are intended to incentivize effective development, efficient review, and timely market entry of drugs for which there is inadequate generic competition.

To facilitate increased competition for these products, FDA may take certain actions to expedite the development and review[9] of an ANDA for a drug that is designated as a CGT.[10] These actions, as further described below, may help to clarify the regulatory expectations for a particular drug, assist applicants in developing a more complete submission, and ultimately promote a more efficient and effective ANDA review process in order to help reduce the number of review cycles necessary to obtain ANDA approval.

[8] Section 506H(a) of the FD&C Act ("The Secretary may, at the request of an applicant of a drug that is designated as a competitive generic therapy pursuant to [section 506H(b)], expedite the development and review of an abbreviated new drug application under section 505(j) for such drug.").

[9] For the purposes of this guidance, the term *review* is used to align with the statutory language in section 506H of the FD&C Act and is intended to describe the Office of Generic Drug's assessment of submitted data and information in an ANDA to determine whether the application meets the requirements for approval and its process for documenting that determination. See section IV.D.3 of this guidance for additional information.

[10] See also section 803(b)(1)(B) of FDARA (requiring FDA to issue guidance to "specify the process and criteria by which the Secretary makes a designation under section 506H of the [FD&C Act]…[and] specify the actions the Secretary may take to expedite the development and review of a competitive generic therapy pursuant to such a designation").

Historically, the FD&C Act has provided an incentive and potential reward to the first applicant[11] that, among other things, filed a substantially complete ANDA containing a paragraph IV certification to a listed patent in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book),[12] which subjected the applicant to the risk of being sued for patent infringement. Such applicants may qualify for a 180-day period of exclusivity (hereafter, 180-day patent challenge exclusivity) during which approval of certain subsequent ANDAs would not be granted.[13]

FDARA created a new type of 180-day exclusivity, different from 180-day patent challenge exclusivity, for the first approved applicant[14] of a drug with a CGT designation for which there were no unexpired patents or exclusivities listed in the Orange Book at the time of original submission of the ANDA. This new 180-day exclusivity under FDARA (hereafter, CGT exclusivity) is intended to incentivize competition for drugs that are not protected by patents or exclusivities and for which there is inadequate generic competition.

III. COMPETITIVE GENERIC THERAPY DESIGNATION

A. Criteria and Timing for Requests to Designate a Drug as a Competitive Generic Therapy

FDA may designate a drug as a CGT after determining that there is inadequate generic competition for that drug. The term inadequate generic competition is defined to mean, with respect to a drug, that there is not more than one approved drug in the active section of the Orange Book.[15] This may either be the reference listed drug (RLD)[16] or a drug approved in an ANDA referencing the same RLD as the drug for which designation as a CGT is sought.[17]

[11] The use of the term "first applicant" in this guidance means an applicant that meets the definition set out in FDCA Section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act: "As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug." The term "first approved applicant" means an applicant that meets the definition set out in Section 505(j)(5)((B)(v)(III)(bb) of the FD&C Act..

[12] The Orange Book is available at https://www.accessdata.fda.gov/scripts/cder/ob/.

[13] Section 505(j)(5)(B)(iv) of the FD&C Act; see also 21 CFR 314.3(b).

[14] See section 505(j)(5)(B)(v)(III)(bb) of the FD&C Act.

[15] See section 506H(e)(2) of the FD&C Act.

[16] The term *reference listed drug* is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. See 21 CFR 314.3.

[17] See section 506H(e)(2)(A)-(B) of the FD&C Act.

Because each strength of a drug product is a distinct drug product, in evaluating whether there is not more than one approved drug in the active section of the Orange Book, FDA considers whether the product(s) in the active section is the same strength(s) as the product for which CGT designation is being sought. For example, if multiple strengths of a drug are approved under the new drug application (NDA) for the RLD, and some strengths are available for sale and listed in the active section of the Orange Book, but the particular strength for which CGT designation is sought is withdrawn from sale and thus is in the discontinued section of the Orange Book, FDA would not consider the particular strength of the RLD for which CGT designation is sought to be in the active section of the Orange Book. In this instance, an ANDA submitted referencing this particular strength of the RLD as its basis of submission may be eligible for designation as a CGT. For ANDAs submitted or intended for submission pursuant to an approved suitability petition,[18] FDA would evaluate whether there is more than one product in the active section of the Orange Book that is either the RLD identified in the petition[19] or an approved ANDA that relied on the same approved suitability petition as a basis of submission and is pharmaceutically equivalent to the product for which CGT designation is being sought.

Applicants may submit requests to designate a drug as a CGT (hereafter, Requests for Designation) concurrently with, or at any time prior to, the original ANDA submission. FDA will *not* consider Requests for Designation as timely if they are submitted after the submission of the original ANDA, including as an amendment during filing review. One exception is for an application for which a refuse-to-receive (RTR) determination has been made, as explained in the following paragraphs.

FDA may RTR an ANDA that does not satisfy the criteria for a threshold determination that the application is substantially complete.[20] In such cases, FDA will notify the applicant that FDA considers the ANDA not to have been *received*. If the applicant decides to correct the identified deficiencies in the RTR letter and resubmit the ANDA, the ANDA will be received as of the date the ANDA is resubmitted (if it is deemed substantially complete).

