ANDAs: Pre-Submission Facility Correspondence Associated with Priority Submissions

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Nikhil Thakur 301-796-5536.

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

June 2017
Pharmaceutical Quality/ CMC

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

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ANDAs: Pre-Submission Facility Correspondence Associated with Priority Submissions Guidance for Industry[1,2]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 describes the process through which prospective generic drug applicants submit pre-submission facility correspondence (PFC) in advance of *priority*[3] generic drug submissions.

In 2016-2017, the Food and Drug Administration (FDA), regulated industry, and public stakeholders conducted negotiations concerning reauthorization of the Generic Drug User Fee Amendments (GDUFA II).[4] A chief product of these congressionally mandated discussions is the GDUFA II Commitment Letter. The GDUFA II Commitment Letter describes the FDA's performance goals under GDUFA II as well as changes and improvements to the user fee program. The performance goals and program enhancements specified in the GDUFA II Commitment Letter concern aspects of the generic drug review program that are important for facilitating timely access to quality, affordable generic medicines.

As one of the enhancements specified in the GDUFA II Commitment Letter, the PFC is a mechanism to achieve expedited review of *priority* abbreviated new drug applications (ANDAs), prior approval supplements (PASs), and their amendments (collectively ANDAs). Using a PFC, a prospective applicant submits certain information related to manufacturing and bioequivalence facilities (collectively *facilities*)[5] that will be referenced in a *planned ANDA*[6] prior to submission

[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.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] In Section IX of this guidance, the term *priority ANDA* is defined.

[4] See *GDUFA Reauthorization Performance Goals and Program Enhancements, FYs 2018-2022.* All public documents cited in this guidance may be found on the FDA website (www.fda.gov).

[5] In Section IX of this guidance, the term *facilities* is defined.

of the ANDA itself. Pre-submission facility correspondence should also demonstrate that the *planned ANDA* meets the criteria for a *priority* submission. The *priority* designation criteria are described in the Center for Drug Evaluation and Research's (CDER) Manual of Policies and Procedures (MAPP) 5240.3, Rev. 2, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements* (Prioritization MAPP).[7] For example, if the ANDA drug product is the subject of a current drug shortage, the ANDA would potentially qualify for *priority* review.[8]

The information submitted in the PFC provides the Agency with the opportunity to determine whether *facility* inspections will be needed. When deemed necessary, the Agency will initiate inspection planning earlier in the review of the ANDA. Further, it enables FDA to meet the shorter review timeframe (*shorter goal dates*[9]) for the *planned ANDA* as defined in the GDUFA II Commitment Letter. If a PFC successfully demonstrates that the *planned ANDA* may be a *priority* submission and the information is *complete and accurate* and is *unchanged*,[10] the ANDA may qualify for *shorter goal dates* for the *planned ANDA*. Absent extraordinary circumstances, FDA does not expect to utilize its limited resources to review a second PFC on the same submission if the first one is deficient.

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 the performance goals and program enhancements for GDUFA II, FDA agreed to a *shorter goal date* for action on a *priority* generic drug submission if:

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[6] In Section IX of this guidance, the term *planned ANDA* is defined.

[7] Prioritization of review is determined per the criteria established in CDER's MAPP 5240.3, Rev. 2, entitled *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*.

[8] This is an example of an ANDA that could qualify for *priority* designation under the current MAPP. The MAPP is subject to change and should be consulted at the time of PFC submission for FDA's then-current prioritization criteria. To make sure you have the most recent version of a MAPP, check the CDER MAPPs web page at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[9] In Section IX of this guidance, the term *shorter goal date* is defined.

[10] In Section IX of this guidance, the term *change* is defined to reflect the definition of "change, with respect to facility information" as stated in the GDUFA II Commitment Letter.

- A *complete and accurate PFC*[11] is submitted to FDA 2 months ahead of the *planned ANDA* submission, and
- *Facility* information remains *unchanged* in the ANDA.

A *complete and accurate PFC* allows the Agency to begin the *facility* assessment process in advance of the *planned ANDA* submission. This critical 2 month lead time provides the Agency the opportunity to determine whether *facility* inspections will be needed, and when they are, to initiate inspection planning earlier in the review of the ANDA, enabling FDA to meet the shorter review timeframe.

Note: If the criteria above for the *shorter goal date* are not met at any time after PFC submission, the ANDA may still be *prioritized* for review but the standard goal date would apply.

The GDUFA II Commitment Letter states that a *complete and accurate PFC* lists all of the following:

1. All facilities involved in manufacturing processes and testing for the ANDA and corresponding Type II active pharmaceutical ingredient (API) drug master file (DMF) as required by 21 CFR 314.50(d)(1)(i) and (iii).[12] For each manufacturing or testing facility, the correspondence includes facility name, operation(s) performed, facility contact name, address, FEI number (if a required registrant or one has been assigned), DUNS number,[13] registration information (for required registrants), a confirmation that the facility is ready for inspection, a description of the manufacturing process, and a certification by the applicant that any Type II DMF has similarly complete and accurate facility information as required by 21 CFR 314.50(d)(1)(i), including complete facility information (i.e., facility name, operation, facility contact name, address, FEI number, and DUNS number). Facility information that is included in a corresponding Type II DMF is not required to be duplicated in the PFC for the ANDA.

