Guidance for Industry

180-Day Exclusivity: Questions and Answers

DRAFT GUIDANCE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)
Center for Biologics Evaluation and Research (CBER)

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Generic Drugs

Guidance for Industry

180-Day Exclusivity: Questions and Answers

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180-Day Exclusivity: Questions and Answers[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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to address questions that have been raised about the provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) that relate to generic drug exclusivity, which commonly is known as *180-day exclusivity* for generic drug products. As a general matter, the Food and Drug Administration (FDA or the Agency) has implemented these statutory provisions within the context of application-specific decisions. Some FDA decisions have been made publicly available (e.g., in FDA citizen petition responses and documents released in litigation). In addition, in certain circumstances where a novel issue of interpretation was raised by a particular factual scenario regarding forfeiture of 180-day exclusivity, FDA has opened a public docket or otherwise sought comment from affected parties in advance of taking an action. Also, in certain instances, applicants have submitted correspondence to their abbreviated new drug applications (ANDAs) regarding 180-day exclusivity, which FDA has considered in making decisions. FDA believes that a guidance for industry that provides answers to commonly asked questions about 180-day exclusivity would enhance transparency and facilitate the development, approval, and timely marketing of generic drug products. FDA intends to update this guidance to include additional questions and answers (Q&As) as appropriate.

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

II. BACKGROUND

The *Drug Price Competition and Patent Term Restoration Act of 1984* (the Hatch-Waxman Amendments)[2] to the FD&C Act established the ANDA approval pathway for generic drugs.[3] In

[1] This guidance has been prepared by the Office of Generic Drug Policy in the Center for Drug Evaluation and Research at the Food and Drug Administration.
[2] Public Law 98-417.

2003, Congress enacted the *Medicare Prescription Drug, Improvement, and Modernization Act of 2003* (MMA),[4] which, among other things, substantially revised certain statutory provisions related to 180-day exclusivity. In this guidance, we will discuss 180-day exclusivity as it pertains to ANDAs subject to the MMA statutory provisions. This guidance does not discuss 180-day exclusivity as it pertains to ANDAs subject to the pre-MMA statutory provisions. In Section III.A, we describe how to determine which statutory scheme applies to a particular ANDA.

A. ANDA Approval Pathway

The process for obtaining approval to market an innovator drug approved under a new drug application (NDA) differs from that for obtaining approval to market a generic drug under an ANDA. A sponsor of an innovator drug must submit an NDA, which must contain, among other things, a demonstration of the safety and effectiveness of the drug for the conditions of use for which approval is sought.[5] In its application, an NDA applicant must submit information for each patent that claims the drug or method of using the drug and for which a claim of patent infringement could reasonably be asserted against a person engaged in the unlicensed manufacture, use, or sale of the drug product.[6] Upon approval of an NDA, FDA publishes this patent information in its publication *Approved Drug Products with Therapeutic Equivalence Evaluations*, known as the *Orange Book.*[7]

To obtain approval of a generic drug, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug. Instead, the applicant relies on FDA's previous finding that the reference listed drug (RLD)[8] relied upon by the ANDA applicant is safe and effective. The ANDA applicant must identify the RLD on which it seeks to rely and, among other things, demonstrate, with limited exceptions, that the proposed generic drug has the same active ingredient(s), route of administration, dosage form, and strength as the RLD.[9] A generic drug also must have the same conditions of use and the same labeling as the RLD (except for certain permissible labeling differences),[10] and the applicant must demonstrate that its proposed generic drug is bioequivalent to the RLD.[11]

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[3] For the purpose of this guidance, the term *generic drug* refers to a new drug product for which approval is sought or has been obtained in an ANDA submitted under section 505(j) of the FD&C Act.

[4] Public Law 108-173.

[5] Section 505(b)(1) of the FD&C Act.

[6] Id. See also section 505(c)(2) of the FD&C Act.

[7] The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[8] An RLD is the listed drug identified by FDA as the drug product on which an ANDA applicant relies in seeking approval of its ANDA. 21 CFR 314.3(b).

[9] A generic drug with the same active ingredient, dosage form, route of administration, and strength as the RLD is considered pharmaceutically equivalent to that product. See also 21 CFR 314.3(b).

[10] See section 505(j)(2)(A)(i), (v) of the FD&C Act. An example of a permissible difference in labeling would be a difference when an ANDA applicant is not seeking approval for a use protected by patent or exclusivity pursuant to section 505(j)(2)(A)(viii) of the FD&C Act and 21 CFR 314.94(a)(8)(iv).

[11] See section 505(j)(2)(A)(iv) of the FD&C Act. Therapeutically equivalent products are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. 21 CFR 314.3(b).

B. Patent Certification and 180-day Exclusivity

The timing of ANDA approval depends on, among other things, the patent and exclusivity protections for the RLD. An applicant must provide in its ANDA additional information related to any patents for the RLD. In particular, the ANDA applicant generally must submit to FDA one of four specified certifications regarding the patents for the RLD under section 505(j)(2)(A)(vii) of the FD&C Act.

If the Orange Book does not list a patent for the RLD, the ANDA applicant must certify:

1. That such patent information has not been submitted by the NDA holder for listing in the Orange Book (a paragraph I certification).[12]

With respect to each patent listed in the Orange Book for the RLD, the applicant's patent certification must state one of the following:

2. That such patent has expired (a paragraph II certification)
3. The date on which such patent will expire (a paragraph III certification)
4. That such patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).[13]

If an applicant submits a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant submits a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking final approval of its ANDA. If, however, an applicant wishes to seek approval of its ANDA ***before*** a listed patent has expired by challenging the validity of a patent, claiming that a patent would not be infringed by the product proposed in the ANDA, or claiming a patent is unenforceable, the applicant must submit a paragraph IV certification to FDA.

The FD&C Act describes only one circumstance in which an ANDA applicant need not certify to a listed patent. Specifically, when a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use from the generic drug's labeling can submit a *section viii statement*, acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval.[14]

An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner notice of its paragraph IV certification, including a description of the legal and factual basis for the ANDA applicant's assertion that the patent is invalid,

[12] 21 CFR 314.94(a)(12)(i)(A). If in the opinion of the ANDA applicant and to the best of its knowledge there are no patents claiming the drug product, drug substance, or method of use of the drug product, the applicant must submit to its ANDA a certification stating that opinion. 21 CFR 314.94(a)(12)(ii).

[13] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).

[14] See section 505(j)(2)(A)(viii) of the FD&C Act. See also 21 CFR 314.94(a)(12)(iii).

unenforceable, or will not be infringed.[15] If a patent is listed at the time an ANDA is submitted and, in response to notice of a paragraph IV certification, the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the later of the date of receipt of the notice by any owner of the patent or the NDA holder or such shorter or longer time as the court might order.[16] If a patent is listed in the Orange Book after an ANDA is submitted but before it is approved, the applicant for the pending ANDA generally must amend its application and provide an appropriate patent certification or statement to the newly listed patent; however, no 30-month stay will be available in this circumstance.[17]

The statute provides an incentive and a reward to generic drug applicants that expose themselves to the risk of patent litigation. It does so by granting a 180-day period of exclusivity *vis-à-vis* certain other ANDA applicants to the applicant that is first to file a substantially complete ANDA containing a paragraph IV certification to a listed patent. If only one such ANDA is filed on the first day, there is only one *first applicant*; if two or more such ANDAs are filed on the first day, the ANDA applicants share first-applicant status.[18] If an ANDA contains a paragraph IV certification for a relevant patent and the ANDA is not that of a first applicant, the ANDA applicant is regarded as a *subsequent applicant*.[19]

If an ANDA meets the substantive requirements for approval, but cannot be finally approved due to unexpired patents or exclusivities, FDA will tentatively approve the ANDA. *Tentative approval* "means notification to an applicant by [FDA] that an [ANDA] meets the requirements of [section 505(j)(2)(A) of the FD&C Act] but cannot receive effective approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section 505A, or there is a 7-year period of exclusivity for the listed drug under section 527."[20]

The FD&C Act describes a number of conditions under which an ANDA applicant may forfeit eligibility for 180-day exclusivity. These forfeiture events can be generally described as: (1) failure to market; (2) withdrawal of application; (3) amendment of certification; (4) failure to obtain tentative approval; (5) entry into agreement with another applicant, the listed drug

[15] Section 505(j)(2)(B) of the FD&C Act.