In this circumstance, a Request for Designation may be considered timely if, after the applicant receives an RTR letter, the request is included as part of, or is submitted any time prior to, the resubmission of the amended ANDA that FDA determines to be substantially complete. However, FDA may deny a Request for Designation if at the time the request is submitted a Request for Reconsideration and/or Request for Formal Dispute Resolution related to an RTR decision remains pending with the Agency. If the RTR decision is upheld, ANDA applicants should submit the Request for Designation as part of the ANDA resubmission (because the resulting amended ANDA will be considered the original ANDA submission, if FDA finds the resubmission to be substantially complete). If FDA's RTR decision is rescinded, such that the date of receipt for the ANDA will correspond to the date of the initial submission of the ANDA, FDA will consider any Request for Designation submitted after the date of receipt untimely.

[18] 21 CFR 314.93

[19] See section 506H(e)(2)(A) of the FD&C Act.

[20] See generally 21 CFR 314.101(b)(1).

FDA intends to make a determination on a Request for Designation within 60 calendar days of receipt of the applicant's request and will send the determination to the applicant via FDA correspondence. FDA, in assessing whether inadequate generic competition for a particular drug exists, will rely on the information contained in the Orange Book at the time it makes its determination. If an applicant believes that the information listed in the Orange Book is incorrect (i.e., if an applicant has information indicating that a drug listed in the active section of the Orange Book has been withdrawn from sale), the applicant should submit a controlled correspondence prior to submitting a Request for Designation seeking correction of the relevant information in the Orange Book.[21] The Request for Designation should be submitted only after FDA removes the drug from the active section of the Orange Book.

B. Process for Submitting a Request for Designation

1. Requests for Designation Made Prior to Submission of an ANDA

As noted in section III.A of this guidance, Requests for Designation may be made at any time prior to the submission of an original ANDA or concurrently with the submission of an original ANDA. If a Request for Designation is made at any time prior to submission of an original ANDA, the request should be made in writing and may be submitted as a stand-alone request to FDA or as an accompaniment to the pre-submission facility correspondence (PFC) for an ANDA.[22] If an applicant plans to request a pre-ANDA meeting for a drug for which it also wishes to seek designation as a CGT (see section IV.B of this guidance), the applicant should submit a Request for Designation before submitting a meeting request. The applicant should obtain, from FDA, a pre-assigned ANDA number prior to submitting a Request for Designation either as a stand-alone request or as part of a PFC.[23]

a. Content of Requests for Designation

Applicants should include the following information in their cover letter for a Request for Designation:

- Pre-assigned ANDA number

[21] See FDA's draft guidance for industry *Controlled Correspondence Related to Generic Drug Development* for more information on how to submit controlled correspondence to FDA. When final, this guidance will represent 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/RegulatoryInformation/Guidances/default.htm.

[22] Information on the submission of a PFC may be found in FDA's draft guidance for industry *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence)*. When final, this guidance will represent FDA's current thinking on this topic.

[23] Information on how to submit a request for a pre-assigned ANDA number may be found at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm.

- A statement supporting the Request for Designation under section 506H of the FD&C Act. This statement should include sufficient identification of the particular drug product that will serve as the basis of submission for the applicant's proposed application (i.e., the application number, the proprietary name (if applicable), and the strength(s) for the drug for which CGT designation is being sought).

- Information supporting the applicant's assertion that there is "inadequate generic competition" as defined in section 506H(e)(2) of the FD&C Act

b. Transmitting the Request for Designation through FDA's Electronic Submissions Gateway.

Requests for Designation (either as stand-alone requests or as part of a PFC) should be submitted electronically in electronic common technical document (eCTD) format[24] through the Electronic Submissions Gateway (ESG) following the Agency's instructions.[25] When transmitting via the ESG, choose "CDER" when selecting the appropriate Center, and choose "eCTD" when selecting the submission type. A Form FDA 356h should be submitted with the Request for Designation. Submitting the Form FDA 356h will enable the Agency to process the request.

2. Requests for Designation Submitted with an Original ANDA

Requests for Designation may also be made concurrently with the submission of an original ANDA. If applicants submit a Request for Designation concurrently with submission of an original ANDA, they should prominently identify the request in the cover letter to the submission in Module 1 of the Common Technical Document. Additionally, the following information should be included in the cover letter for the request:

- Pre-assigned ANDA Number.

- A statement supporting the Request for Designation under section 506H of the FD&C Act. This statement should include sufficient identification of the reference listed drug that is the basis of submission for the applicant's ANDA (i.e., the NDA number, the proprietary name, and the strength(s) for the drug for which CGT designation is being sought).

[24] See FDA's guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. See also the eCTD Technical Conformance Guide at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm535180.htm.

[25] See the Electronic Submissions Gateway web page at https://www.fda.gov/forIndustry/ElectronicSubmissionsGateway/default.htm for technical details related to submitting documents through FDA's ESG.

- Information supporting the applicant's assertion that there is "inadequate generic competition"[26] as defined in section 506H(e)(2) of the FD&C Act.

