ANDAs: Pre-Submission Facility Correspondence Related to Prioritized Generic Drug Submissions

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Ranjani Prabhakara, (240) 402-4652.

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

December 2022
Pharmaceutical Quality/CMC

Revision 2

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Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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ANDAs: Pre-Submission Facility Correspondence Related to Prioritized Generic Drug Submissions Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

The Food and Drug Administration (FDA) is issuing this revised draft guidance to incorporate program enhancements related to the content, timing, and assessment of a pre-submission facility correspondence (**PFC**)[2] within the abbreviated new drug application (ANDA) assessment program[3] agreed upon by the Agency and industry as part of the reauthorization of the Generic Drug User Fee Amendments (GDUFA III), as described in *GDUFA Reauthorization Performance Goals and Program Enhancements, Fiscal Years 2023 through 2027* (GDUFA III commitment letter).[4] This guidance replaces the November 2017 draft guidance for industry on *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence)*.[5]

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.

[1] This guidance has been prepared by a multidisciplinary workgroup including members from the Office of Pharmaceutical Quality, the Office of Translational Sciences, the Office of Generic Drugs, and the Office of Business Informatics in the Center for Drug Evaluation and Research at the Food and Drug Administration, and in consultation with the Office of Regulatory Affairs, the Office of Combination Products, and the Center for Devices and Radiological Health.

[2] In this guidance, terms that are found in Section VIII, the Glossary, are bolded at first use.

[3] In this guidance, the terms "review" and "assessment" are used interchangeably.

[4] The GDUFA III commitment letter is available at https://www.fda.gov/media/153631/download.

[5] FDA issued the previous revised draft pursuant to 21 CFR 10.115 in November 2017. See Federal Register notice at 82 FR 51421.

II. BACKGROUND

The Generic Drug User Fee Amendments of 2012 (GDUFA I)[6] amended the FD&C Act to authorize FDA to assess and collect user fees to provide FDA with resources[7] to help ensure patients have access to quality, affordable, 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.[8] As described in the GDUFA III commitment letter applicable to this latest reauthorization, FDA has agreed to performance goals and program enhancements regarding aspects of the generic drug assessment program that build on previous authorizations of GDUFA. New enhancements to the program are designed to maximize the efficiency and utility of each assessment cycle, with the intent of reducing the number of assessment cycles for ANDAs and facilitating timely access to generic medicines for American patients.

III. SCOPE

This revised draft guidance generally references the terms of the GDUFA III commitment letter and describes and provides recommendations on the content, timing, and assessment of a PFC for a **priority** ANDA, such that the ANDA will be eligible for **priority review** under the provisions of the GDUFA III commitment letter.[9,10] This guidance also provides information regarding FDA's assessment process for a PFC. Specifically, the guidance describes:

- the content and format of the **facility** information that should be submitted to enable FDA's assessment of **facilities** listed in the PFC*;*

[6] Title III of the Food and Drug Administration Safety and Innovation Act, Public Law 112-144.

[7] User fees are available for obligation in accordance with appropriations acts.

[8] Title III of Division F (the FDA User Fee Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023.

[9] On August 18, 2017, the FDA Reauthorization Act (FDARA) (Public Law 115-52), which reauthorized GDUFA (Title III) and added other provisions related to generic drugs (Title VIII), was signed into law. FDARA added section 505(j)(11) to the FD&C Act, which provides for priority review of certain original ANDAs, while permitting FDA to otherwise prioritize applications, as done under the GDUFA III commitment letter (which defines priority submissions to include those submissions affirmatively identified as eligible for expedited assessment pursuant to CDER's MAPP 5240.3 Prioritization of the Review of Original ANDAs, Amendments, and Supplements (Prioritization MAPP)). Accordingly, as described in the glossary to this revised draft guidance, FDA intends to consider an ANDA to be a priority ANDA if it meets the criteria listed in section 505(j)(11) of the FD&C Act, with respect to an original ANDA, or if it meets the criteria in the Prioritization MAPP. The criteria for affording an original ANDA priority status under the Prioritization MAPP and the terms of the GDUFA III commitment letter are generally broader than under section 505(j)(11), and certain prior approval supplements (PASs), PAS amendments, and ANDA amendments are also eligible for prioritization under the MAPP and the commitment letter; see also the GDUFA III commitment letter, sections I.A.2, I.B, and I.A.5. The applications granted priority review under section 505(j)(11) generally represent a subset of the applications eligible for priority review under the GDUFA III commitment letter.

