Certain Postapproval Requirements and Resources for ANDAs

Guidance for Industry

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

June 2026
Generic Drugs

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Contains Nonbinding Recommendations

Certain Postapproval Requirements and Resources for ANDAs Guidance for Industry [1]

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

I. INTRODUCTION

This guidance is intended to assist holders of abbreviated new drug applications (ANDAs) approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) by highlighting certain postapproval statutory and regulatory requirements for ANDAs, as well as by identifying related guidances and other resources available to reference.

Historically, FDA has highlighted certain postapproval requirements in ANDA approval letters.[2] The letters have included general and largely standardized information to serve as reminders to ANDA holders of certain postapproval statutory and regulatory obligations. In addition, FDA has provided various publicly available resources, including guidances for industry, which discuss and may provide recommendations on the same ANDA postapproval requirements typically highlighted in the approval letters. In an effort to streamline ANDA approval letters, the Agency has been removing some of the information on postapproval requirements typically included in the letters, while continuing to provide ANDA holders with a helpful resource to reference for reminders about certain postapproval requirements.

This guidance highlights certain statutory and regulatory postapproval requirements for ANDAs, as well as identifies related guidances and other resources available for reference. The requirements and resources highlighted in this guidance apply to ANDAs that have received *final* approval. However, this guidance does not identify or discuss all statutory and regulatory requirements that may apply to an approved ANDA and may highlight statutory and regulatory requirements that do not apply to all ANDAs (e.g., Risk Evaluation and Mitigation Strategies). This guidance also does not identify all CDER guidance documents relevant to approved

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at https://www.regulations.gov/docket?D=FDA-2017-D-6821). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

[2] FDA also highlights certain postapproval requirements for ANDAs on FDA's "Requirements and Resources for Approved ANDAs" webpage, available at https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

ANDAs. Holders of approved ANDAs should consider all other relevant CDER guidance documents for additional recommendations related to postapproval requirements.[3]

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

Under applicable statutes and regulations, an approved ANDA may be subject to certain requirements postapproval, including requirements regarding changes to an approved ANDA, postmarketing reporting (regardless of the marketing status of the product), promotional materials, and annual facilities fees, among others. It is the responsibility of each holder of an ANDA to be aware of these requirements and submit any required information to the Agency in a timely manner. Section III of this guidance highlights certain statutory and regulatory postapproval requirements for ANDAs, as well as identifies related guidances and other resources available for reference.

III. CERTAIN POSTAPPROVAL REQUIREMENTS AND RESOURCES FOR ANDAS

A. Changes to an Approved ANDA

On November 21, 1997, the President signed into law the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).[4] Section 116 of the Modernization Act amended the FD&C Act by adding section 506A, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. Under section 506A of the FD&C Act (21 U.S.C. 356(a)), certain changes in the conditions described in approved ANDAs require an approved supplemental application before the change may be made. FDA regulations on supplements and other changes to an approved application (21 CFR 314.70 and 314.97) conform to section 506A of the FD&C Act.

- See also guidance for industry *Changes to an Approved NDA or ANDA* (April 2004, Rev. 1).[5]

B. Conversion of ANDA Approval to Tentative Approval Because of Court Order

[3] A list of CDER guidances is available on the Internet at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[4] Public Law 105-115.
[5] 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.

The timing of an ANDA approval depends on, among other things, the patent and/or exclusivity protections for the reference listed drug (RLD)[6]. Not later than 30 days after the date of approval of a new drug application (NDA), the NDA applicant must submit certain information to FDA for each patent that claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent, or that claims a method of using such drug for which approval has been granted in the NDA, and for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug.[7] FDA publishes (or "lists") certain patent information submitted by the NDA holder under section 505(c) of the FD&C Act in its publication *Approved Drug Products With Therapeutic Equivalence Evaluations*, known as the *Orange Book.*[8] An ANDA must contain an appropriate patent certification for each patent that claims the RLD or a method of using the RLD for which the ANDA applicant seeks approval in its ANDA and for which the NDA applicant is required to submit information.[9] In particular, the ANDA applicant generally must submit to FDA one of four specified certifications regarding such patents, under section 505(j)(2)(A)(vii) of the FD&C Act (21 U.S.C. 355(j)(2)(A)(vii)):