2. All sites or organizations involved in bioequivalence and clinical [endpoint bioequivalence] studies used to support the ANDA submission as described in 21 CFR 314.94(a)(7) [and 21 CFR 320.24(b).][14] This information is provided using a

[11] In Section IX of this guidance, the term *complete and accurate Pre-Submission Facility Correspondence (PFC)* is consistent with the definition provided in the GDUFA II Commitment Letter.

[12] The GDUFA II Commitment Letter captures the term manufacturing sites under the definition of complete and accurate PFC as, "All facilities involved in manufacturing processes, packaging and testing for the ANDA and corresponding Type II API DMF as required by 21 CFR 314.50(d)(1)(i) and (iii)."

[13] The Data Universal Numbering System (D - U - N - S) is a unique nine-digit sequence provided by Dun & Bradstreet, which serves as a unique identifier for each physical location of a business. See the guidance for industry *Self-Identification of Generic Drug Facilities, Sites, and Organization* (Sept. 2016).

[14] The GDUFA II Commitment Letter captures the term bioequivalence sites under the definition of complete and accurate PFC as, "All sites or organizations involved in bioequivalence and clinical studies used to support the

standardized electronic format and includes unique identifiers that are current and accurate, including site or organization name, address and website; and study information including a listing of study names, dates of conduct and main investigators.

For the purpose of this guidance, the term *facility* is inclusive of all sites that are considered to be *manufacturing sites* AND *bioequivalence sites* as defined in this guidance.[15]

This guidance describes PFC content and format, as well as the Agency's approach to assessing this information.

III. SCOPE

This guidance establishes FDA's expectations for the content, timing, and assessment of the PFC. Specifically, the guidance defines:

- The content and format of the information that should be submitted in the PFC to enable FDA's assessment of *facilities* listed in the PFC.
- PFC timeframes and their intersection with the subsequent ANDA submissions.
- The possible outcomes of the Agency's assessment of the PFC.
- When and how the PFC submitter is notified by the Agency about the status of the PFC.

IV. PRE-SUBMISSION *FACILITY* CORRESPONDENCE CONTENT

A *complete and accurate PFC*, as defined by the GDUFA II Commitment Letter, provides the information needed for FDA to conduct a meaningful assessment of the *facilities* that will be used to support the *planned ANDA* submission. Notably, the PFC should include a thorough description of the manufacturing process as outlined in Section IV.C and all study information as outlined in Section IV.D.

The PFC should include the following information:

A. General Information

- *Planned ANDA* Pre-Assigned Number
- Date of PFC Submission
- PFC Submitter Information:
    - Name of PFC Submitter
        - Telephone Number (include country code, if applicable, and area code)

ANDA submission as described in 21 CFR 314.94(a)(7)." For purposes of this guidance, the term "clinical studies" in this definition refers to clinical "endpoint bioequivalence" studies. PFC Submitters / Applicants should also refer to 21 CFR 320.24(b) "Types of evidence to measure bioavailability or establish bioequivalence."

[15] In Section IX of this guidance, the terms *manufacturing site* and *bioequivalence site* are defined.

137 ▪ Facsimile (FAX) Number (include country code, if applicable,
138 and area code)
139 ▪ Address (Street Address, City, State/Province/Region, Country,
140 Zip or Postal Code)
141 ▪ Secure Email Address
142 o Contact or U.S. Agent Name
143 ▪ Telephone Number (include country code, if applicable, and
144 area code)
145 ▪ Facsimile (FAX) Number (include country code, if applicable,
146 and area code)
147 ▪ Address (Street Address, City, State/Province/Region, Country,
148 Zip or Postal Code)
149 ▪ Secure Email Address
150 o DMF Right of Reference Letter
151 o As applicable – Statement from the DMF holder permitting FDA to
152 access the DMF information such that FDA is authorized to review
153 relevant confidential information as a part of the review of the PFC[16]
154
155 • NOTE Regarding PAS or PAS Amendments:
156
157 If the PFC is associated with a PAS or PAS Amendment,[17] then a statement
158 should be provided, describing:
159 o The reason for the PAS (or Amendment)[18]
160 o Whether the submission is a PAS or PAS Amendment
161 o The anticipated disciplines that would review the PAS, when it is
162 submitted to the Agency (e.g., Chemistry, Labeling, DMF,
163 Bioequivalence, Microbiology or Clinical)
164
165 This description will enable the Agency to effectively route the submission for
166 appropriate review.
167
168 If the PFC is associated with "Grouped Supplements,"[19] then it will be
169 assessed on behalf of all the supplements within the group.
170
171 **B. Statement of ANDA Eligibility for *Priority* Review**
172

[16] See FDA.gov, "Drug Master Files (DMFs)" – DMF holders should submit the Letter of Authorization (LOA) to the DMF, and a copy of that LOA to the ANDA applicant.