[16] Section 505(j)(5)(B)(iii) of the FD&C Act and 21 CFR 314.107(b)(3)(i).

[17] Id. See also 21 CFR 314.94(a)(12)(vi).

[18] As described in Question 2, an applicant that submitted a substantially complete ANDA without a paragraph IV certification may become eligible for 180-day exclusivity by amending its application to contain a paragraph IV certification to a listed patent on the first day that an ANDA or amendment containing a paragraph IV certification is submitted for that RLD.

[19] See section 505(j)(5)(B)(iv)(I), (II)(aa) and 505(j)(5)(D)(iii) of the FD&C Act. See also 21 CFR 314.107(c)(1); *Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule*, 81 FR 69580, 69627-69628 (Oct. 6, 2016).

[20] Section 505(j)(5)(B)(iv)(II)(dd)(AA) of the FD&C Act. See also 21 CFR 314.3(b) (defining *tentative approval* to also include, among other things, notification that an ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved 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 ANDA may be approved no earlier than the date specified) and 21 CFR 314.105.

application holder, or a patent owner; and (6) expiration of all patents.[21] Under these provisions, if certain events occur, an applicant eligible for 180-day exclusivity at the time its ANDA was submitted (first applicant) may forfeit eligibility for 180-day exclusivity. If all first applicants forfeit their eligibility for 180-day exclusivity, no applicant will be eligible for 180-day exclusivity, and FDA may approve subsequent applicants' ANDAs, subject to the approval requirements of the FD&C Act.

FDA has received a number of questions about 180-day exclusivity and has identified the following commonly asked questions for inclusion in this guidance. FDA expects the following information to enhance transparency and facilitate the development, approval, and timely marketing of generic drugs. FDA intends to update this guidance to include additional Q&As as appropriate.

III. QUESTIONS AND ANSWERS

A. Applicable Statutory Scheme

Q1. How does FDA determine whether the pre-MMA or MMA provisions of the FD&C Act apply to a particular ANDA?

Section 1102(b)(1) of the MMA provides that the MMA 180-day exclusivity provisions are effective only with respect to an ANDA filed after the date of enactment (i.e., December 8, 2003) for a listed drug for which no paragraph IV certification was made before that date.[22] The following list illustrates how FDA has applied this *effective date* provision in particular situations:

- If all ANDAs referencing a particular RLD are submitted to FDA after December 8, 2003 (and thus no paragraph IV certification could have been submitted before December 8, 2003), the MMA 180-day exclusivity provisions apply to all of the ANDAs.
- If at least one ANDA with a paragraph IV certification to a listed patent for the RLD was submitted before December 8, 2003, all ANDAs referencing that RLD (including ANDAs submitted after December 8, 2003) are governed by the pre-MMA statutory provisions.
- If one or more ANDAs referencing a particular RLD were submitted before December 8, 2003, but the first paragraph IV certification was submitted after December 8, 2003, the pre-MMA provisions govern for any ANDA referencing that RLD (whether or not that particular ANDA was filed before or after December 8, 2003), because section 1102(b)(1) of the MMA is based on the date of submission of the first application, not on the date of the first paragraph IV certification.

FDA has concluded that the effective date provision imposes the same statutory scheme on all ANDAs referencing a specific RLD. An attempt by FDA to apply both pre-MMA and MMA

[21] Section 505(j)(5)(D) of the FD&C Act.
[22] Section 1102(b)(1) of the MMA.

statutory schemes to a single group of applications with a common RLD could result in conflict between the MMA and pre-MMA provisions. The eligibility, triggering, and forfeiture features of the different 180-day exclusivity schemes could render one applicant ineligible for exclusivity while another applicant could retain its eligibility. To avoid these inequitable outcomes, all ANDAs submitted referencing the same RLD will be subject to one statutory scheme.

B. First Applicants

Q2. How does an ANDA applicant qualify as a "first applicant"?

A *first applicant* is an ANDA "applicant that, on the first day on which a substantially complete application containing a [paragraph IV] certification … is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a [paragraph IV] certification … for the drug."[23]

An applicant that previously submitted a substantially complete ANDA that did not contain a paragraph IV certification may become eligible for 180-day exclusivity by amending its ANDA to contain a paragraph IV certification to a listed patent for the RLD on the first day that an ANDA or amendment containing a paragraph IV certification is submitted.

The listed patent or patents to which an ANDA applicant submitted a paragraph IV certification that gives rise to the eligibility for 180-day exclusivity is referred to in this draft guidance as the *qualifying patent(s)*.

Q3. What constitutes a substantially complete application?

A s*ubstantially complete application* is an ANDA that on its face is sufficiently complete to permit a substantive review. 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).[24] FDA indicates its determination that an ANDA is substantially complete when the Agency *receives* the ANDA for review under 21 CFR 314.101. If FDA determines, after an initial evaluation, that an ANDA was substantially complete as of the date it was submitted to FDA, FDA will consider the ANDA to have been received as of the date of submission.[25]

Q4. Does an ANDA applicant have to be the first to submit a paragraph IV certification to all of the RLD's listed patents to be a first applicant?

No. The statute requires "a" paragraph IV certification;[26] it does not require a first applicant to be the first to submit a paragraph IV certification to more than a single patent (or all of the patents), even if multiple patents are listed for the RLD.

[23] Section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act; see also 21 CFR 314.3(b).
[24] 21 CFR 314.3(b); see also section 505(j)(5)(B)(iv)(II)(cc) of the FD&C Act.
[25] 21 CFR 314.101(b)(2).
[26] Section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act.

There can be multiple patents that could qualify a single ANDA applicant as a first applicant, so long as they are certified to on that same first day that the first paragraph IV certification in an ANDA for that RLD is submitted. As a result, each qualifying patent separately can affect exclusivity. For example, if an ANDA applicant submitted paragraph IV certifications to two separate patents on the same first day and the first patent expires prior to triggering of 180-day exclusivity, the paragraph IV certification to the second patent can remain a basis for first-applicant status and for 180-day exclusivity.

Q5. Can an ANDA applicant qualify as a first applicant when it includes both a paragraph IV certification and a section viii statement to a single listed patent?

Yes. FDA has determined that when both drug product or drug substance claims and method-of-use claims are contained within the same patent, an applicant may file a paragraph IV certification with respect to the drug product or drug substance patent claim(s) and a section viii statement with respect to the method-of-use claim(s) in the patent. This type of certification is commonly referred to as a *split certification*. This approach preserves the NDA holder's statutory right to assert its patent rights regarding the drug substance or drug product claims before ANDA approval while permitting the ANDA applicant to exercise its statutory right to avoid infringing a method-of-use claim by seeking approval for fewer than all of the approved conditions of use for the RLD. Consistent with this principle, the paragraph IV certification in a split certification can qualify an applicant for first applicant eligibility.

Q6. Can an ANDA applicant be a first applicant if the applicant includes a paragraph III certification to a patent that expires after the patent to which a paragraph IV certification was submitted?

Yes. The statutory definition of "first applicant" requires "a" paragraph IV certification. The statute does not require that the paragraph IV certification be to the latest expiring patent. For example, a first applicant could have a paragraph IV certification to a patent expiring on January 1, 2020 (the only qualifying patent) and a paragraph III certification to a patent expiring on June 1, 2030.

Q7. Could the timing of sending notice of paragraph IV certification affect first applicant status?