- That such patent information has not been filed (a paragraph I certification)
- That such patent has expired (a paragraph II certification)
- The date on which such patent will expire (a paragraph III certification)
- 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).[10]

Once FDA has received an ANDA for review,[11] an applicant that submitted 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, unenforceable, or will not be infringed.[12] If a patent is listed at the time an original ANDA is submitted and, in response to a 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.[13]

FDA may issue final approval to an ANDA at the conclusion of a 30-month stay if a patent infringement lawsuit about the drug product at issue in that ANDA is pending, the ANDA does

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[6] 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).
[7] Section 505(c)(2) of the FD&C Act.
[8] Section 505(j)(7)(A)(iii) of the FD&C Act. The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
[9] Section 505(j)(2)(A)(vii) of the FD&C Act and 21 CFR 314.94(a)(12)(i)(A).
[10] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).
[11] See 21 CFR 314.101(b).
[12] Section 505(j)(2)(B) of the FD&C Act.
[13] Section 505(j)(5)(B)(iii) of the FD&C Act and 21 CFR 314.107(b)(3)(i).

not contain any paragraph III certifications, the ANDA is not blocked by any unexpired exclusivities, and all other requirements for approval have been met. However, after the ANDA is approved, the NDA holder or patent owner may be successful in its patent infringement lawsuit against the ANDA holder. In such a case, the district court may order that the patent is infringed and that the approval of the ANDA is not effective before expiration of the infringed patent pursuant to 35 U.S.C. 271(e)(4)(A). Under these circumstances, FDA must determine whether it is appropriate to convert the approval status of the ANDA to tentative approval (TA)[14] and, if that conversion is appropriate, the timing of such conversion. To facilitate FDA's timely conversion of the approval status of an ANDA to TA, ANDA applicants are required to submit any and all documents pursuant to 21 CFR 314.107(e) within 14 days of the date of entry by the court or the date of appeal or expiration of the time for appeal.[15]

FDA considers certain factors when determining whether it is appropriate to convert the approval status of an approved ANDA to TA and, if that conversion is appropriate, the timing of such conversion. Upon receipt of a federal district court judgment that the patent is infringed and the approval of the ANDA is not effective before expiration of the infringed patent, as described in 35 U.S.C. 271(e)(4)(A), FDA will consider the judgment and will also consider any documents showing (1) that the district court judgment has been stayed or (2) that there is a pending motion for stay of the district court judgment.

- See also FDA Manuals of Policies and Procedures (MAPP) 5220.2 *Conversion of ANDA Approval to Tentative Approval Because of Court Order*[16]

C. Postmarketing Reporting

Postmarketing reporting requirements applicable to ANDAs are set forth in FDA regulations at 21 CFR 314.80-81 and 314.98. Among other things, FDA regulations require ANDA holders to notify the Agency of the marketing status of drug products approved under ANDAs.[17]

In addition, on August 18, 2017, the President signed into law the FDA Reauthorization Act of 2017 (FDARA). Section 804 of FDARA amended the FD&C Act by adding section 506I[18] (21 U.S.C. 356i), which imposes additional marketing status reporting requirements applicable to ANDAs in certain circumstances.

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[14] 21 CFR 314.107(g) ("If FDA issues an approval letter in error or a court enters an order requiring, in the case of an already approved 505(b)(2) application or ANDA, that the date of approval be delayed, FDA will convert the approval to a tentative approval if appropriate.").
[15] 21 CFR 314.107(e). We note that FDA may become aware of the court order through other means, such as receiving a copy from the patent owner or NDA holder.
[16] For the most updated MAPPs, see the search page for CDER MAPPs, available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp. We note that, among others, FDA MAPP 5200.7 *ANDA Amendments and Supplements Reviewed by the Division of Filing Review* may also be a helpful resource for ANDA holders.
[17] See, e.g., 21 CFR 314.81(b)(2)(ii)(a) and 314.81(b)(3)(iv).
[18] Public Law 115-52.

- See also guidance for industry *Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format* (August 2020).