[17] 21 CFR 314.70(b) describes the types of changes that require prior approval.

[18] Examples of reasons for submitting a PAS include, but are not limited to, new strength, reformulation, Rx to OTC switch, or change in manufacturing processes.

[19] "Grouped Supplements" as defined by CDER's MAPP 5015.1, Rev. 1, entitled *Review of Grouped Product Quality Supplements.*

As a prerequisite for the *planned ANDA* to be eligible for the *shorter goal date*, the product to be submitted in the *planned ANDA* should appear to meet the *priority* designation criteria as described in the Prioritization MAPP. To aid FDA's determination regarding eligibility for *priority* review, the PFC should include a statement explaining which of the *priority* designation criteria in the Prioritization MAPP are met.

C. Manufacturing Process and Testing *Facility* Information

The PFC should contain the following information to inform the Agency's assessment of the *manufacturing site* associated with the *planned ANDA*.

1. Administrative Information about facilities (including those referenced in a Type II DMF)

The PFC should include the following administrative information for each *manufacturing site* associated with the *planned ANDA*, including any relevant *manufacturing site* identified in a corresponding Type II DMF:

- Facility Name
- Facility Contact
- Facility Address
- Telephone Number
- Fax Number
- Email Address
- FEI Number
- DUNS Number[20]
- Operation(s) performed at the facility
- Confirmation that the facility is ready for inspection

When site and manufacturing process information for a drug substance is provided in a corresponding Type II DMF, the following additional information should be provided in the PFC:

- Reference to the corresponding DMF Number
- A certification that FDA has performed its "Completeness Assessment" for the referenced Type II DMF[21] and found it complete, and that the Type II DMF was "active" at the time the PFC was submitted[22],[23]

[20] Some *manufacturing sites* might not have a DUNS number. If a DUNS number is assigned, then it should be provided in the PFC.

[21] See the guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA*, Section III.

[22] Ibid., Definition of "Active DMF."

Although *manufacturing site* information that is included in a corresponding Type II DMF is not required to be duplicated in the PFC, the PFC submitter should include all of the basic information about the Type II DMF *facility* as described above to ensure that FDA identifies and assesses the relevant sites listed in the DMF.

2. Information about the Drug Substance and Drug Product

The following information about the drug substance and drug product should be provided in the PFC or incorporated by reference to a Type II DMF that contains this information:

- Nomenclature (drug substance)
- Structure (drug substance)
- General Properties (drug substance)
- Description and Composition of Drug Product – including the drug product batch formula (drug product)
- Specification (drug substance and product)
- Batch Analyses (drug product)

3. Information about the Manufacturing Process for the Drug Substance and Drug Product

The following information about the manufacturing process should be provided in the PFC or incorporated by reference to a Type II DMF that contains this information:

- Description of Manufacturing Process and Controls – this includes a description of the process and controls for the drug product
- Control of Materials, Critical Steps, and Intermediates
- Drug Product Manufacturing Process Development Information
- Available Process Validation Information – to demonstrate that the proposed process can successfully manufacture the drug product/substance

4. Manufacturing and Testing for Non-Drug Constituent Parts[24] *and Combination Products*

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[23] See the list of DMFs that have passed the "Completeness Assessment" and are available for reference by *planned ANDAs* at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls.

[24] The drugs, devices, and biological products included in combination products are referred to as "constituent parts" of the combination product.

If the product in the *planned ANDA* is a combination product defined in 21 CFR Part 3.2(e)(1) or (2), the PFC should also include the following information regarding the *facilities* involved in manufacturing and testing of the non-drug constituent part(s) (i.e., biologic or medical device) and the finished combination product (e.g., final kit assembly for co-packaged drug and device constituent parts):

- Administrative Information for Non-Drug Constituent Part and Combination Product *Manufacturing Sites*, including the following:
    - *Manufacturing site* information as listed above in Section IV.C.1
    - Indication of whether the *manufacturing site* follows the streamlined approach to demonstrate compliance with the current good manufacturing practice (CGMP) requirements and, if so, identify the streamlined approach (e.g., drug CGMP-based or device QS-based streamlined approach) used[25, 26]
- Information about the Combination Product and Non-Drug Constituent Parts, including the following:
    - Description of the manufacturing or assembly process at the finished combination product facility and, where applicable, the non-drug constituent part
    - For single-entity and co-packaged combination products[27] with a device constituent part, we recommend that the PFC submitter provide general descriptions/summaries of basic Quality System procedures, including management review procedures (21 CFR 820.20(c) and (e)), design controls (21 CFR 820.30), purchasing

[25] 21 CFR 4.4.