IV. CONSIDERATIONS FOR EXPEDITED DEVELOPMENT AND REVIEW OF COMPETITIVE GENERIC THERAPIES

Applicants for drugs that FDA has designated as CGTs may request expedited development and review of their ANDAs. This section describes factors that FDA will consider in determining whether to expedite the development and review of an ANDA for a drug designated as a CGT, and the actions that FDA may take to expedite the development and review of an ANDA for a drug designated as a CGT.[27]

A. Considerations for Expedited Development

To facilitate expedited development, applicants may request to meet with FDA to discuss specific scientific and/or regulatory questions related to an ongoing development program, or to discuss the content and format of an ANDA submission, for a drug designated as a CGT. In determining whether to grant certain requests to facilitate the development of a drug designated as a CGT, FDA will consider, among other factors:

- The complexity of developing an application for the specific drug subject to the request[28]
- The potential public health impact of the product, including the severity of the condition treated and the size of the impacted patient population, as well as the availability of therapeutic alternatives
- The impact on FDA resources and other existing workload commitments

[26] As discussed more fully in section V.A, drug products for which there is "inadequate generic competition," as defined under section 506H(e)(2), may be designated as a CGT, but may not qualify for 180-day marketing exclusivity under section 505(j)(5)(B)(v) of the FD&C Act if, at the time of the original ANDA submission, unexpired patents and/or exclusivities were listed in the Orange Book for the RLD.

[27] See section 803(b)(1)(B) of FDARA (requiring FDA to issue guidance to "specify the process and criteria by which the Secretary makes a designation under section 506H of the [FD&C Act]…[and] specify the actions the Secretary may take to expedite the development and review of a competitive generic therapy pursuant to such a designation").

[28] For example, if development of an ANDA may raise specific scientific questions, such as when (1) FDA has not issued a product-specific guidance (PSG) for the drug and published general guidance on bioequivalence is not applicable or (2) the applicant has proposed an alternative equivalence evaluation (i.e., a change in study type, such as from an in vitro study to a comparative clinical endpoint study) for a product for which FDA has issued a PSG, FDA may grant an applicant's request to meet with FDA to discuss these questions.

As described more fully below, applicants may request a pre-ANDA meeting (i.e., either a product development meeting or a pre-submission meeting) for a CGT using the CDER Direct NextGen Collaboration Portal.[29] FDA will consider requests for meetings that may expedite the development of a drug designated as a CGT on a case-by-case basis.

B. Actions FDA May Take to Expedite Development

1. Product Development Meetings

Applicants may submit requests for product development meetings for a drug designated as a CGT if an applicant wants to discuss specific scientific issues or questions with FDA (e.g., a proposed study design, alternative approach, or additional study expectations) and receive FDA's targeted feedback regarding an ongoing ANDA development program. To engage in a substantive discussion, FDA expects that the prospective ANDA applicant has enough knowledge of the product to allow FDA to provide appropriate feedback that will advance product development early in the process.

Applicants should submit requests for a product development meeting consistent with the format outlined in FDA's draft guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (hereafter, Formal Meetings draft guidance).[30] In addition to the information identified in section V of the Formal Meetings draft guidance, applicants should provide documentation that FDA has designated the drug under development as a CGT.

2. Pre-Submission Meetings

Applicants may submit requests for pre-submission meetings for a drug designated as a CGT if an applicant wants to discuss and explain the format and content of the ANDA to be submitted (e.g., the types of data that will be contained in the ANDA, the data that will support equivalence claims). A pre-submission meeting does not include substantive review of summary data or full study reports but provides an opportunity for FDA to identify items or information that should be clarified before submission of the ANDA.

Applicants should submit requests for pre-submission meetings consistent with the format outlined in the Formal Meetings draft guidance. In addition to the information identified in section V of the Formal Meetings draft guidance, applicants should provide documentation that FDA has designated the drug under development as a CGT.

[29] See the Pre-ANDA Program web page at https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm578012.htm.

[30] When final, this guidance will represent FDA's current thinking on this topic. For the purposes of this guidance, *GDUFA* refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012 and the Generic Drug User Fee Amendments of 2017.

C. Considerations for Expedited Review

FDA may take certain actions to expedite the review of an ANDA for a drug that has been designated as a CGT. FDA generally intends to expedite the review of ANDAs for drugs designated as CGTs when the applicant has participated in the pre-ANDA meeting program prior to the submission of the ANDA (e.g., when the drug is a complex product). FDA generally does not intend to expedite the review of ANDAs covering CGTs if, at the time of ANDA submission, unexpired patents or exclusivities were listed in the Orange Book for the RLD.[31] FDA believes that these considerations are consistent with Congress's intent to facilitate the efficient development and the timely market entry of drugs for which there is inadequate generic competition.

As part of expediting the review of a drug that has been designated as a CGT, FDA will strive to act on the ANDA as soon as possible, including prior to the GDUFA goal date, if possible. However, an expedited review does not result in a shorter GDUFA goal date. If an applicant is seeking a shorter GDUFA goal date, the applicant should determine whether a particular drug is eligible for prioritization pursuant to section 505(j)(11) of the FD&C Act[32] or the criteria in CDER Manual of Policies and Procedures (MAPP) 5240.3 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*.[33] If an ANDA meets the criteria listed in either section 505(j)(11)(A) of the FD&C Act or MAPP 5240.3, FDA intends to consider it a priority ANDA, and applicants submitting such priority ANDAs can qualify for review with a shorter 8-month GDUFA goal date by pre-submitting complete, accurate information regarding facilities involved in manufacturing processes and testing of the drug that is the subject of the application, as outlined in FDA's draft guidance for industry *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications*,[34] not later than 60 days prior to ANDA submission.