Yes. For original ANDAs, notice of paragraph IV certification must be provided on or after the date on which the applicant receives a paragraph IV acknowledgment letter from FDA, but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter.[27] The paragraph IV acknowledgment letter is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that an ANDA containing a paragraph IV certification is sufficiently complete to permit a substantive review and has been received for

[27] 21 CFR 314.95(b)(1).

review.[28] Any notice sent before the ANDA applicant's receipt of a paragraph IV acknowledgment letter is invalid.[29]

For amendments containing a paragraph IV certification submitted before the ANDA has been received for review (i.e., before receipt of a paragraph IV acknowledgment letter), the ANDA applicant must send notice according to the timeframe described above for original ANDAs. If an ANDA applicant's notice of its paragraph IV certification is timely provided and the applicant has not submitted a previous paragraph IV certification, FDA will base its determination of whether the ANDA applicant is a first applicant on the date of submission of the amendment containing the paragraph IV certification.[30]

For amendments submitted after the ANDA has been received for review (i.e., after receipt of an acknowledgment letter or a paragraph IV acknowledgment letter) and supplements, notice of paragraph IV certification must be provided at the same time that the amendment or supplement is submitted to FDA. If notice is not sent simultaneously with an amendment or supplement, FDA considers the paragraph IV certification not to be effective until notice is provided.[31] For example, if an ANDA applicant submitted a supplement containing a paragraph IV certification, but notice of the paragraph IV certification was not provided until 30 days after the submission of the supplement, FDA would evaluate whether the applicant was a first applicant based on the date notice was provided, rather than the date of submission of the supplement. Thus, a delay in giving notice of certain amendments or supplements could mean a later date for the paragraph IV certification to become effective which could result in failure to obtain first applicant status (if another applicant submits a certification that becomes effective in the interim).

Regardless of whether it is an original ANDA, an amendment, or a supplement, a paragraph IV certification must not be submitted earlier than the first working day after the day the patent is published in the Orange Book.[32] Any notice sent before the first working day after the day the patent is published in the Orange Book is invalid.[33]

Q8. What does it mean to "lawfully maintain" a paragraph IV certification?

The definition of first applicant requires that the applicant "lawfully maintain[] a [paragraph IV] certification."[34] This requires an uninterrupted paragraph IV certification to the qualifying patent or patent claim. For example, an applicant has not lawfully maintained its paragraph IV certification if the applicant initially submits a paragraph IV certification to a patent or patent claim, and then later amends its ANDA to include a paragraph III certification or a section viii statement to the qualifying patent or patent claim, and then amends its ANDA again to include a paragraph IV certification to the same patent or patent claim. However, if the applicant initially submits a paragraph IV certification to a qualifying patent or patent claim and subsequently

[28] See 21 CFR 314.3(b).
[29] 21 CFR 314.95(b)(2).
[30] 21 CFR 314.95(d)(2). See also 21 CFR 314.94(a)(12)(viii)(C)(*1*)(*ii*).
[31] Cf. *Purepac Pharmaceutical Co. v. Thompson*, 354 F. 3d 877 (D.C. Cir. 2004).
[32] See 21 CFR 314.94(a)(12)(viii)(C)(*1*)(*ii*).
[33] See 21 CFR 314.95(b)(2).
[34] Section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act and 21 CFR 314.3(b).

submits an amendment that contains a paragraph IV certification to the same qualifying patent or patent claim (and notice of the paragraph IV certification is sent in accordance with 21 CFR 314.95(d)), the first applicant has lawfully maintained the paragraph IV certification to the patent or patent claim upon which eligibility for 180-day exclusivity is based.[35]

In addition, if a district court decides that the qualifying patent has been infringed (and the patent is valid), and the judgment of the district court is not appealed or is affirmed, the ANDA applicant's paragraph IV certification that the patent was invalid, unenforceable, or not infringed is no longer accurate. The applicant would be required to amend its ANDA to change its paragraph IV certification to a paragraph III certification, which acknowledges the date the patent expires.[36]

Q9. Can there be more than one first applicant for a single drug product?

Yes. The 180-day exclusivity provisions contemplate that there can be multiple first applicants.[37] Multiple ANDAs that include paragraph IV certifications to one or more patents listed for an RLD often will be submitted to FDA on the day the first such application (or the first paragraph IV certification) is submitted. If multiple applicants submit paragraph IV certifications on the first day that paragraph IV certifications for that RLD are submitted, all will be considered first applicants. In addition, different ANDA applicants each can qualify as first applicants by certifying to different listed patents on the same first day.

Q10. Do multiple first applicants for a single drug product each get their own 180-day exclusivity period?

No. There is one 180-day exclusivity period for each drug product. Accordingly, whether multiple first applicants enjoy the full 180-day exclusivity period depends on when those ANDAs are approved in relation to when the 180-day exclusivity period is triggered.[38]

Q11. Can there be different first applicants for different strengths of a drug product?

Yes. Separate 180-day exclusivity periods are available for each strength of the same drug product, because each strength is a distinct drug product. Thus, it is possible for there to be different first applicants for different strengths of the RLD. For example, assume ANDA A applicant submitted the first substantially complete application that contained a paragraph IV certification for a 30 mg strength RLD and lawfully maintained that certification. A few days later, ANDA B applicant submitted its ANDA containing a paragraph IV certification for the 30 mg strength RLD. The Agency then approves a 60 mg strength RLD, and lists a patent in the Orange Book submitted by the NDA holder for that strength. ANDA B applicant amends its ANDA to include the 60 mg strength and includes the first paragraph IV certification to the patent listed for the 60 mg strength and lawfully maintains that certification. ANDA A applicant

[35] 81 FR 69580, 69617 (Oct. 6, 2016).
[36] See 21 CFR 314.94(a)(12)(viii)(A).
[37] See, e.g., section 505(j)(5)(D)(iii) of the FD&C Act (refers to "first applicants").
[38] See Question 17 below.

similarly amends its ANDA to include the 60 mg strength, but three days later. In these circumstances, ANDA A applicant is the first applicant for the 30 mg strength, and ANDA B applicant is the first applicant for the 60 mg strength.

C. 180-day Exclusivity and Patents

Q12. Does an ANDA applicant need to win its patent litigation to be considered a first applicant that retains eligibility for 180-day exclusivity?

No. An applicant potentially may retain eligibility for 180-day exclusivity even if it is not sued as a result of its qualifying paragraph IV certification or, if sued, the case is resolved, for example, through settlement that allows the applicant to enter the market before the patent expires.[39]

Q13. Can a patent that an NDA holder requests to remove from the Orange Book still give rise to 180-day exclusivity?

Yes. An NDA holder can request that FDA remove a patent from the Orange Book in certain circumstances: for example, if a court declared the patent invalid. However, if an NDA holder requests that a patent be removed from the Orange Book and one or more first applicants are already eligible for 180-day exclusivity based on a paragraph IV certification to that patent, FDA will not remove the patent until any 180-day exclusivity stemming from the listed patent has expired, or has been extinguished or relinquished.[40] Until the patent is removed from the Orange Book—after any associated 180-day exclusivity has expired or has been extinguished or relinquished—ANDA applicants must submit or maintain appropriate certifications to the patent notwithstanding the NDA holder's request to remove the patent. This practice ensures that NDA holders cannot unilaterally extinguish an ANDA applicant's eligibility for 180-day exclusivity by requesting removal of the patent from the Orange Book prior to ANDA approval.[41] In such circumstances, FDA will indicate in the Orange Book that the NDA holder has requested removal of the patent.[42]

Q14. Does an ANDA applicant retain 180-day exclusivity after the qualifying patent expires?

No. In keeping with the statutory language and purpose of 180-day exclusivity, FDA has construed the statute such that 180-day exclusivity attaches based only on paragraph IV certifications to unexpired patents. A paragraph IV certification does not survive the expiry of a listed patent. Upon patent expiry, the statute and FDA's regulations require ANDA applicants to

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[39] Cf. *Mova Pharms. Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998).

[40] See 21 CFR 314.94(a)(12)(viii)(B); see also discussion in sections E and F of this guidance.

[41] See *Teva Pharms. USA, Inc. v. Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010); see also 21 CFR 314.53(f)(2)(i).

[42] See FDA's website on *Orange Book Data Files*, at http://www.fda.gov/drugs/informationondrugs/ucm129689.htm (describing use of the *patent delist request flag* as indicating that the "[s]ponsor has requested [that the] patent be delisted [but the] patent has remained listed because, under [s]ection 505(j)(5)(D)(i) of the [FD&C] Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period").

amend their certifications from a paragraph IV certification to a paragraph II certification, which states that the patent has expired.[43] If an applicant neglects to amend its certification to a paragraph II certification after a patent expires, FDA will construe the application as including a paragraph II certification.[44] As noted above, applications with only paragraph II certifications are eligible for immediate effective approval.[45] Therefore, once the only qualifying patent expires, there are no longer any ANDAs blocked by 180-day exclusivity.