[26] See the guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products*, Section 2.C "Overview of the Final Rule." As described in this guidance, for drug-device combination products, 21 CFR part 4 identifies two ways to demonstrate compliance with CGMP requirements. Under the first option, manufacturers demonstrate compliance with all CGMP regulations applicable to each of the constituent parts included in the combination product. Under the second option, manufacturers implement a streamlined approach for combination products that include both a drug and a device by demonstrating compliance with either the drug CGMPs (21 CFR parts 210 and 211) or the device Quality System (QS) regulation (21 CFR part 820), and also demonstrating compliance with specified provisions from the other of these two sets of CGMP requirements.

[27] 21 CFR Part 3.2(e)(1) and (2) – single entity and co-packaged combination products defined.

controls (21 CFR 820.50), and corrective and preventive action procedures (21 CFR 820.100)[28]

D. Bioequivalence Summary and Site/Organization Information

The following information should be submitted in the PFC for each *bioequivalence site* associated with the *planned ANDA* submission:

1. Information about Bioequivalence Sites

- Site or Organization Name
- Contact Name
- Address at which study was conducted
- Telephone Number
- Fax Number
- Email Address
- Website
- Confirmation that the site or organization is ready for inspection

2. Study Information

- Study Names and Numbers
- Dates Conducted
- Main Investigators
- Summary of Biopharmaceutic Studies and Associated Analytical Methods
- Synopsis
    - Study Report
    - Protocol and Amendments
    - List and Description of Investigators
    - Randomization Schemes
    - Discontinued Subjects
    - Protocol Deviations
    - Subjects excluded from the statistical analysis (for example, adverse effects and serious adverse effects)
- Comparative Bioavailability and Bioequivalence Study Reports and related information
- In-Vitro – In-Vivo Correlation Study Reports and Related Information
- Reports of Bioanalytical and Analytical Methods for all bioequivalence studies

[28] See the guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products*.

V. ANDA SUBMISSION WINDOW

According to the GDUFA II Commitment Letter, the PFC should be submitted 2 months ahead of the submission date for the *planned ANDA* in order for it to be eligible to receive the *shorter goal date*. This timing allows the Agency to initiate the assessment in advance of receiving the *planned ANDA.* FDA believes if the time elapsed between submission of the PFC and submission of the *planned ANDA* is too long, it is less likely that *facility* information will remain *unchanged*, as defined by the GDUFA II Commitment Letter. Thus, FDA's PFC *facility* assessment may become out-of-date and need to be repeated after the *planned ANDA* is submitted, eliminating the benefit of the PFC submission to both FDA and the applicant. Therefore, this guidance establishes a window of time between 2 and 3 months after PFC submission during which applicants should submit their *planned ANDA* ("ANDA Submission Window").

If the *planned ANDA* is submitted within 2 months of submission of the PFC, the ANDA will not generally be eligible for the *shorter goal date*. Applicants should submit the *planned ANDA* no more than 3 months after submission of the PFC to reduce the likelihood of *changes* that result in the loss of eligibility for the *shorter goal date*.

For example, if the PFC is submitted on November 1, then the *planned ANDA* should be submitted between January 1(i.e., 2 months after submission of the PFC) and February 1(i.e., 3 months after the submission of the PFC). Similarly, if the PFC is submitted on November 30, then the *planned ANDA* should be submitted between January 31(i.e., 2 months after submission of the PFC) and February 28 (i.e., 3 months after submission of the PFC).

VI. RECEIPT AND ASSESSMENT PROCESS (FOR PFC AND *PLANNED ANDA*)

The following section describes the process for the PFC submission and how it interfaces with the *planned ANDA*:

A. PFC Receipt and Assessment

The following section summarizes the process for PFC receipt and assessment.

1. Obtaining a Pre-Assigned ANDA Number

The applicant should request a pre-assigned application number, which will also be used in the *planned ANDA.*

2. Submitting the PFC

The PFC should be submitted as an Adobe® Portable Document Format (PDF) file through the FDA electronic submissions gateway (ESG)

following the Agency's PDF Specifications.[29] The PFC submitter should index the information submitted within the PDF file using the "bookmark feature." The PFC should be electronically submitted in non-electronic Common Technical Document (non-eCTD) format via the Agency's Electronic Submission Gateway (ESG). When submitting the PFC through the ESG, choose "CDER" when selecting the appropriate Center, and should choose "PFC" when selecting the submission type.

If the PFC will be submitted via "Electronic Physical Media,"[30] it should be submitted to:

U. S. Food and Drug Administration
Office of Generic Drugs – HFD-600
Center for Drug Evaluation and Research
Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773

The PFC should contain the necessary information to allow the Agency to successfully conduct the *facility* assessment. Any information that is missing from the PFC will be considered for its impact on our ability to complete the *facility* assessment. If the missing information precludes the Agency from completing its *facility* assessment, the PFC will be not be eligible for further assessment, and the *planned ANDA* will be assigned the standard goal date.