D. Actions FDA May Take to Expedite Review

1. Mid-Review-Cycle Meetings

Based on the considerations above, FDA may offer a mid-review-cycle meeting to an applicant of an ANDA for a drug designated as a CGT during the first review cycle. The mid-review-cycle

[31] See section V.A. of this guidance.

[32] Section 505(j)(11) of the FD&C Act states, in part, that the Secretary shall prioritize, subject to the process described in 505(j)(11)(B), and act within 8 months of the date of the submission of an original ANDA that has been submitted for a drug for which there are not more than 3 approved drug products listed in the Orange Book or for drug products under drug shortage as defined under section 506E of the FD&C Act (21 U.S.C. 356e).

[33] We update MAPPs periodically. For the most recent version of a MAPP, check the CDER Manual of Policies & Procedures web page at

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[34] When final, this guidance will represent FDA's current thinking on this topic.

meeting will generally take place 30 days after the mid-point of the review cycle. The mid-review-cycle meeting affords an opportunity for FDA to discuss issues identified during review with the applicant. The Office of Generic Drugs (OGD) Regulatory Project Manager (RPM) assigned to the ANDA will contact the applicant to schedule the meeting (held by teleconference); these meetings are optional and can be declined by the applicant. During the mid-review-cycle meeting, the RPM and certain members of the review team, as appropriate considering any deficiencies or requests for clarification communicated to the applicant, will participate in a 30-minute teleconference during which FDA will provide the applicant with an update on the status of the review of its application. If an applicant wishes to decline the mid-review-cycle meeting, FDA recommends that the applicant submit a letter to the ANDA file indicating that it wishes to decline the mid-review-cycle meeting.

2. Coordinated Review of CGTs

FDA may involve experienced review and regulatory health project management staff in a collaborative, cross-disciplinary review of an ANDA for a drug designated as a CGT. Senior management will be involved in the review consistent with the processes described in MAPP 5241.3 *Good Abbreviated New Drug Application Assessment Practices*. When appropriate, FDA may also assign a cross-disciplinary project lead for the review team to facilitate an efficient review of the application, including manufacturing inspections. The cross-disciplinary project lead will serve as a scientific liaison between members of the assessment team (e.g., those with expertise in bioequivalence, quality, or labeling), facilitating coordinated internal interactions and communications with the applicant through the OGD RPM assigned to the ANDA.

3. Good ANDA Assessment Practices

FDA is committed to improving the predictability and transparency of all ANDA assessments, including assessments of ANDAs for drugs designated as CGTs, to help minimize the number of review cycles necessary for approval. Program enhancements, as agreed to under the re-authorization of GDUFA, are intended to foster the development of high-quality submissions, promote the efficiency and effectiveness of the review process, minimize the number of review cycles necessary for approval, increase the overall rate of approval, and facilitate greater access to generic drug products.

Applicants are encouraged to refer to FDA's draft guidance for industry *Good ANDA Submission Practices*,[35] which highlights common, recurring ANDA deficiencies that may lead to a delay in the approval of an ANDA. It also makes recommendations to applicants on how to avoid these ANDA deficiencies with the goal of minimizing the number of review cycles necessary for approval. In conjunction with the *Good ANDA Submissions Practices* draft guidance, FDA issued MAPP 5241.3 *Good ANDA Assessment Practices,* which establishes good ANDA assessment practices for the Office of Generic Drugs and the Office of Pharmaceutical Quality to increase their operational efficiency and effectiveness. FDA will review ANDAs for drugs designated as CGTs consistent with this MAPP.

[35] When final, this guidance will represent FDA's current thinking on this topic.

V. COMPETITIVE GENERIC THERAPY EXCLUSIVITY

FDARA created a new type of 180-day marketing exclusivity period for ANDA applicants of certain drugs that FDA has designated as CGTs. Specifically, section 808 of FDARA amended the FD&C Act by adding provisions at section 505(j)(5)(B)(v) and 505(j)(5)(D)(iv) of the FD&C Act to grant a 180-day period of exclusivity (hereafter, CGT exclusivity) *vis-à-vis* certain other ANDA applicants to the first approved applicant that:

- Obtains approval of an ANDA for a drug that has been designated as a CGT and for which there were no unexpired patents or exclusivities listed in the Orange Book for the relevant RLD at the time the applicant submitted the original ANDA to the Agency; and

- Commercially markets such drug within 75 calendar days after the approval of the ANDA.

As mentioned above, this new type of exclusivity provides an incentive and a reward to generic drug applicants that submit, obtain approval of, and promptly market ANDAs for drugs with inadequate generic competition and where the approval of the ANDA would not be blocked by patents or exclusivities.

