

How to Cite:

Hiwrale, R. S., Tayade, G. S., Pennamareddy, R., Salunkhe, K., Shendge, R. S., & Kulkarni, A. D. (2022). Pre-submission facility correspondence for generic dosage form with an expedited-approval in 8 months. *International Journal of Health Sciences*, 6(S3), 8478–8484. <https://doi.org/10.53730/ijhs.v6nS3.8005>

Pre-submission facility correspondence for generic dosage form with an expedited-approval in 8 months

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Abstract---PFC (Pre-Submission Facility Correspondence) is the initial submission for an ANDA (Abbreviated New Drug Application), comprising information for the application similar to the original ANDA, and only valid in the United States Agency For a pre-determined inspection of the finished drug product's facility information. The Applicant can be introducing their Drug Product into the Market before the ANDA's Goal date of 8 months, according to the Pre-Submission Facility Correspondence. The submission type Original ANDA, PAS (Prior approval supplement), and PAS Amendment is based on prior review goal submission. The FDA (Food and Drug Administration) approves PFC submission for a range of

reasons, including drug product shortfalls, COVID-19 emergency dosage medication, Patent paragraph-IV (patent is invalid or will not be infringed), and market-availability of one RLD (Reference listed drug) and one generic. The complete submission process gone through the eCTD submission format from the ESG (Electronic Submission Gateway).

Keywords--ANDA, eCTD, PAS, PFC, RLD (Reference listed drug).

Introduction

PFC is an initial submission allowing priority ANDA, PAS and amendments to also be approved more expeditiously. Prior to submission, an applicant provides certain information regarding Manufacturing and BE (Bio-equivalence) premises, that will be placed in a planned ANDA. 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. (1) Moreover, it enables FDA to satisfy the GDUFA-II (Generic Drug Under Fee Amendment) Commitment Letter's shorter review period (shorter goal dates) for the anticipated ANDA. PFC is submitted to the agency before two months ahead and not more than three months of the planned ANDA and Facility information remains unchanged for the consequences with ANDA. (2)

Comprehensive and Precise PFC – Lists entirely of the followed

For any manufacturing or testing facility associated with manufacturing processes and testing for such ANDA and related Type II API DMF (Drug master File), the following information is needed:

- Facility name, Business operation(s) executed,
- Facility contacts information containing Name, address and Fax.
- FEI (Facility FDA Establisher identifier) number (if a mandatory registrant),
- DUNS (Drug Universal Numbering System) number,
- Registration information (for required registrants),
- A confirmation that the facility is ready for inspection, also specify in Form FDA 356h
- A certification by the applicant that any Type II DMF has similarly complete and accurate facility information (Facility information that is included in a corresponding Type II DMF does not need to be replicated in the ANDA's Pre-Submission Facility Correspondence.) (3)

As described in 21 CFR 314.94(a) (7), all sites or organisations included in BE and Clinical studies are being used to support the ANDA submission. (4) This data is provided in an electronic format which comprises recent available unique identifiers including the name of the site or company, its location, and its website, and also study data. A list of study names, conducted dates, and main investigators would be included.

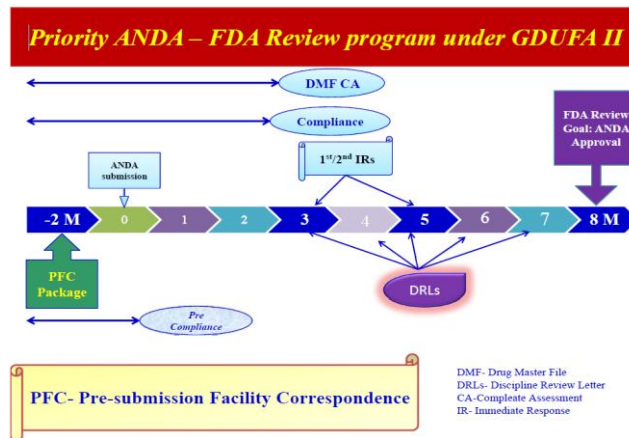


Figure 1. Priority ANDA – FDA Review program under GDUFA II

According to the figure above, the PFC Package of Compliance includes the filing of the PFC Submission, an 8-month (goal date) assessment, DRLs (Deficiency Review Letter), and an immediate response. The PFC submitted before the two months ahead of ANDA, while in the imminent months if the agency will ask any query related to the submission, the manufacturers/Applicants have to give the justification for that reason. If they will not be positioned to justify, the FDA will give the RTR (Refuse to Receive).