The applicant should submit the *planned ANDA* within the "ANDA Submission Window" described above in Section V. If the applicant determines that the *planned ANDA* will not be submitted within the "ANDA Submission Window" for any reason, FDA should be notified in writing before the start of the "ANDA Submission Window." The letter should reference the PFC number, and state the applicant's intent not to submit the *planned ANDA* within the "ANDA Submission Window." Upon receipt of this letter, the Agency will terminate the assessment of the PFC.

3. FDA's Initial Assessment of the PFC

After receiving the PFC, the Agency will preliminarily assess whether the product with the *planned ANDA* appears to meet the *priority* designation

[29] See Fda.gov, "Electronic Submissions Gateway," for technical details related to submitting documents through FDA's Electronic Submission Gateway.

[30] See Transmitting Electronic Submissions Using eCTD Specifications, Revision 1.6, March 4, 2016, for definition of accepted Electronic Physical Media Format.

criteria under the Prioritization MAPP, at the time that the PFC is assessed. The preliminary assessment of *priority* designation is influenced not only by information in the PFC, but also by other factors and circumstances. For example, if the drug product associated with a PFC is no longer in shortage, and not anticipated to be in future shortage, then the PFC may not result in a *priority* designation.

Based on this preliminary assessment, the Agency will send an acknowledgement letter to the PFC submitter to indicate whether or not the *planned ANDA* appears to meet the *priority* designation criteria.

Note that this assessment of *priority* is preliminary. *Priority* designation will be reevaluated using the Prioritization MAPP after the *planned ANDA* is submitted. Applicants will be notified of *priority* status in the ANDA acknowledgement letter sent by FDA.

4. FDA's Assessment of the PFC Content

If the *planned ANDA* appears to meet the *priority* designation criteria, FDA will begin the *facility* assessment process with the expectation that the *planned ANDA* will be submitted within the "ANDA Submission Window," as described above in Section V.

Please note that specifically with regard to "Grouped Supplements," each of the supplements in the group should meet the *priority* designation criteria to qualify for the *shorter goal date*.

If the PFC is found to be missing information that precludes the Agency from completing its *facility* assessment, the PFC will be not be eligible for further assessment and the Agency will notify the applicant that the *planned ANDA* will not be eligible for the *shorter goal date*.

B. ANDA Submission

When seeking a *shorter goal date* through *priority* designation and submission of a *complete and accurate PFC*, FDA recommends that:

- The *planned ANDA* be submitted within the "ANDA Submission Window" described above in Section V.
- The *planned ANDA* be submitted in the appropriate format as described above in Sections VI.A.1 and 2.
- The *planned ANDA* include the *facility* information that was originally submitted as part of the PFC. The *facility* information should be located in the appropriate eCTD section of the *planned ANDA*.
- The *planned ANDA* cover letter clearly reference the PFC, the date it was submitted, and date of FDA's acknowledgement letter indicating the PFC's

eligibility for further assessment. A copy of the FDA's acknowledgement letter related to the PFC should be included in the *planned ANDA*.

- A stand-alone certification letter be included stating that the *facility* information that was initially submitted in the PFC, "has not *changed*" in the *planned ANDA*. The certification letter should identify any and all differences between the *facility* information submitted in the ANDA versus the PFC, and certify that all differences between the PFC and *planned ANDA* have been identified. If a certification letter is not submitted with the *planned ANDA*, the submission will not be eligible for a *shorter goal date*.

FDA's review of the *planned ANDA* will be performed in accordance with its established statutes, regulations, policies and procedures for ANDA reviews. The following additional elements will be included:

- Receipt of the ANDA by the Agency will result in an Acknowledgement Letter to the applicant as described below in Section VII.
- The Agency will assess whether the product in the ANDA submission is *priority* under the Prioritization MAPP. The *priority* designation is based on the information submitted in the ANDA, and/or external factors and circumstances, such as the likelihood of drug shortage for the drug product, its designation as a President's Emergency Plan for AIDS Relief drug, and others that would impact the Agency's assessment for *priority* designation based on the Prioritization MAPP.

C. Differences in *Facility* Information between the PFC and the *Planned ANDA*

Under the GDUFA II Commitment Letter, in order to maintain eligibility for the *shorter goal date*, the information in the PFC must be accurate, complete, and remain *unchanged*. Accordingly, if there are differences between the *facility* information in the PFC and the ANDA, an important question will be whether those differences constitute a *change, with respect to facility* information, as defined by the GDUFA II Commitment Letter. If the *facility* information in the *planned ANDA* differs from the PFC in any respect, those differences should be specifically identified in the certification letter to be included with the *planned ANDA*. FDA will determine whether these differences constitute a *change*. If the Agency determines that a difference between the PFC and the *planned ANDA* constitutes a *change*, the *planned ANDA* will be assigned the standard goal date as described in the GDUFA II Commitment Letter.