A. Eligibility for CGT Exclusivity

In order to be eligible for CGT exclusivity under section 505(j)(5)(B)(v) of the FD&C Act, an ANDA applicant must qualify as a "first approved applicant," which is defined as an applicant that has submitted an application that:

- Is for a competitive generic therapy that is approved on the first day on which any application for such designated competitive generic therapy is approved

- Is not eligible for a 180-day exclusivity period under section 505(j)(5)(B)(iv) for the drug that is the subject of the application for the competitive generic therapy

- Is not for a drug for which all drug versions have forfeited eligibility for a 180-day exclusivity period under section 505(j)(5)(B)(iv) pursuant to section 505(j)(5)(D)[36]

For purposes of the CGT exclusivity provisions, a *CGT* is defined as a drug that (1) "is designated as a competitive generic therapy under section 506H [of the FD&C Act]" and (2) "for which there are no unexpired patents or exclusivities [listed in the Orange Book]…at the time of

[36] See section 505(j)(5)(B)(v)(III)(bb) of the FD&C Act.

submission."[37] This is distinguishable from how that same term is used in section 506H(b)(3) of the FD&C Act, in that eligibility for designation as a CGT in section 506H(b)(3) requires only that FDA determine that a particular drug has inadequate generic competition. In other words, drugs may be designated as a CGT consistent with section 506H(b)(3) of the FD&C Act but may not be eligible for 180 days of CGT exclusivity under section 505(j)(5)(B)(v), if unexpired patents or exclusivities are listed in the Orange Book at the time the applicant submits the original ANDA for that drug to FDA.

Furthermore, a first approved applicant must obtain approval of its ANDA for a CGT "on the first day on which any application for such competitive generic therapy is approved."[38] FDA notes that there can be multiple first approved applicants for the same CGT, if all such ANDA applicants obtain approval for their ANDAs for the same CGT on the same day, and such approvals constitute the first ANDA approvals for this CGT.

An ANDA applicant may still qualify as a first approved applicant even if another ANDA referencing the same RLD, but without a competitive generic therapy designation, is approved prior to the approval of the first approved applicant's ANDA. This is possible because FDA does not consider the prior ANDA approval to constitute the first approval of an ANDA for a CGT. Approval of an ANDA for a drug designated as a CGT may, however, block subsequent approvals of ANDAs for the same drug if that ANDA applicant qualifies as the first approved applicant and the date of approval is the first day on which any application for such competitive generic therapy is approved and other criteria are met.[39]

The definition of *first approved applicant* also includes two additional criteria that an ANDA applicant must meet to qualify as a first approved applicant. First, the potential first approved applicant must not otherwise be eligible for 180-day exclusivity under section 505(j)(5)(B)(iv) (i.e., 180-day patent challenge exclusivity) for the same drug that has been designated as a competitive generic therapy.[40] Second, the potential first approved applicant's ANDA cannot be for a drug for which other ANDA applicants were eligible for 180-day exclusivity under section 505(j)(5)(B)(iv) of the FD&C Act and all such ANDA applicants have forfeited eligibility for such 180-day exclusivity. These two additional criteria are discussed in more detail below.

B. CGT Exclusivity Trigger and Scope of CGT Exclusivity

The 180-day CGT exclusivity period described under section 505(j)(5)(B)(v) of the FD&C Act is triggered by the "first commercial marketing of the competitive generic therapy (including the

[37] See section 505(j)(5)(B)(v)(III)(aa) of the FD&C Act.

[38] See section 505(j)(5)(B)(v)(III)(bb) of the FD&C Act.

[39] See section 505(j)(5)(B)(v)(III)(bb)(AA) of the FD&C Act.

[40] See Section 505(j)(5)(B)(v)(III)(bb)(BB) of the FD&C Act.

commercial marketing of the listed drug)[41] by any first approved applicant."[42] After this exclusivity is triggered, the 180-day period runs without interruption.

The first approved applicant's trigger of the 180-day CGT exclusivity period impacts other first approved applicants because there is only one exclusivity period available for each CGT.[43] Any first approved applicant's trigger of the exclusivity period triggers the 180-day CGT exclusivity period for *all* first approved applicants for that CGT, and exclusivity for all first approved applicants ends 180 days after the initial trigger of that exclusivity period. Other first approved applicants will benefit from the exclusivity only to the extent that they commercially market during the exclusivity period.

The FD&C Act also specifies that only an ANDA "for a drug that is the same as a competitive generic therapy for which any first approved applicant has commenced commercial marketing" can have its approval blocked.[44] As such, once the first approved applicant has commenced commercial marketing, FDA is restricted from approving ANDAs for a drug that is the same as a CGT approved in the first approved applicant's ANDA.[45] Therefore, FDA would not be restricted from approving other ANDAs covering a drug that is the same as the CGT prior to or after the approval of a first approved applicant's ANDA for the CGT *unless and until* the first approved applicant has commenced commercial marketing and triggered the exclusivity period. Likewise, the trigger of the exclusivity period by the first approved applicant would not restrict other ANDA applicants that were approved prior to the trigger of such exclusivity from commercially marketing their products.

C. Relinquishment and Waiver of CGT Exclusivity

FDA intends to permit a first approved applicant to relinquish and/or grant selective waiver of CGT exclusivity, similar to FDA's longstanding practice of permitting relinquishment and selective waiver of 180-day patent challenge exclusivity. *Relinquishment* refers to the voluntary and complete abandonment of eligibility for exclusivity. *Selective waiver* refers to a first approved applicant's waiver of exclusivity to permit approval during the exclusivity period of a particular ANDA or ANDAs. Relinquishment and selective waiver of CGT exclusivity promote the overall purpose of the exclusivity — that is, to increase marketplace competition.

