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Development of Abbreviated New Drug Applications During the COVID-19 Pandemic – Questions and Answers

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Guidance for Industry

April 2021

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

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA web page titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, and the FDA web page titled "Search for FDA Guidance Documents," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents. You may also send an e-mail request to GenericDrugs@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Questions

For questions about this document, contact FDA's Office of Generic Drugs in the Center for Drug Evaluation and Research at GenericDrugs@fda.hhs.gov.

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Table of Contents

Development of Abbreviated New Drug Applications During the COVID-19 Pandemic – Questions and Answers

Guidance for Industry

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide general recommendations to prospective applicants and applicants of abbreviated new drug applications (ANDAs) related to generic drug product development and regulatory submissions in the form of questions and answers that have been received and addressed by FDA during the COVID-19 public health emergency.

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)).

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019," *available at* https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

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

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[1] In addition, on March 13, 2020, there was a Presidential declaration of a national emergency in response to COVID-19.[2]

FDA has received questions from prospective applicants and applicants of ANDAs about generic drug product development and application assessment during the COVID-19 public health emergency. FDA has collected these questions and is providing the responses in this guidance document for the benefit of all stakeholders. FDA intends to revise and update this guidance as appropriate to address new questions.

The questions and answers are presented in the following categories: A) generic drug product development; B) submission and assessment of ANDAs; and C) marketing and exclusivity.

III. Questions and Answers

A. Generic Drug Product Development[3]

The questions and answers in this section generally assume that bioequivalence (BE) studies being conducted to support the submission and approval of an ANDA have been delayed, interrupted or have not started due to the COVID-19 public health emergency. As a result, prospective applicants are faced with difficulty obtaining reference products (i.e., the reference standard (RS), which in

[1] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[2] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (March 13, 2020), *available at* https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/. On February 24, 2021, there was a Presidential Declaration continuing the national emergency concerning the COVID-19 pandemic beyond March 1, 2021. See Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic (February 24, 2021), available at https://www.federalregister.gov/documents/2021/02/26/2021-04173/continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic.

[3] As applicable to all questions and answers in this section, note that ultimately, whether an ANDA will be received for substantive review would be determined during the filing review of the ANDA. The acceptability of BE study data supporting the application would be determined during the scientific assessment of the ANDA.

most cases also will be the reference listed drug (RLD))[4] or with expiring reference products and/or test products. The questions and answers in this section address those concerns.

As a general matter, we recommend that prospective applicants take adequate precautions and have written procedures in place to ensure safety of study subjects and staff involved in the conduct of a BE study during/after the COVID-19 public health emergency.[5] Prospective applicants also must submit required premarket reports, including all serious adverse event reports required under 21 CFR 320.31(d)(3).[6]

Q1. If a test product batch used in the conduct of a BE study expires while the study is interrupted due to the COVID-19 public health emergency, can a prospective applicant continue using the test product batch or manufacture an additional test product batch to resupply the study when the study resumes?

A prospective applicant may use a test product batch that is beyond the currently established expiration dating period to resupply its BE studies as long as sufficient evidence can be provided to demonstrate the acceptability of the test product batch. A prospective applicant that wants to utilize this approach should submit data to ensure the test batch samples stored at the long-term stability conditions beyond the current expiration date are in compliance with the finished drug product shelf-life specifications at the time of conducting the BE study. The test batch may be considered acceptable if the submitted stability data meet the drug product shelf-life specifications. The acceptability of this approach will be determined during the ANDA review.

Alternatively, a prospective applicant generally would be permitted to manufacture additional test product to resupply its BE studies, subject to the following recommendations:

- The new test product batch (with the same formulation) should be manufactured using the same equipment under the same manufacturing conditions as those for the previously manufactured test batches, that is, using the same equipment under the same conditions as those for full-scale production.[7] The batch size of the proposed new test product batch should be based on the batch size recommendations provided in the guidance for industry *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* (May 2014).

- If the test product batch has expired after in vitro BE studies but before the in vivo pharmacokinetic (PK) BE study can be completed and an applicant decides to manufacture a new test product batch, the newly manufactured unexpired test product batch(es) should be used in the in vivo PK BE study as well as in repeat in vitro BE studies. If an in vivo comparative clinical endpoint BE study, coupled with in vivo

[4] See 21 CFR 314.3(b) defining reference listed drug and reference standard and the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020). 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-fda-guidance-documents.