[10] ANDAs that are not eligible for priority review under section 505(j)(11) or the GDUFA III commitment letter because of failure to follow the applicable PFC process and/or criteria might still receive an expedited review under the Prioritization MAPP, but the standard review goal will apply.

- timeframes for the PFC, and the intersection of these timeframes with submission of an ANDA;

- the possible outcomes of the Agency's assessment of a PFC; and,

- when and how the Agency communicates with an applicant about receipt of the PFC and assignment of a goal date for the ANDA.

IV. PRE-SUBMISSION FACILITY CORRESPONDENCE – CONTENTS

A **complete and accurate PFC** should contain all information needed to inform FDA's decision regarding the need for facility inspections that support the assessment of an ANDA.[11] The PFC provides the information FDA needs to assess the facilities involved in manufacturing processes and testing of the drug product, including facilities in corresponding Type II active pharmaceutical ingredient drug master files (API DMFs) referenced in an ANDA,[12] and all sites or organizations involved in bioavailability/bioequivalence analytical and clinical studies used to support an ANDA.[13]

FDA assesses facility information submitted in a PFC[14] to determine earlier in the review cycle for the subsequent application submission whether an inspection is necessary. In order to qualify for a **priority review goal**, an applicant should submit a PFC no later than 60 days prior to the date of ANDA submission. In general, under the terms of the GDUFA III commitment letter, if the PFC is found to be incomplete or inaccurate, or there are **significant changes** to information contained in a PFC when submitted in the ANDA, or if information received in a final bioequivalence study report included in the ANDA leads FDA to a decision that an inspection is

[11] See compliance programs 7348.003: *In Vivo Bioavailability-Bioequivalence Studies – Clinical,* 7348.004: *In Vivo Bioavailability – Analytical*, and 7346.832: *Preapproval Inspections*.

[12] Section II.F.1.b of the GDUFA III commitment letter clarifies that information needed to inform FDA's decision regarding the need for a preapproval inspection, such as a description of the drug substance manufacturing process, is not required to be duplicated in the PFC if it is included in a corresponding Type II DMF. If an ANDA does not reference a Type II DMF, all information needed to inform FDA's decision regarding the need for a preapproval inspection should be provided in the PFC by the ANDA applicant.

[13] An applicant is responsible for identifying all the facilities that impact its ANDA, including the name and address of each API and drug product manufacturer (i.e., facility). In addition, an applicant must also submit a complete bioequivalence study report in their ANDA; see 21 CFR 314.70, 314.94, and 314.96 for requirements related to content of ANDAs.

[14] See the GDUFA III commitment letter, section II.F.1.

necessary,[15] the 10-month standard review goal will generally apply instead of the priority review goal.[16]

The complete and accurate PFC[17] must be submitted in the electronic common technical document (eCTD) format.[18]

A. Drug Substance and Drug Product Manufacturing and Testing Facilities

Preapproval evaluations and inspections support the assessment of an ANDA by ensuring that any facility named or referenced in support of an ANDA can perform a proposed manufacturing operation as described in the application, in conformance with current good manufacturing practice requirements, and that manufacturing data submitted in the ANDA are accurate and complete. FDA utilizes a risk-based approach to assess whether a preapproval inspection (PAI) is needed before an ANDA can be approved from a quality perspective. This approach focuses on understanding risks to critical quality attributes[19] associated with a facility, process, or product.[20]

A complete and accurate PFC should provide the information necessary for FDA to determine each facility's manufacturing operation capabilities for drug product[21] or API,[22] and to identify the need for a PAI. This information should include a description of the manufacturing process, controls of critical steps, and anticipated differences between pilot/exhibit scale and commercial

[15] To note, in implementing section 505(j)(11) of the FD&C Act for priority review of certain original ANDAs, FDA determined (per authority to identify necessary information in that context) that a final bioequivalence study report is required to make a determination under that provision regarding whether an inspection of a facility is necessary. Thus, a PFC submission under section 505(j)(11) without the final study report would not qualify the ANDA for priority review under that provision. However, for purposes of priority review under the GDUFA III commitment letter, FDA agreed that a prospective applicant can submit a PFC without the final bioequivalence study report and qualify for a priority review goal, if certain conditions are met. Notably, if the data and information contained in that report as submitted in the ANDA do not raise issues that provide a basis for inspection of the facility, the ANDA will receive a priority goal date under the GDUFA III commitment letter. If that data and information do raise issues that provide a basis for inspection, the ANDA will not receive a priority goal date under the GDUFA III commitment letter.