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[41] For the purposes of CGT exclusivity, FDA interprets the statutory phrase "including the commercial marketing of the listed drug" to mean that exclusivity can be triggered by the marketing of an authorized generic by a first approved applicant.

[42] Section 505(j)(5)(B)(v)(I) of the FD&C Act; see also 21 CFR 314.3(b) (defining commercial marketing).

[43] See, e.g., section 505(j)(5)(B)(v)(II) of the FD&C Act. As discussed above, FDA will designate CGTs on a drug product-by-drug product basis, meaning that different strengths covered under a single ANDA can be considered different competitive generic therapies. As a result, there are separate 180-day CGT exclusivity periods available for each strength of the same drug because each strength is a distinct drug product. Thus, it is possible for there to be different first approved applicants for different strengths of the same drug.

[44] Section 505(j)(5)(B)(v)(I) of the FD&C Act.

[45] In this case, if the ANDA is otherwise ready for approval, FDA would issue a tentative approval.

A first approved applicant that is eligible for CGT exclusivity may relinquish its exclusivity at any time. In contrast, a first approved applicant may only selectively waive CGT exclusivity after the exclusivity period has been triggered. As a general matter, when all first approved applicants have relinquished their claims to CGT exclusivity, FDA may inform other, non-first-approved applicants that are otherwise eligible for approval that their ANDAs may be approved. For selective waivers, FDA may notify only the applicable applicant in whose favor the exclusivity has been waived.[46]

D. Forfeiture of CGT Exclusivity

The FD&C Act includes a provision under which a first approved applicant will forfeit eligibility for CGT exclusivity. Specifically, section 505(j)(5)(D)(iv) of the FD&C Act provides that the 180-day CGT exclusivity period will be forfeited by "a first approved applicant if the applicant fails to market the competitive generic therapy within 75 days after the date on which the approval of the first approved applicant's application for the competitive generic therapy is made effective."[47] Because CGTs are drugs that, by definition, have lacked adequate generic competition, this forfeiture provision reflects Congress's intent that a first approved applicant must both obtain approval of and promptly market its product(s) in order to enjoy the benefits of CGT exclusivity.

FDA interprets this language to mean that the first approved applicant will forfeit eligibility for CGT exclusivity if the applicant fails to market within 75 days, beginning on the day *after* the date on which approval of the first approved applicant's application for the CGT is made effective, and not the date of approval itself. FDA further interprets this language to mean that a first approved applicant forfeits only its own eligibility for CGT exclusivity and such forfeiture does not affect the eligibility of any other first approved applicants. For example, assume the applicants for ANDA A and ANDA B are both first approved applicants. The applicant for ANDA A forfeits its eligibility for CGT exclusivity for failure to market within 75 days after the date of approval, but the applicant for ANDA B markets within 75 days after the date of approval and thus maintains its eligibility for CGT exclusivity. In such case, ANDA B would trigger the 180-day CGT exclusivity. Because ANDA A was approved prior to ANDA B triggering the 180-day CGT exclusivity, the applicant for ANDA A could market its CGT during the 180-day CGT exclusivity period (and thus benefit from ANDA B's exclusivity), even though the applicant for ANDA A forfeited its own eligibility for CGT exclusivity.

[46] If a first approved applicant's CGT exclusivity were triggered and selectively waived in favor of an applicant with an unapproved ANDA, the fact of the selective waiver in favor of the other applicant could be considered information in an unapproved ANDA. As such, FDA generally would not disclose that the selective waiver had occurred to anyone except the applicant in whose favor CGT exclusivity was waived, at least until the ANDA benefited by the waiver was approved. See 21 CFR 314.430(d)(1).

[47] Section 505(j)(5)(D)(iv) of the FD&C Act.

In the event that all first approved applicants forfeit their eligibility for CGT exclusivity, the CGT exclusivity is extinguished. The CGT exclusivity is only available to those ANDA applicants that meet the statutory definition of a first approved applicant, and the exclusivity does not *roll* to the next approved ANDA following forfeiture by all first approved applicants.[48]

In order to take advantage of this CGT exclusivity, eligible applicants should be prepared to begin commercially marketing the CGT within the requisite time period described above. For planning purposes, applicants can use their assigned GDUFA goal date as a guide to when action is expected and be prepared to commercially market the CGT within 75 days after that date.

E. Date of First Commercial Marketing

The date of the first approved applicant's first commercial marketing determines whether (and when) the 180-day CGT exclusivity period under section 505(j)(5)(B)(v) of the FD&C Act begins and whether that first approved applicant has forfeited its eligibility for exclusivity under section 505(j)(5)(D)(iv).[49] FDA generally would not be aware of the date of the first commercial marketing by a first approved applicant unless the first approved applicant notified FDA of the commencement of such marketing.[50]

Because the orderly operation of the 180-day CGT exclusivity period under section 505(j)(5)(B)(v)(I) of the FD&C Act and the forfeiture provision under section 505(j)(5)(D)(iv) requires that FDA know the date of the first approved applicant's first commercial marketing, we (1) will assume, for approval purposes, that no holder of CGT exclusivity has begun commercial marketing, and thus that no CGT exclusivity blocks approval of a subsequent ANDA, unless the first approved applicant provides FDA with written notification confirming that it has commenced commercial marketing of the CGT and (2) will assume that CGT exclusivity has been forfeited and thus would not block a subsequent approval if the first approved applicant has not provided FDA with written notification within the 75-day period confirming that it has commenced commercial marketing of the CGT.