VII. OUTCOMES

A. Eligibility of the PFC for Further FDA Assessment

If FDA determines that the product to be submitted in the *planned ANDA* preliminarily appears to meet *priority* designation criteria as defined in the Prioritization MAPP, the Agency will send a letter to:

- Acknowledge that the PFC is eligible for further assessment;
- Inform the submitter that a *priority* designation determination will be made after submission of the *planned ANDA*; and
- Inform the submitter that they should calculate their "ANDA Submission Window" as identified above in Section V.

If FDA determines that the drug product is not *priority* under the Prioritization MAPP, the Agency will send a letter stating that the PFC is not eligible for further assessment.

B. Determining the Goal Date for the *Planned ANDA*

After receiving the *planned ANDA*, FDA will determine the applicable goal date or set of goal dates as outlined in the GDUFA II Commitment Letter. Establishing the appropriate goal date for the *planned ANDA* is based on the Agency's *priority* designation assessment, assessment of the *facility* information submitted in the PFC, and the stand-alone certification letter described in Section VI.B – bullet 5 (i.e., a comparative assessment of the *facility* information submitted in the ANDA and the PFC). The Agency will convey the outcomes of these assessments, and the resulting goal date, in the acknowledgement letter associated with the application, supplement, or amendment. Under the terms of the GDUFA II Commitment Letter, a *shorter goal date* applies only to *priority* ANDAs. If, upon receiving the ANDA, FDA determines that the application does not meet FDA's *priority* designation criteria as defined in the Prioritization MAPP, the ANDA will receive a goal date consistent with a *standard ANDA*[31]—even if the PFC is otherwise found to be complete, accurate, and the information provided in it is *unchanged*.

An ANDA that is not eligible for the *shorter goal date* may still be treated as *priority* if it meets the criteria in the Prioritization MAPP.

In addition, if the *facility* information in the PFC does not remain complete, accurate, and *unchanged* upon submission of the ANDA, under the terms of the GDUFA II Commitment Letter, the standard goal dates as outlined in the GDUFA II Commitment Letter will apply.

If, during the course of ANDA review, FDA determines that there are any differences between the PFC and ANDA that were not identified in the applicant's certification letter as described in Section VI.B of this guidance, the review goal will be converted to the standard goal date.

[31] In Section IX of this guidance, the term *Standard ANDA* is defined.

VIII. QUESTIONS AND ANSWERS

A. What types of submissions may be eligible for the PFC process?

Priority abbreviated new drug applications (ANDAs), prior approval supplements (PASs), and their amendments can be eligible for the PFC process.

B. If a *facility* identified in the PFC closes, will FDA consider that as a *change, with respect to facility information?*

Yes, FDA considers *facility* closures to be a *change, with respect to facility information* as defined in the GDUFA II Commitment Letter because closures are *changes* in operations performed by *facilities* in the PFC or *planned ANDA.*

C. What is the purpose of the stand-alone certification letter to which Section VI refers?

The stand-alone certification letter ensures that FDA is made aware of any differences between the *facility* information submitted in the PFC versus the *planned ANDA.* The Agency will determine whether these differences constitute a *change, with respect to facility information* as defined in the GDUFA II Commitment Letter. If any differences are considered to meet this definition of *change,* then the *planned ANDA* will not receive a *shorter goal date.*

D. When the *planned ANDA* is submitted, should it include the *facility* information that was originally provided in the PFC?

Yes. The *planned ANDA* should include the *facility* information that was originally submitted as part of the PFC. The *facility* information should be located in the appropriate eCTD sections of the *planned ANDA.* The applicant should also submit a certification letter in their ANDA as described above in Section VI.

E. Why should applicants submit the *planned ANDA* 2 to 3 months after submission of the PFC?

The GDUFA II Commitment Letter states that the PFC will be submitted 2 months prior to the date of the ANDA. The Agency recommends 3 months prior to submission of the ANDA as the outside timeframe for a PFC to be submitted because within 3 months of the PFC submission the *facility* information related to the *planned ANDA* is more likely to remain factually accurate and unlikely to *change* prior to submission of the *planned ANDA.*

F. If there are differences between the *facility* information submitted in the PFC versus the *planned ANDA*, how should they be reported?

As described in Section VI, the applicant's stand-alone certification letter should identify any differences between the *facility* information submitted in the ANDA versus the PFC, and certify that all differences have been identified in the stand-alone certification letter.

G. When could an applicant not receive the *shorter goal date* for their *planned ANDA*?

A *planned ANDA* may not receive the *shorter goal date* if, among other reasons:

- Differences between the *facility* information submitted in the *planned ANDA* versus the PFC constitute a ***change, with respect to facility information***, as defined in the GDUFA II Commitment Letter.
- A *facility* is not ready for inspection.
- The PFC is not complete, or not accurate. FDA recommends that applicants include the *facility*-related information described in this guidance.
- FDA determines that the PFC or the ANDA is not a *priority* as defined by the Prioritization MAPP.
- The ANDA is not submitted within the submission window as described in Section V.