This interpretation of the statute effectuates the goals of the Hatch-Waxman Amendments. The 180-day exclusivity provisions were drafted to give ANDA applicants an incentive to be the first to challenge a listed patent, potentially removing that patent as a barrier to approval. Once a listed patent expires and is no longer a barrier to ANDA approval, there is no longer a need to provide an incentive to challenge it in court. Thus, an expired patent does not serve as the basis for a 180-day exclusivity award, and 180-day exclusivity does not extend beyond the life of the patent.

D. 180-day Exclusivity Trigger and Scope of 180-Day Exclusivity

Q15. How is 180-day exclusivity triggered?

The FD&C Act provides that the 180-day exclusivity period is triggered by "first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant."[46] FDA has interpreted the statutory phrase "including the commercial marketing of the listed drug" to provide that exclusivity can be triggered by the marketing of an authorized generic[47] by a first applicant, even if that first applicant's ANDA has not yet been approved.

Concluding that 180-day exclusivity is triggered upon the first applicant's commercial marketing of an authorized generic or the RLD prevents potential subversion of the statutory scheme through collusion between NDA holders and first applicants. If 180-day exclusivity were triggered only by commercially marketing the first applicant's ANDA product, a first applicant that struck a deal with the NDA holder to commercially market the authorized generic or RLD

[43] Section 505(j)(2)(A)(vii)(II), (IV); 21 CFR 314.94(a)(12)(viii)(C)*(1)(i)* ("An applicant must amend a submitted certification or statement if, at any time before the date of approval of the ANDA, the applicant learns that the submitted certification or statement is no longer accurate").

[44] 81 FR 69580, 69615 (Oct. 6, 2016).

[45] Section 505(j)(2)(A)(vii)(II); (j)(5)(B)(i) (when an applicant submits only a paragraph II certification, approval of the applicant's ANDA "may be made effective immediately"); 21 CFR 314.94(a)(12)(viii).

[46] Section 505(j)(5)(B)(iv)(I) of the FD&C Act; see also 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.").

[47] Section 505(t)(3) of the FD&C Act defines an authorized generic as "a listed drug (as that term is used in subsection (j)) that: (A) has been approved under subsection (c); and (B) is marketed, sold, or distributed directly or indirectly to retail class of trade under a different labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark than the listed drug." See also 21 CFR 314.3(b).

instead of marketing the product described in its ANDA potentially could block approval of subsequent ANDAs until patent expiration.

Q16. Once triggered, can 180-day exclusivity be suspended or postponed?

Once triggered, the 180-day period runs without interruption.

Q17. How does the trigger of the 180-day exclusivity period by one first applicant affect other first applicants?

The effect of one first applicant's trigger of the 180-day exclusivity period on other first applicants flows from the fact that there is only one exclusivity period available for each drug product (see Question 10 above). Any first applicant's trigger of the exclusivity period triggers the 180-day exclusivity period for all first applicants for that drug product and exclusivity for all first applicants ends 180 days after the initial trigger. Other first applicants will benefit from exclusivity only to the extent they commercially market during this exclusivity period. The following examples illustrate how shared 180-day exclusivity might operate. Assume ANDA A, ANDA B, and ANDA C all qualified as first applicants.

- If all three ANDAs are approved on the same day, and if all three first commercially market that same day, triggering the exclusivity period, all three applicants benefit from the full 180-day exclusivity period.
- If all three ANDAs are approved on the same day, but only ANDA A is commercially marketed on that first day triggering the exclusivity period, it is triggered for all three ANDAs. Thus, if ANDA B is not commercially marketed until day 30, that applicant will benefit from exclusivity only for the remainder of the 180-day period (i.e., 150 days). If ANDA C is not commercially marketed until day 179, it will benefit from only one day of exclusivity.
- If one or more ANDAs are approved on the same day, but one or more applicants first commercially market the drug product 60 days after approval, the 180-day exclusivity period is triggered upon commercial marketing and runs for 180 days.

Q18. Does 180-day exclusivity block approval of all ANDAs that reference the same RLD?

No. 180-day exclusivity blocks only the approval of subsequent ANDAs that also contain a paragraph IV certification.[48] There are several examples in which 180-day exclusivity does not block approval of another ANDA referencing the same RLD:

- If an ANDA was approved before the NDA holder submitted a patent that provides the basis for first applicant status for a pending ANDA, any related 180-day exclusivity would not affect the previously approved ANDA.

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

- If an ANDA applicant seeks to omit the approved method(s) of use covered by a listed patent with a section viii statement, another ANDA applicant's paragraph IV certification to that same patent, and any related 180-day exclusivity, would not block approval of the ANDA that contained the section viii statement.
- If a patent was *late-listed* vis-à-vis a pending ANDA under FDA's regulations, a first applicant's paragraph IV certification to that patent, and any related 180-day exclusivity, would not block approval of the ANDA for which the patent is late-listed and for which as a result no patent certification was required.[49]

Q19. Can an authorized generic be marketed during the 180-day exclusivity period?

Yes. 180-day exclusivity only blocks approval of subsequent applicants' ANDAs under section 505(j) of the FD&C Act and does not affect the approval of or marketing under NDAs, including marketing of authorized generics.

Q20. Can pediatric exclusivity affect the timing of approval of subsequent applicants' ANDAs after the 180-day exclusivity period is triggered?

Yes. Under section 505A(b)(1)(B)(i) of the FD&C Act (addressing pediatric exclusivity), if pediatric exclusivity attaches to a listed patent, the period during which an ANDA may not be approved under section 505(j)(5)(B) of the FD&C Act may be extended by 6 months after the date the patent expires. An ANDA with a paragraph IV certification is required to change its certification to a paragraph II certification when the patent expires (and will be treated as containing a paragraph II certification even if it fails to affirmatively change its certification). Under section 505A(b)(1)(B)(i)(I), an ANDA that was previously blocked by another applicant's eligibility for 180-day exclusivity and that must change to a paragraph II certification (when the patent that formed the basis of the exclusivity expires) will be blocked from approval by pediatric exclusivity after the qualifying patent (and any associated 180-day exclusivity) has expired.

For example, a first applicant's ANDA contains a paragraph IV certification to a patent that has an associated 6-month period of pediatric exclusivity. The ANDA is approved 178 days before the patent expires, immediately commences commercial marketing, and enjoys 178 days of the 180-day exclusivity. The patent expires, all ANDAs that have not yet been approved must change to paragraph II certification to that patent, the 6-month pediatric exclusivity period commences, and FDA generally cannot approve any ANDA with a paragraph II certification during the 6-month pediatric exclusivity period. Because the first applicant was approved prior

[49] A *late listed* patent is one for which an NDA holder submits the patent for listing later than required by statute or regulations. See, e.g., 21 CFR 314.53(d) and 21 CFR 314.94(a)(12)(vi). An applicant that submitted an ANDA for that RLD that contained an appropriate patent certification or statement before the submission of the patent information is not required to submit a patent certification or statement to address the patent or patent information that is late-listed with respect to the pending ANDA. 21 CFR 314.94(a)(12)(vi). Applicants with pending ANDAs that did not contain an appropriate patent certification or statement before the late listing of a patent or patent information and applicants with ANDAs submitted after the patent or patent information is listed must provide an appropriate patent certification or statement to the newly listed patent or patent information. Id.

to the start of pediatric exclusivity, it does not need to change its certification upon patent expiry and pediatric exclusivity does not affect the approval of the first applicant's ANDA. However, any subsequent applicant's ANDA will need to contain a paragraph II certification and will not be eligible for approval until the pediatric exclusivity expires. Thus, the first applicant may enjoy an additional six months of de facto exclusivity before FDA can approve another ANDA.

E. 180-day Exclusivity Relinquishment and Waiver

Q21. Can a first applicant relinquish or waive its 180-day exclusivity?