[5] See the guidance for industry *Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency* (January 2021).

[6] See the draft guidance for industry *Sponsor Responsibility – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability / Bioequivalence Studies* (June 2021).

[7] See 21 CFR 320.25(i)(2).

PK BE study and in vitro BE studies, is recommended in the product-specific guidance, the same unexpired test product batch should be used where possible for all three studies (i.e., in vivo comparative clinical endpoint BE study, in vivo PK BE study, and in vitro BE studies). Where possible, an in vivo comparative clinical endpoint BE study should be conducted using at least one batch of the reference products that were used in vivo PK BE study and in vitro BE studies.

- The instrument and testing conditions should be the same as those used for any in vitro and/or in vivo BE studies already conducted with the previous test product and reference product batches. Any differences should be clearly indicated and scientifically justified in the ANDA submission.

Regarding a comparative clinical endpoint BE study, a PK endpoint BE study, or an in vitro BE study, a prospective applicant should include the complete data sets, protocols, reports, and statistical analyses in the ANDA submission.

A prospective applicant should also include the certificate of analysis of test and reference product batches used in the pivotal BE study(ies) in the ANDA submission. In addition, prospective applicants should retain a sufficient quantity of reserve samples (both test and reference product).[8]

Q2. If a development program was interrupted by the COVID-19 public health emergency, and a reference product batch used in BE studies expires before the program can be resumed and prior to completion of all necessary studies, can the prospective ANDA applicant utilize another, unexpired batch of the reference product to complete the remaining studies?

It may be acceptable to utilize a different batch of unexpired reference product to complete a BE study, so long as the prospective applicant provides adequate scientific justifications for the use of different batches of reference product in the BE studies. A prospective applicant that intends to use a different batch of reference product for such purposes may submit additional inquiries with specific proposals or alternative proposals to demonstrate BE for the development program via the controlled correspondence pathway,[9] or, if applicable, via the pre-ANDA meeting request pathway.[10]

Q3. Can a prospective ANDA applicant utilize an expired batch of reference product to complete BE studies that have been interrupted?

In general, use of a batch of expired reference product to complete BE studies is not acceptable. A drug product's expiration date, as determined by appropriate stability testing, provides assurance that the drug product meets the applicable standards of identity, strength, quality, and purity at the time of use.[11] Use of an expired reference product batch for BE

[8] See 21 CFR 320.38; 21 CFR 320.63. See also the guidance for industry *Compliance Policy for Quantity of Bioavailability and Bioequivalence Samples Retained Under 320.38(c)* (August 2020).
[9] See the guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020).
[10] See the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (November 2020).
[11] 21 CFR 211.137.

testing would generally not be acceptable to determine BE, because the safety and effectiveness of the product beyond the labeled expiration date is not known.

A prospective applicant may choose to propose alternative approaches to demonstrate BE between test and reference products that utilize testing conducted thus far. Prospective applicants may submit additional inquiries with any specific proposals or alternative proposals to demonstrate BE for their individual development program via the controlled correspondence pathway, or, if applicable, via the pre-ANDA meeting request pathway.[12]

Q4. Can a prospective ANDA applicant use two or more batches of the reference product to complete a BE study?

In general, it is permissible to use more than one batch of reference product when conducting a BE study. A prospective applicant using more than one batch of reference product is reminded to record the batch numbers of both test and reference products and the expiration date for the reference product, as well as retain a sufficient quantity of reserve samples (of both test and reference products).[13] The certificate of analysis of test and reference product batches used in the pivotal BE study should be included in the ANDA submission.

Q5. Can a prospective applicant use a product that was not approved in the United States as a reference standard to conduct BE studies?

FDA has issued a response to a citizen petition on the permissibility of using a product not approved in the United States in BE testing.[14] As described in that response, section 505(j)(2)(A)(iv) of the FD&C Act requires ANDA applicants to include information showing that their proposed new drug is bioequivalent to a previously approved *listed drug*. Listed drugs are those that have been approved for safety and effectiveness under section 505(c) of the FD&C Act or approved under section 505(j) of the FD&C Act (section 505(j)(7) of the FD&C Act; 21 CFR 314.3). A non-U.S.-approved product has not been approved under section 505(c) or (j) of the FD&C Act and is not a listed drug within the statutory meaning. Because of the potential for bioequivalence inconsistencies that may result from even slight differences between a non-U.S.-approved product and the U.S. RLD (for example: small differences in critical specifications could potentially affect key performance characteristics), it is Agency policy not to accept BE studies based on a non-U.S.-approved product to show that a drug is bioequivalent to the U.S. RLD.