[16] See the GDUFA III commitment letter, sections I.A.2.b, I.A.6, I.B.2.c, and I.B.4.c. Of note, FDA will only review the original PFC submitted by an applicant. If FDA determines a PFC is not complete and accurate, as described in the GDUFA III commitment letter, the PFC may not be revised, and no additional review of the PFC will be undertaken. In such cases, FDA intends to assess and act on the ANDA within 10 months of the date of ANDA submission.

[17] See the GDUFA III commitment letter, section II.F.1.

[18] The electronic submission requirements of Section 745A(a) of the FD&C Act are implemented in the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, Revision 7* (February 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. See also eCTD Technical Conformance Guide, at https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/ectd-resources.

[19] See FDA guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009) and *Q11 Development and Manufacture of Drug Substances* (November 2012).

[20] See compliance program 7346.832: *Preapproval Inspections*.

[21] See 21 CFR 210.3(b)(12) which states "Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products."

[22] See FDA guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).

scale processes.[23] Information regarding the conformance of exhibit batches to specifications should be provided.[24]

For each manufacturing facility, an applicant should also provide the following: facility name, operation(s) performed, facility contact name, address, FDA Establishment Identifier (FEI) number (if a required registrant or one has been assigned), DUNS number, registration information (for required registrants), confirmation that the facility is ready for inspection,[25] and certification that any Type II DMF has similarly complete and accurate facility information.[26]

A summary of facility information that should be submitted in a complete and accurate PFC, including corresponding eCTD sections and eCTD Module Numbers[27] is provided in Table 1.

B. Clinical Bioequivalence Study Sites and Organizations

Sites or organizations that perform the clinical portions of BE studies used to support an ANDA are subject to inspection to evaluate the overall quality of subject safety and data integrity at the site.[28] A complete and accurate PFC should contain the information needed to inform FDA's decision regarding the need for a bioresearch monitoring inspection of these sites, including the site name, address, and website; study numbers; a list and description of all study investigators consistent with section 16.1.4 of the guidance *ICH E3 Structure and Content of Clinical Study Reports* (July 1996);[29] study conduct dates; and study protocols and any available amendments.[30]

A summary of clinical site or organization information that should be submitted in a complete and accurate PFC, including corresponding eCTD sections and eCTD Module Numbers, [31] is included in Table 1.

C. Analytical Bioequivalence Sites and Organizations

Sites or organizations that perform the analytical portions of clinical bioequivalence studies or in vitro bioequivalence studies (collectively referred to as analytical sites), are subject to inspection to ensure that these studies are conducted using the highest laboratory standards and in accordance with applicable regulations.[32] A complete and accurate PFC should contain the information needed to inform FDA's decision regarding the need for a bioresearch monitoring inspection of analytical sites, including the site name, address, and website.

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[23] See-the GDUFA III Commitment letter section II.F.1.a.ii.

[24] See FDA guidance for industry *ANDA Submissions – Content and Format* (June 2019).

[25] See the GDUFA III commitment letter, section II.F.1.a.i.

[26] See the GDUFA III commitment letter, section II.F.1.a.iii.

[27] Per normal submission practices, information for some subsections in eCTD section 3.2.S may be incorporated through reference to a type II DMF, where a letter of authorization (LOA) has been submitted to the DMF by the DMF holder, and the Statement of Right of Reference is included by the Applicant in eCTD section 1.4.2 of the ANDA.

[28] See FDA compliance program 7348.003: *Bioresearch Monitoring – Clinical*.

[29] See ICH guidance for industry *E3 Structure and Content of Clinical Study Reports* (July 1996).

[30] See the GDUFA III commitment letter, section II.F.1.c; see also See 21 CFR 314.94(a)(7).

[31] See footnote 18.

[32] See FDA compliance program 7348.004: *Bioresearch Monitoring – Analytical*.

For those analytical studies that were initiated no later than 60 days prior to the ANDA submission, additional recommendations are: a list of investigator name(s); study conduct dates; and the analytical method validation, if completed before dosing.[33]

A summary of analytical site or organization information that should be submitted in a complete and accurate PFC, including corresponding eCTD sections and eCTD Module Numbers[34] is provided in Table 1.