1. Postmarketing safety surveillance

All drugs have risks, and health care practitioners and patients must balance the risks and benefits of a drug when making decisions about medical therapy. As a drug is used postapproval more widely and under diverse conditions, new information regarding the risks and benefits of a drug may become available. This may include new risks or new information about known risks. Accordingly, all holders of approved ANDAs are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.[19] Application holders must promptly review all adverse drug experience information obtained or otherwise received by the application holder from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers, and must comply with applicable reporting and recordkeeping requirements.[20] FDA guidance for industry explains that "[a]fter a [safety] signal is identified, it should be further assessed [by the application holder] to determine whether it represents a potential safety risk and whether other action should be taken."[21]

Holders of approved ANDAs are required to submit periodic adverse drug experience reports to FDA at regular intervals for review.[22] ANDA holders also must comply with requirements for other postmarketing reports under § 314.81 (21 CFR 314.81) and section 505(k) of the FD&C Act. These requirements include submission of an annual report that includes a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product and a description of actions the applicant has taken or intends to take as a result of this new information (e.g., if appropriate, proposed revisions to product labeling).[23]

- See also draft guidance for industry *Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines* (March 2001) and final guidance for industry *E2D(R1) Postapproval Safety Data: Definitions and Standards for Management and Reporting of Individual Case Safety Reports* (March 2026, Revision 1).

2. Combination product safety reporting

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[19] See, e.g., 21 CFR 314.80(b) and 314.98.
[20] See, e.g., 21 CFR 314.80(b), (c), and (j). For more information on individual case safety reports, see https://www.fda.gov/industry/fda-data-standards-advisory-board/individual-case-safety-reports.
[21] See FDA guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005), available at https://www.fda.gov/media/71546/download, at 9.
[22] 21 CFR 314.80(c)(2). Postmarketing periodic safety reports must be submitted quarterly for the first 3 years following the U.S. approval date and annually thereafter, and they must contain the information described in § 314.80(c)(2)(ii).
[23] See 21 CFR 314.81(b)(2)(i).

In the *Federal Register* of December 20, 2016 (81 FR 92603), FDA published a final rule for postmarketing safety reporting (PMSR) for combination products as defined by FDA regulation at 21 CFR 3.2(e).[24] ANDA products that are combination products as defined by 21 CFR 3.2(e) are subject to PMSR requirements for combination products.[25]

- See also guidance for industry *Postmarketing Safety Reporting for Combination Products* (July 2019).[26]

3. Notice of permanent discontinuation or interruption in manufacturing

Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA), enacted on July 9, 2012,[27] and section 3112 of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), enacted on March 27, 2020,[28] amended the FD&C Act to help the Agency address the problem of drug shortages in the United States, including by adding requirements related to notifying FDA about finished product and active pharmaceutical ingredient (API) manufacturing discontinuances and interruptions. While some supply disruptions and product shortages cannot be predicted or prevented, early communication and detailed notifications from manufacturers to the Agency play a significant role in decreasing the incidence, impact, and duration of supply disruptions and product shortages. Timely notifications that include specific information about the situation allow the Agency to evaluate the situation and determine an appropriate course of action. When FDA does not receive timely, informative notifications, the Agency's ability to respond appropriately is limited.

Section 506C(i) of the FD&C Act (as amended by FDASIA) required FDA to issue regulations implementing section 506C of the FD&C Act. On July 8, 2015, FDA issued the final rule, "Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products" (80 FR 38915) to implement section 506C and other drug shortage provisions of the FD&C Act, as amended by FDASIA (see, e.g., 21 CFR 310.306 and 314.81(b)(3)(iii)).

Under section 506C of the FD&C Act and FDA's implementing regulations,[29] holders of approved ANDAs must notify FDA of (1) a permanent discontinuance in the manufacture of certain finished drug products, (2) an interruption in the manufacture of certain finished drug products that is likely to lead to a meaningful disruption in supply of those products in the United States, (3) a permanent discontinuance in the manufacture of API for certain finished drug

[24] Codified in 21 CFR Part 4, Subpart B.
[25] Ibid.
[26] When finalized, this guidance will represent FDA's current thinking on this topic.
[27] Public Law 112-144. The FDASIA amendments to section 506C of the FD&C Act took effect on July 9, 2012.
[28] Public Law 116-136. The CARES Act amendments to section 506C of the FD&C Act took effect on September 23, 2020.
[29] As noted above, the CARES Act amended section 506C of the FD&C Act by, among other things, adding requirements related to notifying FDA about discontinuances and interruptions in manufacturing of certain APIs. Prior to the CARES Act, section 506C contained notification requirements applicable to covered finished products only. As such, the regulations implementing section 506C, which FDA promulgated in 2015, contain notification requirements applicable to covered finished products only. These regulations do not contain the notification requirements that are applicable to API for covered finished products; rather, such API notification requirements arise directly under section 506C, as amended by the CARES Act.