To ensure that FDA receives timely notification of the date of first commercial marketing, FDA recommends that the first approved applicant submit a general correspondence to the ANDA

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[48] See section 505(j)(5)(B)(v)(II) and 505(j)(5)(B)(v)(III)(bb)(AA) of the FD&C Act.

[49] See generally 21 CFR 314.3(b) ("*Commercial marketing* is the introduction or delivery for introduction into interstate commerce of a drug product described in an ANDA, outside the control of the ANDA applicant, except that the term does not include transfer of the drug product for investigational use under part 312 of this chapter or transfer of the drug product to parties identified in the ANDA for reasons other than sale. Commercial marketing includes the introduction or delivery for introduction into interstate commerce of the reference listed drug by the ANDA applicant.").

[50] FDA's regulations and the statute do not require that a first approved applicant provide FDA with notification of the first commercial marketing of a competitive generic therapy. FDA's regulations at 21 CFR 314.107(c)(2) require that a "first applicant" (as defined in section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act) provide FDA with notice within 30 days of the first applicant's first commercial marketing. However, this requirement is limited only to a *first applicant* and does not apply to a *first approved applicant*, which is an ANDA applicant eligible for CGT exclusivity under section 505(j)(5)(B)(v) of the FD&C Act.

informing FDA that it has commenced marketing, with a duplicate copy of this correspondence submitted to the Office of Generic Drug's Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov.

F. Relationship Between CGT Exclusivity and 180-Day Patent Challenge Exclusivity

The CGT exclusivity period described at section 505(j)(5)(B)(v) and the 180-day patent challenge exclusivity period described at section 505(j)(5)(B)(iv), while sharing some basic structural similarities, are separate exclusivity schemes with their own specific eligibility criteria that generally function independently of each other. As noted above, the intent of each exclusivity is different, as 180-day patent challenge exclusivity provides an incentive to generic drug applicants to be the first to expose themselves to the risk of patent infringement litigation, which could enable generic drugs to be approved prior to patent expiry. CGT exclusivity provides an incentive to generic drug applicants to undertake the work to obtain the first approval of and promptly market drugs that had inadequate competition (and for which there were no unexpired patents or exclusivities listed in the Orange Book at the time of submission).

Although CGT exclusivity and 180-day patent challenge exclusivity remain distinct exclusivities, Congress included some limitations on an ANDA applicant's eligibility for CGT exclusivity related to 180-day patent challenge exclusivity for the applicable drug. Specifically, as noted earlier, the definition of first approved applicant in the CGT exclusivity provisions of the statute specifies that a potential first approved applicant must not: (1) otherwise be eligible for 180-day patent challenge exclusivity "for the drug that is the subject of the application for the competitive generic therapy"[51] or (2) have submitted an ANDA "for a drug for which all drug versions have forfeited eligibility for [180-day exclusivity]" under section 505(j)(5)(B)(iv) pursuant to section 505(j)(5)(D).[52]

With respect to the first eligibility limitation described above, FDA interprets this limitation to mean that a potential first approved applicant for a particular drug must not otherwise be eligible for 180-day patent challenge exclusivity for the same drug.[53] In most cases, a potential first approved applicant that otherwise meets the criteria for CGT exclusivity will not be excluded as a result of this limitation, as eligibility for CGT exclusivity requires that there be no unexpired patents listed in the Orange Book at the time of submission.[54] In contrast, eligibility for 180-day patent challenge exclusivity requires, among other things, the submission of a patent certification

[51] See section 505(j)(5)(B)(v)(III)(bb)(BB) of the FD&C Act.

[52] See section 505(j)(5)(B)(v)(III)(bb)(CC) of the FD&C Act.

[53] See section 505(j)(5)(B)(v)(III)(bb)(BB) of the FD&C Act.

[54] See section 505(j)(5)(B)(v)(III)(aa)(BB) of the FD&C Act.

asserting that a patent listed in the Orange Book is invalid, unenforceable, or will not be infringed.[55]

With respect to the second eligibility limitation described above, FDA interprets this limitation to mean that a potential first approved applicant's ANDA for a particular drug cannot be for a drug for which another ANDA applicant or applicants were eligible for 180-day patent challenge exclusivity and for which all such ANDA applicants have forfeited eligibility for 180-day patent challenge exclusivity.[56] This means that, for example, if prior to a potential first approved applicant's submission of its ANDA, other ANDA applicants for the same drug were eligible for 180-day patent challenge exclusivity but all such applicants forfeited their eligibility for 180-day patent challenge exclusivity, the potential first approved applicant would not qualify as a first approved applicant for the purposes of CGT exclusivity, even if the potential first approved applicant submitted its ANDA several years after the relevant forfeiture of the 180-day patent challenge exclusivity.