[33] See the GDUFA III commitment letter, section II.F.1.d.
[34] See footnote 18.

Table 1. List of Facility Information that should be submitted in the PFC for a Priority ANDA[a]	
eCTD Module Number	Description
1.1	Form FDA 356h[b,c] — the Form FDA 356h should be submitted with the PFC. Submitting the Form FDA 356h will enable the Agency to expedite processing of the PFC. Consider the following when submitting a Form FDA 356h associated with a PFC: • "Submission" Field— this field accommodates selection of all the choices that apply. For a PFC related to a priority ANDA, select "Product Correspondence" and "Other." In the "Other" field, specify that this is a "Pre-Submission of Facility Information Related to a Priority ANDA." This option should be selected for PASs, PAS amendments, and ANDA amendments, as well as for original ANDAs. • "Submission Sub-Type" Field – for this field, select "Pre-submission."
1.2	Cover Letter — the Cover Letter accompanying the PFC should include: • Statement of inspection readiness • Statement identifying the Reference Listed Drug • Anticipated date of original ANDA, PAS, PAS amendment, or ANDA amendment submission
1.3.1.2	U.S. Agent Appointment Letter (if applicable)
1.4.2	Statement of Right of Reference – this includes the DMF Right of Reference Letter, if applicable
2.7	Summary of Biopharmaceutic Studies and Associated Analytical Methods (Tables 2 and 10)[d]
3.2.S.1.1	Nomenclature[e]
3.2.S.1.2	Structure[e]
3.2.S.1.3	General Properties[e]
3.2.S.2.1	Manufacturer(s)[f]
3.2.S.2.2	Drug Substance Manufacturing Process Description[g]
3.2.S.2.4	Control of Critical Steps and Intermediates[g]
3.2.S.2.6	Manufacturing Process Development[g]
3.2.S.4.1	Drug Substance Specifications
3.2.S.4.4	Batch Analyses
3.2.P.1	Description and Composition of the Drug Product
3.2.P.2	Pharmaceutical Development — Manufacturing Process Development
3.2.P.3.1	Manufacturer(s)
3.2.P.3.2	Batch Formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls
3.2.P.3.4	Control of Critical Steps and Intermediates
3.2.P.3.5	Sterilization Validation Documentation and Data[h]
3.2.P.5.1	Drug Product Specifications
3.2.P.5.4	Batch Analyses

3.2.P.7	Facility Information for Non-Drug Constituent Parts of a Combination Product
5.3.1.2	Information related to bioequivalence and clinical studies. Specifically: • Site names, addresses, and websites • Study Titles • Study Numbers • Study Conduct Dates • Study Protocol and Available Amendments – ICH E3 (16.1.1)[i] • List and Description of all Study Investigators – ICH E3 (16.1.4)[i] • Study Report if available at the time of the PFC
5.3.1.4	Information related to analytical studies. Specifically: • Site names, addresses, and websites • Study Titles • Study Numbers • Study Conduct Dates • A list of investigator name(s) • Analytical Method Validation Report(s) if the analytical method validation was completed before dosing • Study Report if available at the time of the PFC

[a.] See 21 CFR 314.70, 314.94, 314.96 and 314.97 for requirements related to ANDA content.
[b] See FDA's guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers* (October 2019).
[c] See draft guidance for industry *Facility Readiness: Goal Date Decisions Under GDUFA* (October 2022). When final, this guidance will represent the FDA's current thinking on this topic.
[d] See Model Bioequivalence Data Summary Tables: Technical Specifications Document, at https://www.fda.gov/media/75081/download.
[e] See section III.C.1, Topic 3.2.S.1 in FDA's guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications* (June 2019), which states that 3.2.S.1 "should not include any references to the DMF."
[f] See section III.C.1, Topic 3.2.S.2.1 in FDA's guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications* (June 2019), which states that 3.2.S.2.1 "Contains information about each drug substance manufacturer, including…Type II DMF number for the API or any critical or final intermediates, if applicable."
[g] See section III.C.1, Topics 3.2.S.2.2 through 3.2.S.2.6 in FDA's guidance for industry *ANDA Submissions — Content and Format* (June 2019), which states that that "Subsections 3.2.S.2.2 through 3.2.S.2.6 may refer to the DMF. If there is no DMF referenced in the application, detailed information should be provided in these subsections."
[h] For further information on sterilization validation documentation expectations in a marketing application, see FDA's guidance for industry for the *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994).
[i] See ICH guidance for industry *E3 Structure and Content of Clinical Study Reports* (July 1996).