Q6. Can a prospective ANDA applicant utilize staggered dosing and/or bioanalysis for samples collected from a group of dosed participants, in an effort to preserve social distancing at the study site or in the bioanalytical laboratory?

In general, conducting a study in multiple groups in a staggered fashion may be acceptable. Prospective applicants interested in such an approach should consider the following:

- Whether amendments may be needed to any study protocol, which detail the proposed changes

[12] See footnotes 9 and 10.
[13] See 21 CFR 320.63.
[14] Letter from Janet Woodcock to Michael H. Hinckle (November 17, 2014), Docket No. FDA-2013-P-0846.

- The potential influence of a group effect for the statistical analysis
- How to minimize bias based on timing of dosing and/or bioanalysis of all samples
- How to ensure proper blinding of sample testing personnel
- The need for prespecified modification of the statistical analysis plan (ideally prior to sample collection)
- The potential need for supportive stability data to establish sample stability (from time of first sample collection to time of completion of sample analysis)

Additionally, in line with the recommendations in the guidance for industry *Conduct of Clinical Trials of Medical Products During the COVID-19 Pandemic* (March 2020) prospective applicants should establish and implement (or revise, as applicable) policy and procedures to describe the approaches and controls to be used to ensure the reliability of the statistical analyses and to maintain the study blind.[15]

Q7. Can a prospective ANDA applicant submit its in vivo BE study data with a truncated sampling scheme if some of the last ambulatory study samples could not be collected?

In general, if the drug product has a long terminal elimination half-life (>24 hours) and the missing samples are the last ambulatory study samples, the prospective ANDA applicant may truncate the sampling scheme to appropriate time points (i.e., 72 hours), with the area under the curve (AUC) truncated to 72 hours in place of AUC0-t or AUC0-∞, as long as the data up to 72 hours adequately characterize the peak concentration (Cmax) and time to reach peak concentration (Tmax). There may be certain instances when this option may not be appropriate. We recommend that if you have questions specific to your modified development plan that you utilize the controlled correspondence pathway, or if applicable, the pre-ANDA meeting request pathway.[16]

If the drug product is not a long terminal elimination half-life drug, or the missing samples are more than the last few sampling time points, the prospective ANDA applicant may propose a specific alternative proposal to demonstrate BE for their individual development program via the controlled correspondence pathway, or, if applicable, via the pre-ANDA meeting request pathway.[17]

Q8. Can a prospective ANDA applicant suggest an alternative study proposal such as *interim analysis* or *remote study design* to mitigate the effects of limitations due to the COVID-19 public health emergency?

FDA acknowledges the impact of the COVID-19 public health emergency on the ability to conduct in vivo PK and comparative clinical endpoint BE studies, including for example, the hardship of study recruitment. FDA recommends that prospective ANDA applicants submit their specific alternative study proposal to demonstrate BE for their individual development program via the controlled correspondence pathway, or, if applicable, via the pre-ANDA meeting request pathway.[18]

[15] See the guidance for industry *Conduct of Clinical Trials of Medical Products During the COVID-19 Pandemic* (September 2020), updated January 27, 2021.
[16] See footnotes 9 and 10.
[17] See footnotes 9 and 10.
[18] See footnotes 9 and 10.

B. ANDA Submission, Receipt, and Assessment

The questions and answers in this section focus on questions from prospective applicants related to the submission, receipt, and assessment of ANDAs for drug products: 1) that could be used to help address the COVID-19 public health emergency; and/or 2) for which the development process has been impacted by the COVID-19 public health emergency. In general, the generic drug products that may be used to help address the COVID-19 public health emergency include those drug products being investigated to treat or prevent COVID-19 and drug products that are being used for their labeled use to treat secondary conditions associated with COVID-19.

Q9. If an applicant submits an ANDA for a generic drug product that could be used to help address the COVID-19 public health emergency, will assessment of such an ANDA be expedited?