Yes. FDA has consistently interpreted section 505(j)(5)(B)(iv) of the FD&C Act to permit both relinquishment and selective waiver of 180-day exclusivity. *Relinquishment* refers to the voluntary and complete abandonment of eligibility for exclusivity. *Selective waiver* refers to a first applicant's waiver of exclusivity to permit approval during the exclusivity period of a particular subsequent ANDA, or subsequent ANDAs. Relinquishment and selective waiver of 180-day exclusivity promote the purpose of the exclusivity—to encourage patent challenges and increase marketplace competition.

A first applicant that is eligible for 180-day exclusivity may relinquish its exclusivity at any time. In contrast, selective waiver of 180-day exclusivity may occur only once the exclusivity period has been triggered.

Q22. Will subsequent applicants be notified if 180-day exclusivity is selectively waived or relinquished?

As a general matter, when all first applicants have relinquished their claims to 180-day exclusivity, FDA may inform subsequent applicants that are otherwise eligible for approval that their ANDAs may be approved.

For selective waivers, FDA's practice is to notify only the subsequent applicant in whose favor the exclusivity has been waived. If a first applicant's exclusivity were triggered and selectively waived in favor of a subsequent applicant with an unapproved ANDA, the fact of the selective waiver to the subsequent applicant could be considered information in the unapproved ANDA. As such, FDA generally would not disclose that the selective waiver had occurred to anyone except the applicant in whose favor exclusivity was waived, at least until the ANDA benefited by the waiver was approved.[50]

F. Forfeiture of 180-day Exclusivity

Q23. How does FDA determine whether a first applicant has forfeited its eligibility for 180-day exclusivity?

To ascertain whether a first applicant has forfeited eligibility for 180-day exclusivity, FDA looks at the qualifying patent(s) to determine whether the applicant has lawfully maintained its

[50] See 21 CFR 314.430(d)(1).

paragraph IV certification(s) and whether the applicant has forfeited exclusivity under any of the forfeiture provisions, as discussed below.

1. Failure to Market Forfeiture Provision

Section 505(j)(5)(D)(i)(I) states that a forfeiture event occurs:

> (I) If the first applicant fails to market the drug by the later of-
>
> (aa) the earlier of the date that is-
>
> (AA) 75 days after the date on which the approval of the application of the first applicant is made effective […]; or
>
> (BB) 30 months after the date of submission of the application of the first applicant; or
>
> (bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period […], at least one of the following has occurred:
>
> (AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.
>
> (BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.
>
> (CC) The patent information submitted under subsection (b) or (c) is withdrawn by the holder of the application approved under subsection (b).[51]

Q24. How does FDA determine whether a first applicant has forfeited exclusivity under the "failure to market" provision?

[51] Section 505(j)(5)(D)(i)(I) of the FD&C Act.

Determining whether forfeiture has occurred requires analyzing if and when the events described under the *failure to market* provision occurred. As seen in the statutory provision outlined immediately above, application of this forfeiture provision requires a series of analyses based on the timing of specific events. The statute directs that a forfeiture event occurs when the first applicant fails to market the drug by the later of two dates. One of these dates is calculated under item (aa) by determining the earlier of a date that is either 75 days after the first applicant's ANDA is approved (subitem (AA)) or 30 months after the date of submission of the first applicant's ANDA (subitem (BB)). The date determined under item (aa) then is compared to the date as determined under item (bb). Item (bb) states that the occurrence of at least one of the enumerated events with respect to a first applicant or any other applicant (which other applicant has received tentative approval) as to each of the qualifying patents will begin a 75-day period leading to possible forfeiture of exclusivity. These events include, very generally, when a court enters a final decision that the patent is invalid or not infringed, a court signs a settlement order or consent decree entering final judgment that includes a finding that the patent is invalid or not infringed, or the patent information for the listed drug is withdrawn by the NDA holder.[52] For an event to occur under item (bb) by any other applicant, the same other applicant must receive both tentative approval and a final court decision described in subitem (AA) or (BB). Forfeiture under section 505(j)(5)(D)(i)(I) of the FD&C Act occurs if the first applicant fails to market by the later of the dates under item (aa) or (bb).

A hypothetical example illustrates how FDA determines whether forfeiture has occurred under the "failure to market" provision. For the purposes of evaluating item (aa), presume that on June 1, 2009, the applicant for ANDA A submitted its substantially complete application containing a paragraph IV certification, which it lawfully maintained. FDA approved the ANDA on December 20, 2012, and the 75-day period identified in subitem (AA) of this forfeiture provision ended on March 4, 2013. Thirty months after the date the ANDA is submitted was December 1, 2011 (the date identified in subitem (BB)).[53] The relevant date for item (aa) of the forfeiture analysis is December 1, 2011, the earlier of these two dates.

For the second part of the analysis under item (bb), presume that on January 1, 2013, a court entered a final decision (from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken) that the relevant patent is invalid and not infringed in an infringement action against a subsequent applicant for this RLD whose ANDA received tentative approval at some point before FDA makes the forfeiture determination. The relevant forfeiture date for ANDA A pursuant to subitem (AA) is March 17, 2013, 75 days after the date on which the court issued its decision. Notably, this date applies even though ANDA A in this example was not the subject of the litigation.

In this scenario, the failure to market forfeiture provision requires the first applicant to market by March 17, 2013, the later of the dates applicable under item (aa) (December 1, 2011) and item

[52] See Question 26 below.

[53] Section 505(j)(5)(D)(i)(I)(aa)(BB) of the FD&C Act states that the 30-month period should be calculated from the date of "submission of the application of the first applicant." If an ANDA containing a paragraph IV certification is "received" as substantially complete, FDA considers the date an ANDA containing a paragraph IV certification was submitted to be the date the ANDA is "received" pursuant to 21 CFR 314.101(b).

(bb) (March 17, 2013). In this example, if ANDA A applicant did not begin commercial marketing until after March 17, 2013, it would forfeit its exclusivity.

Q25. Does an event from both items (aa) and (bb) of the "failure to market" provision have to occur to result in forfeiture under this provision?

Yes. The "failure to market" provision results in forfeiture when there are two dates (one from item (aa) and one from item (bb)) on the basis of which FDA may identify the "later" event as described in section 505(j)(5)(D)(i)(I) of the FD&C Act. The provision does not effect a forfeiture when an event under item (aa) has occurred, but no event under item (bb) has yet occurred.

Q26. Does an NDA holder's request to remove the qualifying patent from the Orange Book qualify as a triggering event under subitem (bb)(CC)?

No. An NDA holder's request that the qualifying patent be removed from the Orange Book does not constitute an event under subitem (CC) because as described in Question 13, FDA will not remove a patent from the Orange Book if the removal would deprive a first applicant of 180-day exclusivity to which it is otherwise entitled. This policy prevents an NDA holder from removing a qualifying patent in order to deprive a first applicant of the period of 180-day exclusivity for which it is otherwise eligible.[54]

2. Withdrawal of Application Forfeiture Provision

A forfeiture event occurs under this provision if "[t]he first applicant withdraws the application or [FDA] considers the application to have been withdrawn as a result of [FDA's] determination . . . that the application does not meet the requirements for approval under [section 505(j)(4) of the FD&C Act]."[55]

Q27. How does FDA determine forfeiture under the "withdrawal of application" forfeiture provision?

The *withdrawal of application* provision provides for forfeiture under two conditions: (1) if the first applicant withdraws the application or (2) if FDA considers the application withdrawn for failure to meet the various general requirements for approval laid out in section 505(j)(4) of the FD&C Act. A first applicant's affirmative withdrawal of its ANDA would meet the first condition, resulting in a forfeiture under this provision. FDA has not yet considered a forfeiture under the second condition.

3. Amendment of Certification Forfeiture Provision

[54] See *Teva v. Sebelius*, 595 F.3d at 1318; see also 21 CFR 314.94(a)(12)(viii)(B).
[55] Section 505(j)(5)(D)(i)(II) of the FD&C Act.

A forfeiture event occurs under this provision if "[t]he first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period."[56]

Q28. How does FDA determine forfeiture under the "amendment of certification" forfeiture provision?