NOTE — For PASs, PAS amendments, and ANDA amendments, only the modules applicable to these types of submissions should be submitted.[35]

[35] See 21 CFR 314.70, 314.96, and 314.97.

With regard to combination products (as defined in 21 CFR 3.2(e))[36] and the facility information related to the manufacturing and testing of non-drug constituent parts,[37] refer to both the eCTD Technical Conformance Guide[38] and guidance for industry: *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER – Questions and Answers* (October 2019).[39]

V. RECEIPT AND ASSESSMENT PROCESS FOR PRE-SUBMISSION FACILITY CORRESPONDENCE

The following section describes the process for the receipt and assessment of the PFC related to a priority ANDA.

A. Submitting the PFC through FDA's Electronic Submissions Gateway (ESG)

1. Obtaining a Pre-Assigned ANDA Number (if applicable)

For original ANDAs, the applicant should request a pre-assigned ANDA number before submitting the PFC. For PASs, PAS amendments, and ANDA amendments, the applicant should use the relevant ANDA application number on the Form FDA 356h.

2. Transmitting the PFC through FDA's ESG

The PFC must be submitted electronically in eCTD format[40] through the FDA ESG following the Agency's instructions.[41] When transmitting the PFC through the ESG, choose "CDER" when selecting the appropriate Center, and choose "eCTD" when selecting the submission type.

The applicant should submit the priority ANDA consistent with the "ANDA Submission Timing" described in section V.B. (below). If the applicant decides not to submit the ANDA after submitting the PFC, FDA should be notified in writing. The notice of decision not to submit

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[36] A combination product is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another). The drugs, devices, and biological products included in combination products are referred to as "constituent parts" of the combination product. See section 503(g) of the FD&C Act and 21 CFR part 3.

[37] See 21 CFR part 4. See also guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017), section II.C "Overview of the final rule."

[38] For additional information on how to incorporate information regarding non-drug constituent parts into the eCTD Sequence, please refer to the eCTD Technical Conformance Guide at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm535180.htm.

[39] For additional information on how to incorporate information regarding non-drug constituent parts into the eCTD Sequence, please refer to the guidance for industry *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER – Questions and Answers* (October 2019).

[40] See footnote 18.

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

the ANDA should reference the submission number and be submitted to eCTD section 1.2, Cover Letter.

3. FDA's Assessment of the PFC

The Agency will begin assessment of the PFC upon receipt. FDA will send a letter to the applicant to acknowledge receipt of the PFC. FDA will assess priority status and assign the appropriate review goal date after the ANDA is submitted[42] as further explained in Section VI.B (below).

B. ANDA Submission Timing

In order for an ANDA to be eligible to receive priority review, the PFC should be submitted not later than 60 days prior to the submission of the ANDA itself.[43] This timing allows the Agency to begin assessing the facility information before receiving the ANDA.

Additionally, an ANDA should not contain any significant changes to the information submitted in the PFC.[44] To minimize the possibility of significant changes to facility information between submission of the PFC and the ANDA (and consequently loss of the priority review goal), FDA recommends applicants submit the PFC not earlier than 90 days before submission of the ANDA and refer to guidance for industry *Providing Regulatory Submissions in Electronic Format – Receipt Dates* (February 2014)[45] for further details.

For example:

1. If an original ANDA was submitted on Monday, February 12, 2024, then the PFC would have to have been submitted not later than Thursday, December 14, 2023, to be consistent with the criterion that the PFC be submitted not later than 60 days prior to the submission of the ANDA.

2. If an original ANDA was submitted on Thursday, November 16, 2023, then the PFC would have to have been submitted not later than Friday, September 15, 2023. This scenario accounts for the not later than 60 days period ending on a weekend.

3. If an original ANDA was submitted on Thursday, July 4, 2024, then the PFC would have to have been submitted not later than Monday, May 6, 2024. This scenario accounts for a Federal Holiday.

The applicant should submit a signed certification statement during ANDA submission (in eCTD section 1.2) stating that the applicant has 1) made no significant changes (as described in the

[42] See Section III (Scope) and footnotes 9 and 10.