products, or (4) an interruption in the manufacture of API for certain finished drug products that is likely to lead to a meaningful disruption in the supply of the API for those products. Notifications under section 506C must include disclosure of reasons for the discontinuation or interruption.[30]

- See also draft guidance for industry *Notifying FDA of a Discontinuance or Interruption in Manufacturing of Finished Products or Active Pharmaceutical Ingredients Under Section 506C of the FD&C Act* (February 2024, Rev. 1)[31]

D. Promotional Materials[32]

Under the FD&C Act and FDA's regulations implementing postmarketing reporting requirements, ANDA holders must submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product.[33] Each submission (also referred to as a *2253 submission*) is required to be accompanied by a completed fillable Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use)[34] and is required to include a copy of the product's current professional labeling.[35]

We note that applicants may request advisory comments[36] on proposed introductory advertising and promotional labeling materials prior to dissemination or publication. Please note that such submissions requesting advisory comments are voluntary. To do so, applicants should submit electronically in eCTD format a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable).

- For more information about submitting promotional materials in eCTD format, see guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format — Promotional Labeling and Advertising Materials for Human Prescription Drugs* (April 2022, Rev. 1).

- For more information about submitting promotional materials to the Office of Prescription Drug Promotion (OPDP), see the OPDP web page at https://www.fda.gov/about-fda/cder-offices-and-divisions/office-prescription-drug-promotion-opdp.

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[30] See section 506C(a) of the FD&C Act.
[31] When finalized, this guidance will represent FDA's current thinking on this topic.
[32] For the purpose of this guidance, the term *promotional materials* collectively refers to promotional labeling and advertising materials, regardless of the format, manner, or medium by which they are presented. Promotional materials may include, but are not limited to, television advertisements (ads), brochures, booklets, detailing pieces, internet websites, print ads, exhibits, sound recordings, and radio ads.
[33] See 21 CFR 314.81(b)(3)(i).
[34] Form FDA 2253 is available on the Internet at https://www.fda.gov/about-fda/reports-manuals-forms/forms. Instructions for completing the form can be found at https://www.fda.gov/media/132152/download.
[35] 21 CFR 314.81(b)(3)(i).
[36] Reference in this guidance to the voluntary request for advisory comment(s) on proposed promotional materials by applicants is distinct from and not to be confused with the process identified in 21 CFR 10.85.

E. Annual Facility Fees

On July 9, 2012, the President signed into law the Generic Drug User Fee Amendments of 2012 (GDUFA I) as part of FDASIA.[37] GDUFA authorizes FDA to assess and collect user fees to provide the Agency with resources[38] to help ensure patients have access to quality, safe, and effective generic drugs. GDUFA fee resources bring greater predictability and timeliness to the review of generic drug applications. GDUFA has been reauthorized every 5 years to continue FDA's ability to assess and collect GDUFA fees, and this user fee program has been reauthorized two times since GDUFA I, most recently in the Generic Drug User Fee Amendments of 2022.[39]

GDUFA requires owners of facilities producing generic drug products, APIs, and certain other sites and organizations that support the manufacture or approval of these products to electronically self-identify with FDA and update that information annually. Self-identification is required for two purposes. First, it is necessary to determine the universe of facilities required to pay user fees. Second, self-identification is a central component of an effort to promote global supply chain transparency. The information provided through self-identification enables quick, accurate, and reliable surveillance of generic drugs and facilitates inspections and compliance. Most facilities that self-identify are required to pay an annual facility user fee.[40]

A separate system for the electronic self-identification of generic industry facilities, sites, and organizations was established for GDUFA.

- See also guidance for industry *Self-Identification of Generic Drug Facilities, Sites, and Organizations* (September 2016).

- For more information about the requirements of GDUFA, its fee structure, payment methods, and related information, see FDA's GDUFA web page at https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments.