This subsection provides for forfeiture when a first applicant amends or withdraws the paragraph IV certification for all of the patents or claims of patent(s) for which that applicant submitted a paragraph IV certification qualifying the applicant for the 180-day exclusivity period. For instance, forfeiture under this provision occurs when the ANDA applicant loses related patent litigation and amends its ANDA to include a paragraph III certification to all of the qualifying patents.[57] As noted above, FDA regulations require ANDA applicants to amend their patent certification "if, at any time before the date of approval of the ANDA, the applicant learns that the submitted certification or statement is no longer accurate."[58] FDA recommends that applicants provide this information to the Agency expeditiously to avoid unnecessary expenditure of resources in considering forfeiture on other grounds.

Notably, this forfeiture provision does not require a first applicant to have amended or withdrawn all paragraph IV certifications contained in its ANDA to forfeit, just those that qualified the applicant as a first applicant. Accordingly, a first applicant may forfeit its eligibility for exclusivity under this provision, but still maintain paragraph IV certifications to non-qualifying patents. For example, an ANDA applicant submits a substantially complete ANDA with a paragraph IV certification to patent 1 (the only patent listed at that time) and later amends its ANDA to contain a paragraph IV certification to patent 2, which was newly issued by the U.S. Patent and Trademark Office and timely submitted for listing in the Orange Book. If the ANDA applicant withdraws its paragraph IV certification to patent 1, it will forfeit its eligibility for 180-day exclusivity even though the applicant maintains its paragraph IV certification to patent 2. If, on the other hand, the ANDA applicant withdraws its paragraph IV certification to patent 2, but maintains its paragraph IV certification to patent 1, eligibility for 180-day exclusivity will not be affected. This is because only patent 1 qualified the ANDA applicant for 180-day exclusivity.

Q29. Does a first applicant forfeit exclusivity under the "amendment of certification" provision when, because of a change in formulation of the proposed generic drug, a first applicant is required to resubmit paragraph IV certifications to the qualifying patents?

No. Resubmission of paragraph IV certifications in connection with an ANDA applicant's reformulation of its proposed drug product does not constitute an amendment or withdrawal of the paragraph IV certifications under this forfeiture provision. FDA requires submission of an appropriate patent certification or, for a previously submitted paragraph IV certification, a *recertification*, in certain circumstances. For example, an appropriate patent certification or

[56] Section 505(j)(5)(D)(i)(III) of the FD&C Act.
[57] See 21 CFR 314.94(a)(12)(viii)(A).
[58] 21 CFR 314.94(a)(12)(viii)(C)*(1)(i)*.

statement or a recertification is required, among other bases, when an applicant amends its ANDA to make other than minor changes in product formulation.[59] This practice provides notice of the proposed change in formulation of the ANDA product to the NDA holder and each patent owner so that any patent issues related to the new formulation can be resolved. Under applicable regulations, recertification does not constitute an amendment or withdrawal of the paragraph IV certification resulting in forfeiture of 180-day exclusivity. Rather, an ANDA applicant's resubmission of paragraph IV certifications in connection with reformulation is understood to fulfill the statutory requirement to continuously maintain previous paragraph IV certifications to those patents.[60] As explained in the final rule on *Abbreviated New Drug Applications and 505(b)(2) Applications*, a "subsequent paragraph IV certification to the qualifying patent or patent claim is not an 'amendment' of the previously submitted paragraph IV certification under section 505(j)(5)(D)(i)(III) of the FD&C Act because the type of certification remains the same; rather, it is a reaffirmation of the patent challenge notwithstanding the amendment to the ANDA."[61]

Q30. Does a license agreement between the first applicant and the NDA holder or patent owner constitute an "amendment of certification" under this provision?

No. FDA's regulations provide that a paragraph IV certification remains appropriate if the basis for non-infringement (of an otherwise valid and infringed patent) is that the ANDA applicant has obtained a license from the patent owner with respect to the patent.[62]

Nor does an ANDA applicant's agreement that the qualifying patent is valid and would be infringed in the course of securing a license require the applicant to change the paragraph IV certification to a paragraph III certification, because requiring such a certification change would render the license null. The effect of a paragraph III certification is that the ANDA cannot be approved until the patent expires. If required to change its paragraph IV certification to a paragraph III certification, the ANDA applicant licensee could not have an approved generic drug product to market during the period in which it needed and obtained a license to do so.

4. Failure to Obtain Tentative Approval Forfeiture Provision

A forfeiture event occurs under this provision if "[t]he first applicant fails to obtain tentative approval of the application 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."[63]

Q31. How are the dates of the 30-month forfeiture period determined?

[59] 21 CFR 314.96(d). See 81 FR 69580, 69615 (Oct. 6, 2016).
[60] See 81 FR 69580, 69617-69618 (Oct. 6, 2016).
[61] Id.
[62] 21 CFR 314.94(a)(12)(v).
[63] Section 505(j)(5)(D)(i)(IV) of the FD&C Act.

The starting date of the 30-month period[64] in which a first applicant must obtain tentative or final approval or risk forfeiture is one day after the date that a first applicant submits its substantially complete application.[65] The last day of the 30-month period lands on the 30-month *anniversary date* of ANDA submission. For example, for an ANDA filed on February 10, 2005, the 30-month period began on February 11, 2005, and the last day of the 30-month period was August 10, 2007.[66]

We note that the day after the date of a first applicant's ANDA submission is the date used to determine the start of the 30-month forfeiture period even if the ANDA originally did not contain a paragraph IV certification, but was amended later to contain one that qualified the applicant as a first applicant. Thus, it is possible that FDA could determine that an applicant forfeited its eligibility for exclusivity under this provision based on the 30-month period beginning before submission of a paragraph IV certification.

The *Food and Drug Administration Safety and Innovation Act*[67] (FDASIA) created an exception to this general rule regarding the 30-month forfeiture period and paragraph IV certifications submitted in an amendment. The law provides that for applications submitted on or before July 9, 2012, and amended to first contain a paragraph IV certification between July 10, 2012, and September 30, 2017, the 30-month forfeiture period begins the day after the date of submission of the paragraph IV amendment, rather than the day after the date of submission of the substantially complete ANDA.[68]

Q32. Is the 30-month forfeiture period ever extended or modified?

Yes. First, subsection 505(q)(1)(G) of the FD&C Act, enacted as part of the *Food and Drug Administration Amendments Act of 2007*,[69] concerns the submission of citizen petitions that relate to already pending ANDAs and provides that "[i]f the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and approval of the application was delayed because of a petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which [FDA] received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether [FDA] grants, in whole or in part, or denies, in whole or in part, the petition." Thus, pursuant to this provision, if approval of a first applicant's ANDA was delayed because of a petition submitted under section 505(q) of the

[64] We note that this 30-month period in which a first applicant must obtain tentative or final approval is separate from and calculated differently than the 30-month stay period provided for in section 505(j)(5)(B)(iii) of the FD&C Act.

[65] Section 505(j)(5)(D)(i)(IV) of the FD&C Act. We interpret "the date on which the application is filed" as used in section 505(j)(5)(D)(i)(IV) of the FD&C Act to refer to the date that a substantially complete ANDA is submitted to FDA.

[66] For certain ANDAs, the *Food and Drug Administration Safety and Innovation Act* (FDASIA), enacted on July 9, 2012 (Public Law 112-144) directs that this period be extended to 36 or 40 months, as described in Question 32.

[67] Pub. Law 112-144.

[68] See Section 1133(b) of FDASIA.

[69] Pub. Law 110-85.

FD&C Act[70] such that the time it took FDA to respond to the 505(q) petition prevented approval within 30 months from the date of submission, the 30-month deadline for obtaining a tentative or final approval will be extended by the amount of time the 505(q) petition was under review.

Second, section 1133(a) of FDASIA extended the 30-month period for certain ANDAs. Under FDA's interpretation of these provisions, for applications submitted between January 9, 2010, and July 9, 2012, containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on July 9, 2012, and ending on September 30, 2015, section 1133(a) of FDASIA extended this period to 40 months. For applications submitted between January 9, 2010, and July 9, 2012 (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on October 1, 2015, and ending on September 30, 2016, section 1133(a) of FDASIA extended this period to 36 months. In addition, if an application was submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and FDA had not approved or tentatively approved the application but must consider whether the applicant had forfeited exclusivity because a potentially blocked application is ready for approval, FDA applied the 36-month period if it made the forfeiture determination between the period of time beginning on October 1, 2015, and ending on September 30, 2016. For all other applications, the 30-month period set forth in section 505(j)(5)(D)(i)(IV) of the FD&C Act applies.