[43] The GDUFA III commitment letter sections I.A.2.a, I.A.5.b, I.B.2.b, and I.B.4.b refer to the submission of the PFC "not later than 60 days prior to the date of ANDA submission" in order to be eligible for the 8-month priority review goal. See also section 505(j)(11)(B) of the FD&C Act.

[44] See the GDUFA III commitment letter sections I.A.2.b.iii, I.A.6.c, I.B.2.c.iii and I.B.4.c.iii.

[45] See footnote 18.

GDUFA III commitment letter)[46] to the information contained in the PFC or 2) has made no changes except to exclude a facility not involved in generating data for the application as described in section 505(j)(11)(B) of the FD&C Act.

Significant changes between PFC and ANDA submission will result in assignment of the standard review goal.[47] Such significant changes should be made by including information regarding the significant changes in the appropriate eCTD module with the ANDA submission. Such significant changes should be identified in the cover letter.

FDA's review of the ANDA, which will include an assessment and determination of whether the ANDA meets the priority designation criteria, will be performed in accordance with its applicable statutory and regulatory authorities and policies, and procedures for ANDA reviews. At the time of receipt, FDA will notify the applicant in the ANDA acknowledgement letter whether the ANDA or PAS is subject to priority review.

VI. NOTIFICATIONS TO THE APPLICANT

A. Pre-Submission Facility Correspondence Acknowledgement Letter

As part of its assessment of the PFC, the Agency will send a letter to:

- Inform the applicant that a goal date incorporating any priority designation determination will be provided after submission and receipt for assessment of the ANDA; and

- Remind the applicant that they must not submit their ANDA earlier than 60 days after the date of submission of the PFC date to be eligible for the priority review goal.[48]

The Pre-Submission Facility Correspondence Acknowledgement Letter simply acknowledges receipt of the PFC by the Agency. Eligibility for the priority review goal based on the PFC is determined by FDA when an ANDA is submitted.

B. Determining Whether an ANDA Qualifies for the Priority Review Goal

After receiving the ANDA, FDA will determine the applicable goal date for the submission. Establishing the applicable goal date for the ANDA is based on the Agency's priority designation determination at the time of ANDA submission; assessment of whether the applicant submitted a complete and accurate PFC, including confirmation that all facilities are ready for

[46] The GDUFA III commitment letter, section II.F.2 states that: "Changes to information contained in a PFC when submitted in an ANDA that are considered a 'significant change' include changes in the identified facilities for manufacture of the drug substance or drug product, the proposed manufacturing operations or operating principles, and the order of manufacturing unit operations."

[47] See footnote 44.

[48] See footnote 43.

inspection; and determination that the information submitted in the ANDA does not differ significantly from what was submitted in the PFC.[49] The Agency will convey the outcome and resulting goal date in the ANDA acknowledgement letter.

VII. QUESTIONS AND ANSWERS

A. What types of submissions are addressed by this guidance?

This revised draft guidance includes recommendations for, and applies to, priority original ANDAs, PASs, PAS amendments, and ANDA amendments.

B. What is the rationale for the manufacturing records listed in Table 1?

A complete and accurate PFC supports GDUFA III performance goals and program enhancements designed to maximize the efficiency and utility of each ANDA assessment cycle. To this end, FDA evaluated the records and information required for an ANDA submission to determine which specific records would allow FDA to determine, earlier in the ANDA assessment cycle, if an inspection is necessary to support the assessment of an ANDA.

As described in FDA compliance program 7346.832: *Preapproval Inspections*, FDA determines the need for PAIs based on the cumulative assessment of process, product, and facility risks related to the pending application. Manufacturing information contained in the PFC provides FDA the ability to perform this assessment and determine the need for a PAI earlier in the ANDA assessment process. For example, information contained in a PFC related to manufacturing process development, description of the manufacturing process and controls, controls for critical steps, sterilization validation, specifications, and batch analyses allows FDA to assess whether manufacturing operations were designed and implemented accounting for knowledge gained during development, were executed as intended in support of the application, and that such operations reflect the intended commercial operations. The list of manufacturing sites, proposed manufacturing operations, and description of manufacturing process and controls allows FDA to assess the comparability of proposed operations to the known capabilities of manufacturers in the context of their current compliance status. If there are significant differences between the process used for the development/exhibit batches and the proposed commercial manufacturing process, or if FDA has concerns about knowledge transfer, this could indicate the need for an inspection.