H. Is there a user fee payment required at the time of submitting PFC?

No. Any relevant user fees are paid at the time of the ANDA submission.[32]

I. Which *bioequivalence sites* should be submitted in the PFC?

All sites or organizations involved in bioequivalence and clinical [endpoint bioequivalence] studies used to support the ANDA submission as described in 21 CFR 314.94(a)(7) and 21 CFR 320.24(b).[14]

IX. DEFINITIONS

A. Planned ANDA

For the purposes of this guidance, the term "*planned ANDA*" refers to the ANDA submission that is prospectively associated with the PFC, specifically including: Original ANDA Submissions, Original ANDA Amendments, ANDA Prior Approval Supplements (PASs), and PAS Amendments. The qualifier "planned" indicates that at the time of submitting the PFC, the ANDA has not been submitted. This term also

[32] See Fda.gov - Generic Drug User Fee Cover Sheet and Payment Information.

includes "Grouped Supplements," as defined by CDER's MAPP 5015.1, Rev. 1, entitled *Review of Grouped Product Quality Supplements.*

B. Standard ANDA

The term "*standard ANDA*" refers to Original ANDA Submissions, Original ANDA Amendments, PASs, and PAS Amendments not identified by FDA as eligible for the *priority* designation pursuant to the CDER MAPP 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements.*

C. Complete and Accurate Pre-Submission Facility Correspondence (PFC)

The GDUFA II Commitment Letter defines a "*complete and accurate Pre-Submission Facility Correspondence*" as listing the following information:

1. All facilities involved in manufacturing processes and testing for the ANDA and corresponding Type II API DMF as required by 21 CFR 314.50(d)(1)(i) and (iii).[12] For each manufacturing or testing facility, the correspondence includes facility name, operation(s) performed, facility contact name, address, FEI number (if a required registrant or one has been assigned), DUNS number, registration information (for required registrants), a confirmation that the facility is ready for inspection, a description of the manufacturing process, and a certification by the applicant that any Type II DMF has similarly complete and accurate facility information as required by 21 CFR 314.50(d)(1)(i), including complete facility information (i.e., facility name, operation, facility contact name, address, FEI number and DUNS number). Facility information that is included in a corresponding Type II DMF is not required to be duplicated in the Pre-Submission Facility Correspondence for the ANDA.

2. All sites or organizations involved in bioequivalence and clinical [endpoint bioequivalence] studies used to support the ANDA submission as described in 21 CFR 314.94(a)(7) [and 21 CFR 320.24(b).][14] This information is provided using a standardized electronic format and includes unique identifiers that are current and accurate, including site or organization name, address and website; and study information including a listing of study names, dates of conduct and main investigators.

D. Change, with Respect to Facility Information (also referred to as change)

The GDUFA II Letter defines "*change, with respect to facility information*" to mean a change to information in the Pre-Submission Facilities Correspondence that causes FDA to re-evaluate its *facility* assessment (i.e., assess the impact of the change on its previous recommendation), such as a change in *facility* (as described by address, FEI number, or DUNS number), change in operation(s) performed by a *facility*, addition of a new *facility*, withdrawal of a *facility* used to generate data to meet application requirements or intended for commercial production, or a change in inspection readiness (i.e., a *facility* is no longer ready for inspection).

FDA interprets a "*change* in operation(s) performed by a *facility*" to include closure of the *facility*. FDA uses *change* and *change, with respect to facility information* interchangeably in this guidance.

E. Bioequivalence Sites

All sites or organizations involved in bioequivalence and clinical [endpoint bioequivalence] studies used to support the ANDA submission as described in 21 CFR 314.94(a)(7) [and 21 CFR 320.24(b).][14] For the purposes of this guidance, this term also captures sites that conduct analytical testing in support of the *planned ANDA*.

F. Manufacturing Sites

All *facilities* involved in manufacturing processes, packaging and testing for the ANDA and corresponding Type II API DMF as required by 21 CFR 314.50(d)(1)(i) and (iii).[12] For the purpose of this guidance, this term refers to any manufacturing, packaging or testing site associated with a *planned ANDA* that conducts an operation to support manufacturing or testing of the drug substance and/or product. This definition includes sites listed in Type II DMFs and sites that manufacture non-drug constituent parts of a combination product.

G. Facility

For the purposes of this guidance, the term "*facility(ies)*" means "*manufacturing site*" and "*bioequivalence site*." The terms "*manufacturing site*" and "*bioequivalence site*" are also explicitly defined in this guidance.

H. Shorter Goal Date

The term "*shorter goal date*" refers to the accelerated goal dates identified in the GDUFA II Commitment Letter for ANDAs that are designated *priority* by FDA and have submitted within the proper timeframe, a *complete and accurate PFC* containing *facility* information that remains *unchanged* in the subsequent ANDA.[33]

I. Priority

The term "*priority*" refers to FDA's designation of *priority* for ANDAs as defined by the Prioritization MAPP.