Q33. Does the "failure to obtain tentative approval" forfeiture provision apply to circumstances in which the first applicant was not eligible for tentative approval but failed to obtain final approval by the 30-month forfeiture date?

Yes. Unless the 30-month period is extended for one of the reasons described above,[71] a first applicant that fails to obtain either tentative approval or final approval of its ANDA by the 30-month forfeiture date generally will forfeit eligibility for 180-day exclusivity. Viewed in isolation, the phrase *tentative approval* in section 505(j)(5)(D)(i)(IV) of the FD&C Act might suggest that this section applies only when an ANDA is eligible for a tentative approval due to a patent, 30-month stay, or exclusivity blocking final approval. Such a reading of the statute would result in incongruous circumstances in which first applicants that are eligible for tentative approval can forfeit under this provision, but first applicants that only are eligible for final approval (and arguably closer to marketing) cannot forfeit under this provision. Other references to this forfeiture provision in the statute make clear that the provision has a broader scope. For example, section 505(q)(1)(G) of the FD&C Act expressly states that if "approval" of the first applicant's application was delayed because of a petition, the 30-month period described in section 505(j)(5)(D)(i)(IV) of the FD&C Act will be extended. In light of this language, FDA has concluded that section 505(j)(5)(D)(i)(IV) establishes a 30-month period within which a first applicant generally must obtain either tentative approval or final approval of its ANDA. This interpretation squares both with the statutory language and with the statutory purpose of

[70] In general, section 505(q) of the FD&C Act pertains, in relevant part, to petitions that request an action that could delay approval of a pending ANDA or 505(b)(2) application.

[71] See Question 32.

preventing first applicants' ANDAs that do not meet the substantive requirements for approval from delaying approval of subsequent applicants' ANDAs.

Q34. How does a first applicant qualify for the exception in the "failure to obtain tentative approval" forfeiture provision?

To qualify for the exception to this forfeiture provision, the failure to obtain tentative or final approval must be "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."[72] In other words, two conditions must both be met: (1) FDA changed or reviewed (i.e., considered whether to change) the requirements for approval while the application was under review and (2) this change in, or review of, approval requirements was a cause of the failure to obtain tentative approval or final approval by the 30-month forfeiture date. However, FDA has determined that "but-for" causation is not required to qualify for this exception. In other words, if one of the causes of failure to obtain tentative or final approval by the 30-month forfeiture date was a change in or review of the requirements for approval imposed after the application was filed, an applicant will not forfeit eligibility for exclusivity notwithstanding that there may have been other causes for failure to obtain tentative approval or final approval by the 30-month forfeiture date. Consequently, to qualify for the exception, the record must show that acceptability of at least one aspect of the ANDA (e.g., bioequivalence) was delayed and, irrespective of what other review issues may have been outstanding at the 30-month date, that this delay was caused, at least in part, by a change in, or review of, the requirements for approval. FDA has determined that this interpretation of the statute best effectuates the policy underlying the exception. It does not penalize applicants for FDA's reviews of, or changes in, approval requirements imposed on applicants after their ANDAs are filed that are a cause of the failure to obtain final approval or tentative approval within 30 months. This interpretation also continues to incentivize ANDA applicants to challenge patents by preserving in many instances the opportunity to obtain 180-day exclusivity.

Q35. Can a first applicant qualify for the exception if, at the 30-month forfeiture date, FDA is reviewing an ANDA amendment submitted to address a change in the requirements for approval?

Yes. FDA generally will presume that failure to obtain tentative approval or final approval was caused by a change in, or review of, approval requirements if, at the 30 month date, the evidence demonstrates that there was a change in, or review of, the requirements for approval and that the applicant was actively addressing issues related to the change in, or review of, approval requirements (or FDA was considering such efforts), and these efforts precluded tentative approval or final approval at that time. When the evidence fails to demonstrate that the applicant was actively addressing the change in, or review of, approval requirements, and that these activities precluded tentative approval or final approval at the 30-month date, FDA generally does not presume that the failure was caused by a change in, or review of, approval requirements. If FDA were to hold otherwise, an applicant that receives one or more deficiencies resulting from a change in approval requirements could avoid forfeiture by a delay

[72] Section 505(j)(5)(D)(i)(IV) of the FD&C Act.

in addressing those deficiencies. When evaluating causation for purposes of determining forfeiture under this provision, FDA will take into account how close the change in or review of the requirement for approval occurred to the 30-month date as well as the amount of effort needed to respond to the change. Further, if the applicant's response is submitted after the 30-month date, FDA will consider, among other factors, how close the response is submitted to the 30-month date.

Q36. Does the exception to the "failure to obtain tentative approval" forfeiture provision apply if FDA's review of an ANDA takes longer than 30 months in the absence of a change in or review of the approval requirements?

No. Under this forfeiture provision, exclusivity is forfeited "unless" there is a review of or change in the approval requirements that has delayed final approval or tentative approval of the ANDA. The statute does not permit FDA to consider an exception based on whether the application could have received tentative approval or final approval before the 30-month forfeiture date had FDA's review been conducted differently. Section 1133 of FDASIA (referenced in Question 32), which, among other things, extended the 30-month forfeiture period to 40 months for certain ANDAs and to 36 months for certain other ANDAs, reflects Congress's understanding that, even in the absence of a change in or review of the requirements for approval, FDA's review of an ANDA might take more than 30 months and might contribute to a first applicant's failure to obtain tentative approval or final approval by the 30-month forfeiture date and result in forfeiture of exclusivity.

Q37. What are examples of changes in the requirements for approval that formed the basis of an exception to the "failure to obtain tentative approval" forfeiture provision?

The following are examples of changes in the requirements for approval imposed after ANDA submission that FDA has determined were a cause of failure to obtain tentative or final approval in 30 months and therefore formed the basis of an exception to this forfeiture provision:

- FDA's change in approval requirements related to drug quality that required an applicant to conduct additional testing and include an additional new drug substance specification;
- FDA's change in approval requirements for demonstrating bioequivalence for a drug product;
- Changes in the RLD labeling that required changes in the ANDA applicant's generic drug labeling;
- Changes in an RLD's formulation that required an ANDA applicant to respond (for example, by seeking approval for a change in formulation); and
- The publication in the *United States Pharmacopeia-National Formulary* of a final monograph for a drug product making it necessary for applicants to demonstrate compliance with the new compendial standards.[73]

[73] This list is intended to be illustrative and not exhaustive.

Q38. Can FDA's review of an approval requirement result in an exception to the "failure to obtain tentative approval" forfeiture provision even if the approval requirements ultimately do not change?

Yes. FDA's review, without change, of approval requirements can be a cause of failure to obtain tentative or final approval within 30 months.

For example, assume FDA originally determines a particular bioequivalence method to be acceptable for a tablet dosage form. Sometime before the 30-month forfeiture date, FDA identifies concerns related to certain dissolution data for one or more tablet products and decides to ask pending ANDAs to develop and propose a different dissolution method, which the applicants provide. After the 30-month forfeiture date, FDA asks a first applicant that had proposed a modified dissolution method to repeat its dissolution testing for all strengths of the company's drug product using the new method. The first applicant submits an amendment with the dissolution data derived from the modified method. FDA ultimately determines after the forfeiture date that FDA's originally recommended dissolution method was appropriate. Because FDA's review of the bioequivalence requirements was a cause of the failure to obtain timely tentative or final approval, the exception to the failure to obtain tentative approval forfeiture provision would still apply even though FDA ultimately did not change the dissolution methods.

Q39. Can FDA's consideration of issues raised in a citizen petition related to the requirements for ANDA approval provide the basis of an exception to the forfeiture provision if an ANDA is submitted after the petition is submitted and is reviewed while that petition is pending?

Yes, assuming the other criteria for the exception are met. Specifically, if the review of issues raised in a petition submitted before submission of the first applicant's ANDA continues after ANDA submission and during ANDA review, FDA's consideration of the issues raised in the petition can constitute a change in or review of requirements for approval.