Recognizing the public health emergency related to COVID-19 declared by the HHS Secretary, FDA is prioritizing the review of ANDA submissions that could help address COVID-19. Certain public health priorities (or prioritization factors) may qualify an ANDA for a priority review.[19] One prioritization factor considers whether the submission could help address a declared public health emergency. As part of its evaluation of whether a submission could help address the current public health emergency, FDA will consider whether the ANDA is (1) for a drug being investigated to treat or prevent COVID-19, but is not labeled for this use, or (2) for a drug being used for its labeled use to treat or prevent secondary conditions associated with COVID-19. FDA evaluates whether an ANDA submission meets the criteria for priority review at the time of submission.[20]

Q10. Will an ANDA for a drug product that could be used to help address the COVID-19 public health emergency be subject to a receipt evaluation upon submission?

Each ANDA, including those submitted during the COVID-19 public health emergency and for drug products intended to address this public health emergency, will be subject to a receipt evaluation to ensure the ANDA is substantially complete. FDA evaluates each submitted ANDA to determine whether the ANDA can be received for substantive review. The receipt of an ANDA means that FDA made a threshold determination that the ANDA is a substantially complete application, that is, an ANDA that on its face is sufficiently complete to permit a substantive review.[21] *Sufficiently complete* means that the ANDA contains all the information required under section 505(j)(2)(A) of the FD&C Act and does not contain a deficiency described in 21 CFR 314.101(d) and (e).[22]

[19] CDER's Manual of Policies and Procedures (MAPP) 5240.3 Rev. 5 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements, available at* https://www.fda.gov/media/89061/download.
[20] Ibid.
[21] See 21 CFR 314.101(b)(1) and 314.3(b).
[22] 21 CFR 314.3(b).

Q11. Will FDA receive an ANDA with less than the full complement of recommended batch stability data?

In general, an ANDA applicant should provide 3 pilot-scale batches or 2 pilot-scale and one small-scale batch with both accelerated and long-term stability data provided for each batch covering a period of no less than 6 months (180 days), with data from 3 time points (e.g., 0, 3, and 6 months). If 6 months of accelerated data show a significant change or failure of any attribute in one or more batches, the applicant should also include 6 months' (180 days') worth of intermediate stability studies at the time of submission.[23] Any deviation from the foregoing recommendations should be accompanied by a scientific justification explaining how the relevant data that is submitted in the application meets the applicable statutory and regulatory requirements. Such justification should be provided in the original ANDA, along with a written statement certifying that the omitted stability data will be provided when it becomes available. If a prospective ANDA applicant intends to submit an ANDA with stability data covering a period of less than 6 months, FDA recommends that the prospective ANDA applicant submit a request for FDA concurrence to this approach via the controlled correspondence pathway.[24] FDA will generally accept requests to receive an ANDA with less than the full complement of recommended stability data if the drug product is on FDA's Drug Shortage List or FDA confirms that the drug product is vulnerable to shortage. In addition, during the COVID-19 public health emergency, FDA will generally accept such requests if the drug product meets the criteria for priority review to help address the COVID-19 public health emergency as described above in Question and Answer 9.

Q12. Will FDA receive an ANDA that does not contain complete BE study data, but does contain a commitment to provide such data during the assessment of the ANDA? For example, can a prospective ANDA applicant submit only in vitro dissolution data at filing, and submit in vivo PK BE study data during the ANDA assessment cycle? Or can a prospective ANDA applicant submit partial data from in vivo BE studies (e.g., an in vivo PK BE study data under fasting condition only) at the time of submission, and submit the remaining data from in vivo BE studies (e.g., an in vivo PK BE study data under fed condition) during the ANDA assessment cycle?

FDA likely would not receive an ANDA that does not contain completed BE study data. FDA may refuse to receive an application if the ANDA "does not on its face contain information required under section . . . 505(j) of the Federal Food, Drug, and Cosmetic [FD&C] Act and . . . [21 CFR] 314.94."[25] With respect to BE information, 21 CFR 314.94(a)(7) requires an ANDA to contain information that purports to show that the proposed generic drug product is bioequivalent to the reference listed drug (RLD).