C. What is the purpose of the certification statement to which Section V refers?

The certification statement is the applicant's signed statement that the PFC information is complete and accurate, and the information submitted in the ANDA does not differ significantly from what was submitted in the PFC, as is a condition for priority review goal eligibility under the terms of the GDUFA III commitment letter.[50]

[49] See the GDUFA III commitment letter, section II.F.

[50] See footnote 44.

Applicants that include significant changes to the PFC information in their submitted ANDA should omit the certification statement and identify such significant changes in the cover letter. Such changes will generally result in assignment of the standard review goal.[51]

D. What is considered a significant change?

Significant changes represent any changes to the facility information as submitted in an ANDA, relative to information submitted in the PFC, that have the potential to introduce or increase risk(s) to critical quality attributes associated with the facility or the process.[52] A priority ANDA[53] is eligible for a priority review goal only when there are no significant changes between information contained in the PFC and that submitted in the ANDA. Significant changes include, but are not limited to, changes in the identified facilities for manufacture of the drug substance or drug product, the proposed manufacturing operations or operating principles, or the order of manufacturing unit operations.[54] Significant changes may alter FDA's initial decision regarding the need for a PAI, resulting in the decision to conduct an inspection that was not deemed necessary at the time of PFC assessment. In the case of significant changes, the standard review goal would apply.

Certain revisions of information contained in the PFC when submitted in the ANDA may not be considered a significant change, in that a decision on the need for an inspection would not require reconsideration based on such changes. For example, finalization of the development report without changes to the manufacturing process or control strategy, finalization of process parameters, or the final designation of commercial equipment without changes in design or operating principle are changes that may not be considered significant.

E. Can a final bioequivalence study report in an ANDA impact a priority goal date?

Although an ANDA applicant may submit the final bioequivalence study report (clinical and/or analytical) at the same time as a PFC, a final bioequivalence study report is not a condition for a complete and accurate PFC under the terms of the GDUFA III commitment letter. If an applicant submits the final bioequivalence study report with a complete and accurate PFC and FDA determines that an inspection is needed, the priority goal date may still apply. However, if an applicant instead submits their final bioequivalence study report at the time of ANDA submission and FDA determines, upon assessment of the final bioequivalence study report, that an inspection of the relevant site or sites is necessary, the standard 10-month goal date will apply under the terms of the GDUFA III commitment letter.[55]

F. Should an ANDA include facility information already provided in a PFC?

[51] Ibid.
[52] See footnote 1919.
[53] FDA intends to consider an ANDA to be a priority ANDA per the GDUFA III commitment letter if it is prioritized under the Prioritization MAPP.
[54] See footnote 46.
[55] See the GDUFA III commitment letter, section I.A.2.b.iv.

No. The applicant should not re-submit the facility information contained in the PFC. However, if there have been any significant changes since submission of the PFC, the new information must be included in the ANDA[56] and should be identified in the cover letter.

G. Should an applicant submit more of its ANDA in the PFC than is recommended in this guidance?

Only the information listed in section IV of this revised draft guidance should be submitted in the PFC. A PFC including this information will be considered a complete and accurate PFC under the terms of the GDUFA III commitment letter.[57]

H. Should the facilities be ready for inspection at the time of PFC submission?

The PFC should include confirmation that all facilities involved in manufacturing processes for the ANDA and corresponding Type II API DMF are ready for inspection.[58] The PFC does not need to include confirmation that sites or organizations involved in bioequivalence and clinical studies, or analytical studies used to support the ANDA submission are ready for inspection, as FDA will make inspection determinations for these sites or organizations during assessment of the ANDA.[59]

Under the terms of the GDUFA III commitment letter, for original ANDAs only, if at the time of ANDA submission, any facilities involved in manufacturing processes and testing for the ANDA and corresponding Type II API DMFs are no longer ready for inspection, as indicated in the Form FDA 356h, FDA will set a goal date that is 15 months from the date of original ANDA submission.[60] If the applicant previously submitted an otherwise complete and accurate PFC prior to original ANDA submission, and an amendment stating that all facilities are ready for inspection is submitted at least 30 days prior to the 15-month goal date expiration, FDA will reassign a priority goal date from the date of amendment submission.[61, 62] This 15-month goal date extension for an original ANDA with a facility that is not ready for inspection is not applicable to sites or organizations involved in bioequivalence and clinical studies, or analytical studies used to support an ANDA.