5. Agreement with Another ANDA Applicant, the Listed Drug Application Holder, or a Patent Owner

A forfeiture event occurs under this provision if "[t]he first applicant enters into an agreement with another applicant […] for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of [a paragraph IV] certification […], the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws […]."[74]

[74] Section 505(j)(5)(D)(i)(V) of the FD&C Act.

Q40. Are there examples of forfeiture under the provision related to agreements with another applicant, the NDA holder, or a patent owner?

No. As of the date of publication of this draft guidance, FDA has not determined that a first applicant has forfeited its eligibility for exclusivity under this provision, sometimes referred to as the *collusive agreement* forfeiture provision. We note that the collusive agreement forfeiture provision applies to all pending ANDAs, regardless of when the first ANDA referencing the RLD was submitted.[75] This is not the case for the other forfeiture provisions.[76] We also note that the collusive agreement forfeiture provision applies to only those settlement agreements described in the statute when, among other things, there is a final decision of the Federal Trade Commission or court that the agreement has violated the antitrust laws, and the decision cannot be or has not been appealed.

6. Expiration of All Patents Forfeiture Provision

A forfeiture event occurs under this provision if "[a]ll of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired."[77]

Q41. Does forfeiture under the "expiration of all patents" provision require the expiration of all listed patents to which a first applicant submitted a paragraph IV certification?

No. A forfeiture under this provision occurs upon expiration of only all of the qualifying patent(s). Forfeiture can occur under this provision even if the first applicant has paragraph IV certifications to other listed patents that have not expired as long as the certification to these other patents did not provide the basis for eligibility for 180-day exclusivity. For example, suppose an ANDA applicant is the first applicant based on the submission of a substantially complete ANDA containing a paragraph IV certification to U.S. Patent No. 3,456,879 (the '879 patent). After submission of the ANDA, U.S. Patent No. 6,789,101 (the '101 patent) for the RLD is listed and the ANDA applicant amends its application to include a paragraph IV certification to it. The ANDA applicant will forfeit exclusivity upon expiration of the '879 patent (the only qualifying patent), even if the '101 patent remains unexpired.

7. Effect of Forfeiture

[75] Section 1102(b)(2) of the MMA.

[76] See Question 1. Section 1102(b)(1) of the MMA provides that, except as provided in section 1102(b)(2), the provisions related to 180-day exclusivity "shall be effective only with respect to an application filed under [section 505(j) of the FD&C Act] after the date of the enactment of this Act for a listed drug for which no certification under section 505(j)(2)(A)(vii)(IV) of that Act was made before the date of the enactment of this Act." Section 1102(b)(2) in turn provides that "[i]f a forfeiture event described in section 505(j)(5)(D)(i)(V) of [the FD&C Act] occurs in the case of an applicant, the applicant shall forfeit the 180-day period under section 505(j)(5)(B)(iv) of [the FD&C Act] without regard to when the first certification under section 505(j)(2)(A)(vii)(IV) of [the FD&C Act] for the listed drug was made."

[77] Section 505(j)(5)(D)(i)(VI) of the FD&C Act.

Q42. Does a first applicant that forfeited its eligibility for exclusivity become a "subsequent applicant" blocked from final approval by other first applicants' eligibility for exclusivity?

No. The FD&C Act provides that "[t]he 180-day exclusivity period […] shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant."[78] Neither this statutory provision, nor any other, states that in forfeiting exclusivity, a first applicant becomes a subsequent applicant whose ANDA can be approved only after the 180-day exclusivity period has run. Thus, FDA interprets the statute such that a first applicant that has forfeited exclusivity remains a first applicant and need not await expiration of 180-day exclusivity to obtain approval of its ANDA. A first applicant that has forfeited exclusivity is subject to the same timetable for approval that governs the approval of ANDAs for first applicants that remain eligible for 180-day exclusivity.[79] Section 505(j)(5)(B)(iv) of the FD&C Act, which governs the running of 180-day exclusivity, does not distinguish between first applicants that have forfeited eligibility for 180-day exclusivity and those that have not, providing instead only that a *subsequent* applicant's ANDA may be approved 180 days after the date of first commercial marketing by any first applicant. In addition, once FDA has approved one or more ANDAs, commercial marketing by ***any*** first applicant will trigger the 180-day exclusivity period for all the first applicant ANDAs, even if the triggering applicant is the first applicant that forfeited its eligibility for exclusivity.

For example, assume ANDA A and ANDA B are first applicants. ANDA A forfeits its eligibility for 180-day exclusivity for failure to obtain tentative approval within 30 months but ANDA B maintains its eligibility. ANDA A is not blocked from approval by ANDA B's 180-day exclusivity because ANDA A remains a first applicant. ANDA A also can trigger ANDA B's 180-day exclusivity. However, ANDA A will not itself block subsequent applicants from approval. Only ANDA B, which retained eligibility for exclusivity, will block subsequent applicants from approval.

Q43. If 180-day exclusivity is forfeited by the first applicant(s), does it "roll" to the next-submitted ANDA?

No. 180-day exclusivity is only available to those ANDA applicants that meet the statutory definition of first applicant.[80] Thus, any subsequent applicant that did not submit a substantially complete ANDA that contained a paragraph IV certification on the first day such an application was submitted does not qualify for exclusivity. Once 180-day exclusivity is forfeited by all the first applicants, it no longer blocks approval of any subsequent applicants' ANDAs but subsequent applicants do not become first applicants under those circumstances.

G. Procedural Questions Regarding 180-day Exclusivity Determinations

[78] Section 505(j)(5)(D)(ii) of the FD&C Act.
[79] Section 505(j)(5)(B)(iii) of the FD&C Act.
[80] Section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act.

Q44. When does FDA decide whether an ANDA applicant is eligible for 180-day exclusivity?

It is FDA's practice to make decisions on eligibility for 180-day exclusivity 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). Many factors may influence eligibility for exclusivity up to the time an application is ready for approval (e.g., patent expiration, failure to obtain a tentative or final approval within 30 months, withdrawal of ANDA) and thus could render a premature eligibility determination incorrect. When FDA makes an approval decision with respect to an ANDA, it will inform an applicant affected by exclusivity of its status. For example, FDA generally will inform an ANDA applicant it is (1) a first applicant entitled to exclusivity, (2) a first applicant that has forfeited its exclusivity, (3) eligible only for a tentative approval because one or more first applicants are eligible for 180-day exclusivity, or (4) eligible for final approval because all first applicants have forfeited exclusivity.

In some circumstances, when a first applicant is ready for final approval, FDA may refrain from making a formal determination regarding that applicant's eligibility for 180-day exclusivity. Specifically, if FDA's review of the ANDAs for the drug product indicates that a formal determination of eligibility for 180-day exclusivity is not necessary (e.g., if there are no subsequent ANDAs or the subsequent ANDAs are likely more than 180 days away from final approval), FDA may refrain from making a formal determination regarding eligibility for 180-day exclusivity.

It also is possible that an ANDA applicant could be informed upon approval that it is a first applicant eligible for 180-day exclusivity, but later forfeit exclusivity under section 505(j)(5)(D) of the FD&C Act.

Q45. How can the public know if a paragraph IV certification has been submitted with respect to a particular RLD?

FDA maintains on its website a list of drug products for which an ANDA has been received by the Agency containing a paragraph IV certification. The webpage is titled Paragraph IV Patent Certifications.[81] This list includes the drug product for which a paragraph IV certification has been submitted, the dosage form, strength(s), RLD name, and date on which the first substantially complete ANDA was submitted to FDA or, when applicable, the date of the first paragraph IV certification. FDA will not disclose the identity of the applicants of those ANDAs, nor will FDA indicate the number of such ANDAs submitted on that date. The information is updated twice a month and is as current as the last update. Although FDA makes every effort to ensure the accuracy of the information provided in this list, this information should be used for reference only. Any discrepancies, disparities, or other questions about this information should be discussed with the Office of Generic Drug's Division of Filing Review before making any decisions based on the information.

[81] This FDA webpage is available at http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm047676.htm.