[33] "Submission Review Performance Goals," *GDUFA Reauthorization Performance Goals and Program Enhancements, FYs 2018-2022,* Section I.

APPENDIX – PRE-SUBMISSION FACILITY CORRESPONDENCE SUGGESTED FORMAT

The PFC should be submitted as an Adobe Portable Document Format file, as described in Section VI.A.1 and 2 above. Although the PFC itself is not considered to be an ANDA (or PAS or Amendment), a PFC will be included as an associated record in the regulatory record of any *planned ANDA* upon submission.

A. PFC Title

The PFC title should be prefaced with the label "Pre-Submission Facility Correspondence." This label will enable FDA to appropriately capture the PFC when it is submitted to the electronic submissions gateway.

B. File Format

The PFC should be submitted in an Adobe PDF file format to ensure complete processing of the correspondence by the Agency. The applicant should index the information submitted within the PDF file using the "bookmark feature" to enable the Agency's expedient assessment of the PFC.

C. Layout

Section IV of this guidance establishes the information that should be provided at a minimum in order for the PFC to be considered complete. Although the layout of the PFC is left to the discretion of the submitter, the Agency recommends that the following elements be considered for the PFC format.

1. General Recommendations

The Agency suggests using the headings in Section IV of this guidance to denote the overall layout of the PFC as shown below. If a submitter chooses to use another format, they should ensure that their PFC provides the information requested in Section IV of this document.

A. General Information

B. Statement of ANDA Eligibility for *Priority* Review

C. Manufacturing Process and Testing Facility Information
   1. Administrative Information about Facilities (including those referenced in a Type II DMF)
   2. Information about the Drug Substance and Product
   3. Information about the Manufacturing Process for Drug Substance and Drug Product

4. Manufacturing and Testing Facilities for Non-Drug Constituent Parts and Combination Products
   - Administrative Information for Non-Drug Constituent Part and Combination Product *manufacturing site*
   - Information about the Combination Product and Non-Drug Constituent Parts

D. Bioequivalence Summary and Site/Organization Information
   1. Information about Sites or Organizations
   2. Study Information

2. Recommendations for Specific Headings under Section IV

- Statement of Why ANDA Submission Should Be Considered for *Priority* Review

  This statement and the associated justification should be stand-alone, to expedite the Agency's initial assessment of the PFC, as described in Section VI.A.3 of this guidance.

- Manufacturing Site(s) Information

  When describing the administrative information associated with manufacturing and testing *facilities* (see Section IV.C.1), including where appropriate, those *facilities* listed in a Type II DMF (relevant to the *planned ANDA*), and *facilities* related to the combination product and non-drug constituent parts of a combination product, the submitter is encouraged to use a standardized format to list this information. See the example below:

  Figure 1. Example of Standardized Format for Administrative Information related to Manufacturing and Testing Facilities

	Facility #1	Facility #2	Facility #3
Facility Name			
Facility Contact Name			
Facility Address			
Telephone Number			
Fax Number			
Email Address			
FEI Number			
DUNS Number			
Operation performed at the facility			
Confirmation that the			

facility is ready for inspection			
Reference to corresponding DMF Number (For DMF listed facility)			
A Certification that FDA has performed its "Completeness Assessment" for the referenced Type II DMF and found it complete			
CGMP Approach (For combination product manufacturing facilities only, e.g., drug CGMP-based or device QS-based streamlined approach)			

- *Bioequivalence Site(s)* Information

  Information regarding the *bioequivalence sites* should be included as described in Section IV.D of this document. For information related to *bioequivalence sites* and organizations, the submitter should follow the format.

Figure 2. Sample Study Summary Table (One Table for Each Study)

Study Number				
Study Type	☐ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other
Reports Included in PFC				
Study Report	Included in PFC? ☐ Yes ☐ No			
Validation Report	Included in PFC? ☐ Yes ☐ No			
Bioanalytical Report	Included in PFC? ☐ Yes ☐ No			
Clinical Site (Name, Address)				
Phone #				
Fax #				
Principal Clinical Investigator (Name, Email)				

Dosing Dates	
Analytical Site (Name, Address)	
Phone #	
Fax #	
Analysis Dates	
Principal Analytical Investigator (Name, Email)	
Storage Period of Biostudy Samples **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range:**	
Long-Term Storage Stability Coverage (no. days @ temp ºC)	

797
798

Figure 3. Sample Summary Table of Bioequivalence Studies
(One Table for Each Study)

Study Ref.No	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject (No. M/F) Type Age: mean (Range)	Mean Parameters ±SD							
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-t} (ng.hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng.hr/mL) Mean ± SD (CV %)	$t_{½}$(hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	AUC % Extrap Mean ± SD (CV)	Study Report Included in PFC?
	Primary Objective: **Secondary Objective:**		**Test product (T)** Description Batch No:									Yes ☐ No ☐
			Reference product (R) Description Lot No:									