I. Is there a user fee payment required when submitting the PFC for an original ANDA?

[56] See 21 CFR 314.70, 314.94, 314.96, and 314.97.
[57] See the GDUFA III commitment letter, section II.F.1. As described in Question E, an applicant may submit a final bioequivalence study report (clinical and/or analytical), if available, at the same time an applicant submits a PFC. A determination of priority review will still occur at the time of ANDA submission.
[58] See the GDUFA III commitment letter, section II.F.1.a.i.
[59] See the GDUFA III commitment letter, sections II.F.1.c and II.F.1.d.
[60] See the GDUFA III commitment letter, section I.A.3.
[61] See the GDUFA III commitment letter, section I.A.3.a.
[62] See draft guidance for industry *Facility Readiness: Goal Date Decisions Under GDUFA* (October 2022).

No. There are no user fees associated with the PFC. Under GDUFA, an ANDA filing fee is paid at the time of the original ANDA submission.[63]

[63] Section 744B(a)(3) of the FD&C Act. See also the Generic Drug User Fee Cover Sheet and Payment Information https://www.fda.gov/industry/fda-user-fee-programs for further details.

VIII. GLOSSARY

A. Complete and Accurate PFC

A complete and accurate PFC includes: information for facilities involved in manufacturing processes, including testing, for the drug that is the subject of the application (including facilities in corresponding Type II API DMFs referenced in an application); sites or organizations involved in bioequivalence and clinical studies used to support the application;[64] and includes confirmation that all facilities are ready for inspection.[65] For manufacturing facilities, this includes information needed to inform FDA's decision for a PAI.

B. Facility

For the purposes of this guidance, the term "facility(-ies)" means "manufacturing site" and "bioequivalence site."

"Manufacturing site" means all sites involved in manufacturing processes, packaging, and testing for the ANDA and corresponding Type II API DMF.[66,67] For the purpose of this guidance, this term refers to any manufacturing, packaging, or testing site associated with an ANDA that conducts an operation to support manufacturing or testing of the API or drug product. This includes sites listed in Type II DMFs and sites that manufacture non-drug constituent parts of a combination product. For additional information including guidance regarding those facilities that should be listed on the Form FDA 356h in support of the PFC, please refer to the FDA guidance for industry *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers* (October 2019).

"Bioequivalence site" means all sites or organizations involved in clinical bioequivalence studies with pharmacokinetic, pharmacodynamic or clinical endpoints, and in vitro bioequivalence studies used to support the ANDA submission.[68] For the purposes of this guidance, this term also captures sites that conduct analytical testing in support of the ANDA.

C. PFC

The term "PFC" refers to a submission of facility information prior to ANDA submission that enables a shorter review goal (priority review goal) for certain priority original ANDAs, PASs, PAS amendments, and ANDA amendments, if the PFC meets applicable conditions.

D. Priority

The term "priority" refers to ANDAs that meet the relevant criteria listed in section 505(j)(11) of the FD&C Act, in order to qualify for priority review under that provision, or submissions

[64] See footnote 14.
[65] See footnote 17.
[66] See footnote 2121.
[67] See footnote 22.
[68] See 21 CFR 314.94(a)(7) and 320.24(b).

identified as eligible for expedited assessment pursuant to CDER's Manual of Policies and Procedures (MAPP) 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements* (Prioritization MAPP).

E. Priority Review

The term "priority review" refers to the 8-month review provided for under section 505(j)(11) of the FD&C Act, with respect to original ANDAs subject to that provision, or the 8-month priority review goal provided for under the terms of the GDUFA III commitment letter.

F. Priority Review Goal

The term "priority review goal" refers to the shorter 8-month goal dates identified in the GDUFA III commitment letter for priority original ANDAs, PASs, PAS amendments, and ANDA amendments that are designated priority by FDA and have submitted within the proper timeframe a complete and accurate PFC that is not significantly changed relative to the date of subsequent ANDA submission.[69]

G. Significant Changes

As set forth in the GDUFA III commitment letter, the term "significant changes" includes changes to the identified facilities for manufacture of the drug substance or drug product, to the proposed manufacturing operations or operating principles, and to the order of manufacturing unit operations, when such changes are made between the time of PFC receipt and ANDA submission.[70]

[69] See footnote 16.
[70] See footnote 46.