Given the different eligibility criteria for each exclusivity, CGT exclusivity and 180-day patent challenge exclusivity generally do not overlap in terms of timing or scope. However, there may be limited circumstances in which multiple ANDA applicants potentially are eligible for either CGT exclusivity or 180-day patent challenge exclusivity for the same drug at the same time. This could occur in the event that there are no patents or exclusivities listed in the Orange Book for a particular RLD at the time the original ANDA is submitted for a drug that has been designated as a CGT, but the holder of the NDA for the RLD later lists a patent for which other ANDA applicants first submit paragraph IV certifications to the relevant listed patent.

For example, assume that the applicant for ANDA C and the applicant for ANDA D are seeking approval of the same drug and each submits a substantially complete ANDA to FDA. Both ANDA C and ANDA D cover drugs that have been designated as CGTs consistent with section 506H(b)(3) of the FD&C Act.

ANDA C is submitted first and ANDA D is submitted one week after ANDA C. After ANDA C is submitted but before ANDA D is submitted, the NDA holder for the RLD timely lists a patent in the Orange Book for the RLD. ANDA D is submitted on the next day and includes a paragraph IV certification to the relevant listed patent.[57] The day after ANDA D is submitted, ANDA C is amended to include a paragraph IV certification to the same listed patent. In this scenario, the ANDA C applicant may qualify as a potential first approved applicant (for purposes of CGT exclusivity) because there were no unexpired patents or exclusivities at the time the ANDA was submitted to FDA and because ANDA C would not be eligible for 180-day patent challenge exclusivity. The applicant for ANDA D could qualify as a first applicant (for purposes

[55] See section 505(j)(5)(B)(iv)(I) of the FD&C Act, see also section505(j)(2)(A)(vii) of the FD&C Act and 21 CFR 314.94(a)(12)(i)(A).

[56] Section 505(j)(5)(B)(v)(III)(bb)(CC) of the FD&C Act.

[57] In this example, ANDA D would not qualify for CGT exclusivity due to the existence of unexpired patents listed in the Orange Book for its RLD at the time of submission.

of 180-day patent challenge exclusivity) because, among other things, it was the first applicant to submit a substantially complete ANDA containing a paragraph IV certification to a listed patent.

Because there may be multiple ANDA applicants that are eligible for either CGT exclusivity or 180-day patent challenge exclusivity for the same drug at the same time, questions exist as to how the two exclusivity schemes operate concurrently. As a practical matter, the potential for conflict is avoided because no applicant would be eligible for CGT exclusivity, as described above, until the CGT application is approved.

For 180-day patent challenge exclusivity, on the other hand, the statute restricts FDA from approving subsequent applicants' ANDAs (i.e., non-first applicant ANDAs that have submitted a paragraph IV certification to the relevant patent(s)) until (1) all first applicants have forfeited their eligibility for 180-day patent challenge exclusivity, or (2) the 180-day patent challenge exclusivity period has been triggered and run, or (3) the 180-day patent challenge exclusivity has been relinquished or waived.[58] Consequently, FDA generally could not approve ANDAs, including those ANDAs potentially eligible for CGT exclusivity, until one of these events has occurred.

If one of these events has occurred, an ANDA potentially eligible for CGT exclusivity could be fully approved. If all first applicants had forfeited eligibility for 180-day patent challenge exclusivity, no CGT exclusivity would be available. Otherwise, if the date of the approval constituted the first day on which any ANDA for such CGT is approved, the relevant 180-day CGT exclusivity period could be triggered if the first approved applicant commences marketing within 75 days after the date of approval.[59] Under such circumstances, CGT exclusivity and 180-day patent challenge exclusivity would not overlap and could be triggered in a sequential fashion.

For example, assume that the applicants for ANDA X and ANDA Y submit applications that reference the same RLD but are submitted on different dates with ANDA Y being submitted on a date after ANDA X. The applicant for ANDA X received a CGT designation for the drug in its application and is potentially eligible for CGT exclusivity. Because, among other things, ANDA Y challenges a patent that was listed after ANDA X is submitted, ANDA Y is determined to be eligible for 180-day patent challenge exclusivity.

Subsequently, FDA determines that ANDA X meets the substantive requirements for approval, though ANDA Y is still undergoing review by FDA and has not forfeited eligibility for 180-day patent challenge exclusivity. In this case, FDA generally could only tentatively approve ANDA X due to ANDA Y's continued eligibility for 180-day patent challenge exclusivity. However, once the 180-day patent challenge exclusivity period had been triggered and run, or relinquished/waived, ANDA X could be fully approved and potentially trigger its own 180-day CGT exclusivity period.

[58] See section 505(j)(5)(B)(iv)(I) of the FD&C Act.

[59] See section 505(j)(5)(B)(v)(I) and 505(j)(5)(B)(v)(III)(bb) of the FD&C Act.

G. Procedural Questions Regarding CGT Exclusivity Determinations

FDA will generally make decisions on exclusivity in the context of specific ANDAs that are otherwise eligible for approval (i.e., when a potential first approved applicant's ANDA or other non-first-approved applicant's ANDA is ready for approval). When FDA makes an approval decision for an ANDA, it will inform the applicant affected by exclusivity of its status. For example, for CGT exclusivity, FDA will generally include information in its action letter to the ANDA applicant to inform the applicant that it is (1) a first approved applicant that is eligible for 180 days of CGT exclusivity or (2) eligible only for a tentative approval because one or more first approved applicants are eligible for CGT exclusivity and have triggered the 180-day CGT exclusivity period.