F. Content of Labeling

On December 11, 2003, FDA published final regulations (the electronic labeling rule) requiring the submission of the content of labeling in electronic format for marketing applications.[41] The requirements of the electronic labeling rule can be found in 21 CFR 314.94(d) for ANDAs and 21 CFR 314.81(b) for annual reports to marketing applications. The effective date of the rule

[37] Public Law 112-144, Title III.
[38] User fees are available for obligation in accordance with appropriations acts.
[39] Enacted as Title III of Division F (the FDA User Fee Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023 (Public Law 117-180). On September 30, 2022, the President signed the bill reauthorizing GDUFA III, with provisions that are in effect from October 1, 2022, through September 30, 2027.
[40] See section 744B(a)(4) and (f) of the FD&C Act.
[41] See 68 FR 69009. The *content of labeling* is the labeling required under 21 CFR 201.100(d)(3) including all text, tables, and figures (commonly referred to as the package insert or professional labeling).

was June 8, 2004. The regulations specify that the content of labeling must be submitted electronically in a form that FDA can process, review, and archive.

- See also guidance for industry *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005).

- FDA currently accepts content of labeling in structured product labeling (SPL) format. For additional information, refer to FDA's Structured Product Labeling Resources web page at https://www.fda.gov/industry/fda-data-standards-advisory-board/structured-product-labeling-resources.

All application holders – including ANDA holders – have an ongoing obligation to ensure that their drug product labeling is accurate and up to date. When new information becomes available that causes information in labeling to be inaccurate, false, or misleading, the application holder must take steps to change the content of its labeling.[42] Additionally, ANDA holders should routinely monitor available labeling resources such as the Drugs@FDA webpage[43] and the *Orange Book* for changes to the RLD's labeling and make any necessary revisions to their labeling.

- See also guidance for industry *Revising ANDA Labeling Following Revision of the RLD Labeling* (January 2024).

G. Risk Evaluation and Mitigation Strategies

Section 505-1 of the FD&C Act (21 U.S.C. 355-1), as added by the Food and Drug Administration Amendments Act of 2007 (FDAAA),[44] authorizes FDA to require a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[45] A REMS is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. A REMS may require a Medication Guide (or patient package insert) to provide risk information to patients[46] and/or a communication plan to disseminate risk information to health care providers.[47] For drugs that pose a serious risk of abuse or overdose, FDA may require certain packaging or a safe use disposal system as part of a REMS.[48] FDA may also require certain Elements To Assure Safe Use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug.[49] ETASU may include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe-use conditions.

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[42] See 21 CFR 201.56(a)(2), 314.70, and 314.97.
[43] Drugs@FDA is available at https://www.accessdata.fda.gov/scripts/cder/daf/.
[44] Public Law 110-85.
[45] Section 505-1(a) of the FD&C Act.
[46] Section 505-1(e)(2) of the FD&C Act.
[47] Section 505-1(e)(3) of the FD&C Act.
[48] Section 505-1(e)(4) of the FD&C Act.
[49] Section 505-l(f)(3) of the FD&C Act

REMS with certain ETASU may also include an implementation system through which the applicant is able to monitor and evaluate implementation of the ETASU and work to improve their implementation.[50] A REMS generally must have a timetable for submission of assessments of the strategy.[51]

FDA can require a REMS before initial approval of a new drug or, should FDA become aware of new safety information[52] about a drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks, after the drug has been approved.[53]

If FDA requires a REMS for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS.[54] A REMS for an ANDA must have a Medication Guide or similar, patient PI, and packaging or disposal requirement as the listed drug referenced in the ANDA.[55] In addition, as noted under section 505-1(i)(1)(C) of the FD&C Act (21 U.S.C. 355-1(i)(1)(C)), if the listed drug REMS contains ETASU, then an ANDA approved under 505(j) may use a single, shared system REMS with the applicable listed drug of ETASU or a different, comparable aspect of the ETASU.[56] However, an ANDA is not subject to the requirement for a timetable for submission of assessments of the REMS[57] and an ANDA REMS does not include a communication plan.[58]

- See guidance for industry *Format and Content of a REMS Document* (January 2023).
- See guidance for industry *Development of a Shared System REMS* (June 2018).
- Additional information on REMS is available on FDA's REMS web page at https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems.