FDA recommends that applicants submit a full data package at the time of ANDA submission. An ANDA containing only partial data at the time of submission on the grounds that the applicant cannot complete bioequivalence studies due to the COVID-19 public health emergency does not constitute an acceptable alternative approach that complies with the

[23] See 21 CFR 314.50(d)(1)(i), 21 CFR 314.50(d)(1)(ii), and the guidances for industry *ANDAs: Stability Testing of Drug Substances and Products* (June 2013), and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* (May 2014).
[24] See footnote 9.
[25] 21 CFR 314.101(d)(3).

relevant statute and regulations. Specifically, an ANDA with only partial data would not, on its face, contain information that purports to show that the proposed generic drug product is bioequivalent to the RLD, as required by statute and FDA's implementing regulations.

Q13: If an application includes sites that cannot be inspected because of travel restrictions, will an application automatically receive a complete response letter?

Applications will not automatically receive a complete response letter if FDA cannot conduct an inspection. Decisions regarding applications will be based on the totality of the information available to FDA, including information obtained from use of the tools available to FDA and as described in the guidance for industry *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers* (August 2020), updated on May 17, 2021.

C. Marketing and Exclusivity

The questions and answers in this section are intended to address questions FDA has received about marketing status and the impact on exclusivity that may be granted to certain generic drug products.

Q14. Is there a mechanism to permit marketing of a tentatively approved generic drug product that could be used to help address the COVID-19 public health emergency?

If an ANDA otherwise meets the requirements for approval but cannot be approved by FDA because of an unexpired patent(s) or exclusivity(ies) as described below, FDA will tentatively approve the ANDA. *Tentative approval* (TA)

> is notification that an NDA [new drug application] or ANDA otherwise meets the requirements for approval under the [FD&C] Act, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the [FD&C Act] and [21 CFR] 316.31 …, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the [FD&C Act], but cannot be approved until the conditions in § 314.107(b)(1)(iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the [FD&C Act]; because there is a period of exclusivity for the listed drug under section 505E of the [FD&C Act]; or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the NDA or ANDA may be approved no earlier than the date specified.[26]

Under section 505 of the FD&C Act, a drug product that is the subject of a tentatively approved ANDA is not an approved drug and does not have an effective approval until FDA issues an approval after any necessary additional review of the application.[27] Accordingly, there is no mechanism by which FDA can convert a tentatively approved ANDA to final approval and permit marketing until the ANDA meets all the requirements for final approval.

[26] 21 CFR 314.3(b). See also section 505(j)(5)(B)(iv)(II)(dd)(AA) of the FD&C Act and 21 CFR 314.105(d).
[27] See section 505(j)(5)(B)(iv)(II)(dd)(BB) of the FD&C Act; see also 21 CFR 314.105(d).

Q15. The COVID-19 public health emergency has impacted FDA's ability to conduct certain domestic and foreign inspections. What impact, if any, will that have on forfeiture of a first applicant's eligibility for 180-day generic drug exclusivity?

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) describes, among other things, certain events that can result in the forfeiture of a first applicant's[28] eligibility for 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv) of the FD&C Act, including failure to obtain tentative approval within 30 months after the date on which the application is filed unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.[29]

The "failure to obtain tentative approval" forfeiture provision establishes a bright-line rule: if within 30 months after the date of submission, an ANDA has been determined by the Agency to meet the statutory standards for approval and it is only patent and/or exclusivity protection that prevents full approval, then an applicant will be given a tentative approval and will maintain eligibility for 180-day exclusivity. If tentative approval or final approval is not obtained within 30 months, eligibility for 180-day exclusivity is generally forfeited unless "the failure [to obtain an approval] is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed."

In making forfeiture decisions, the Agency considers the specific facts and circumstances relevant to the ANDA under consideration. In addition, for certain 180-day exclusivity decisions that require analysis by FDA, including those under the "failure to obtain tentative approval" in 30 months provision, it is FDA's practice to make these decisions in the context of specific ANDAs that are otherwise eligible for approval (i.e., when a first applicant's ANDA or a subsequent applicant's ANDA is ready for approval). Accordingly, whether FDA's inability to conduct certain inspections will factor into 180-day exclusivity decisions will be determined on a case-by-case basis.

[28] A *first applicant* is an ANDA applicant that, on the first day on which a substantially complete ANDA containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete ANDA that contains and lawfully maintains a paragraph IV certification. See section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act.
[29] Section 505(j)(5)(D)(i)(IV) of the FD&C Act.