H. Competitive Generic Therapy – Notice of First Commercial Marketing

Section 803 of FDARA amended the FD&C Act to add section 505H, which created a pathway by which FDA may, at the request of the applicant, designate a drug with "inadequate generic competition"[59] as a competitive generic therapy (CGT).

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[50] Section 505-1(f)(4) of the FD&C Act.
[51] Section 505-1(d) of the FD&C Act.
[52] Section 505-1(b)(3) of the FD&C Act.
[53] Section 505-1(a) of the FD&C Act.
[54] See section 505-1(i) of the FD&C Act.
[55] Section 505-1(i)(1)(A) and (B) of the FD&C Act.
[56] Note that FDA may require the ANDA to use a single, shared system if FDA determines that no different, comparable aspect of the ETASU could satisfy the requirements of section 505-1(f) (section 505-1(i)(1)(C)(ii) of the FD&C Act).
[57] Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS. For ANDAs, the schedule for submission of a REMS assessment is included in the approval letter.
[58] Section 505-1(i)(1)(A) of the FD&C Act.
[59] See section 506H(b)(3), (e)(2) of the FD&C Act (21 U.S.C. 356h(b)(3), (e)(2)).

FDARA also created a new type of 180-day marketing exclusivity period for ANDA applicants of certain drugs that FDA has designated as CGTs. Specifically, section 808 of FDARA amended the FD&C Act by adding provisions at section 505(j)(5)(B)(v) and 505(j)(5)(D)(iv) of the FD&C Act to recognize a 180-day period of exclusivity (hereafter, CGT exclusivity) vis-à-vis certain other ANDA applicants to the first approved applicant that (1) obtains approval of an ANDA for a drug that has been designated as a CGT and for which there were no unexpired patents or exclusivities listed in the *Orange Book* for the relevant RLD at the time the applicant submitted the original ANDA to the Agency; and (2) commercially markets such drug within 75 calendar days after the approval of the ANDA.

The first approved applicant's first commercial marketing determines whether (and when) the 180-day CGT exclusivity period under section 505(j)(5)(B)(v) of the FD&C Act begins and whether that first approved applicant has forfeited its eligibility for exclusivity under section 505(j)(5)(D)(iv).[60] FDA generally would not be aware of first commercial marketing by a first approved applicant unless the first approved applicant notified FDA of the commencement of such marketing.[61]

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

To ensure that FDA receives timely notification of first commercial marketing, FDA recommends that the first approved applicant submit a general correspondence to the ANDA informing FDA that it has commenced marketing, with a duplicate copy of this correspondence submitted to the Office of Generic Drug's Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov.

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

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

- See also guidance for industry *Competitive Generic Therapies* (October 2022, Rev. 1).

- Additional information on CGT approvals is available on FDA's web page at https://www.fda.gov/drugs/generic-drugs/competitive-generic-therapy-approvals.

I. 180-Day Exclusivity – Notice of First Commercial Marketing

The FD&C Act recognizes a 180-day exclusivity period[62] 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. 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*.[63]

Section 505(j)(5)(B)(iv)(I) of the FD&C Act provides that the period of 180-day exclusivity is triggered by "first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant."[64] 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[65] by a first applicant, even if that first applicant's ANDA has not yet been approved.

FDA regulations require a first applicant to submit correspondence to its ANDA notifying FDA within 30 days of the date of first commercial marketing of the drug product (including the commercial marketing of the RLD).[66] If the first applicant does not notify FDA within this timeframe, FDA will deem the date of first commercial marketing to be the date of the ANDA's approval.

- See also draft guidance for industry *180-Day Exclusivity: Questions and Answers* (January 2017).[67]

J. Compendial Standards

[62] See 21 CFR 314.3(b) (defining *180-day exclusivity period*); section 505(j)(5)(B)(iv) of the FD&C Act.
[63] 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).
[64] Section 505(j)(5)(B)(iv)(I) of the FD&C Act; see also 21 CFR 314.3(b) (defining "Commercial marketing").
[65] 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).
[66] See 21 CFR 314.107(c)(2) and section 505(j)(5)(B)(iv)(I) of the FD&C Act.
[67] When finalized, this guidance will represent FDA's current thinking on this topic.

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label.[68] FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs.

- Additional information on the USP-NF is available on USP's website at https://www.uspnf.com/.

[68] See section 501(b) of the FD&C Act (21 USC 351(b)).