Research Method

Pre-Submitting Facility Information – Contents Controlled correspondence letter

With and replied from the agency for the Q1 and Q2 determination and compliance with 21 CFR 314.

Controlled Correspondence

- The Controlled Correspondence Letter should be submitted before the PFC.
- After the agency response to the CC the applicant can apply for PFC/ANDA.
- CC has an identified number.
- CC should be included in the description of finished drug product, in that agency's replies on which date the CC was submitted and the identified number.
- In CC, the applicant has to submit the Q1 and Q2 Formulation Assessment to the OGD (Office of Generic Drugs).
- All the information of the RLD e.g. Applicant holder name, Proprietary name, Active ingredient, RLD/RS (Reference standard)-YES/NOT, the dosage form, strength RLD Approval date, and marketing status (Prescription/OTC) – for OTC whoever not listed in the Pharmacopeia
- It is required for changes as per the RLD's proposed formula.

- In CC, the agency ask for excipient is within the maximum potency limits listed for route of administration in the most current FDA/CDER Inactive Ingredient Guide (IIG) as applicable with grades (USP, USP-NF).
- Response based on after the CC, e.g *OGD has made a preliminary determination that it would not likely RTR an ANDA submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act and its implementing regulations based on applicant's proposed formulation pursuant to the requirements pertaining to IID described in 21 CFR 314.101(d)(3) and 21 CFR 314.94(a)(9).* (5)
- All the information of the RLD e.g. Applicant holder name, Propitiatory name, Active ingredient, RLD/RS (Reference standard)-YES/NOT, the dosage form, strength RLD Approval date, and marketing status (Prescription/OTC) – for OTC whoever not listed in the Pharmacopeia

FDA Form 356h

Is required for the ANDA as well as PFC also, while the filing dossier submission for ANDA, the GDUFA Cover sheet is mandatory for the ANDA. It should be signed as per required. (Submission Type-Product Correspondence, Submission Subtype- Pre-submission)

In the Cover Letter

- Statement of justification for Expedited Review request (PAS) under the prioritization of MAPP (Manual of Policies and Procedures) includes Eligibility, Patent Brokerages.
- Statement of Inspection Readiness- 356h Form (mentioned in the application form), 32s21 (Drug substance), 32p31 (Drug Product)
- Statement identifying Reference Listed Drug (Innovated drug/ 1 RLD and 1 Generic)
- Anticipated date of ANDA Submission- before 90 days of ANDA

U.S. Agent

FDA asked information for the US agent containing Company name Email, Fax, DUNS Number and the US appointment letter.

Letter of Authorization

The required DMF e.g., Packaging material, API Supplier's or Intermediate materials and DMF Number should be Provided.

PDR

Pharmaceutical Development for Manufacturing Process Development should be submitted. (It will submit in ANDA also for remaining sections specified in PDR)

Manufacturing Details

Regarding the Process Description of Drug product and the Drug Substance from manufacturer.

General information (Nomenclature, Structure, General Properties) of the API

- Summary of Biopharmaceutical Studies and Associated with the Analytical Methods reports
- Manufacturing Process validation report for drug substance and drug product.
- Control of Critical Steps, and Intermediates for drug substance and drug product.
- Batch formula containing the actual weight strength related with RLD.
- Specifications including CoA for suppliers and the manufactures.
- Batch analyses including CoA for drug product.
- Comparison study between the BA/BE studies report and their related information
- BA/BE Studies for the Generic drug product should be provided
- Reports of Bioanalytical Methods for all BE studies required (6)

PFC package – Submission

- When submitting the PFC through the ESG Portal, "Center for Drug Evaluation and Research" as the appropriate **Center** and **eCTD** as submission type.
- The Agency will send the PFC-applicant an acknowledgement letter based on this preliminary review, identifying whether or not the planned ANDA appears will achieve the prioritised designate requirements.
- FDA will initiate the facility assessment process if the proposed ANDA appears to fulfil the prioritized designate requirements, with anticipation that the scheduled ANDA will be filed within the "ANDA Submission Window."(7)

PFC package – Abbreviated New Drug Application Submission

- As per criteria, the applicants should submit the priority ANDA after the submission of PFC NMT 90 days duration. If not the applicant loss the eligibility for the lesser goal date.
- In case, However PFC is submitted on Jan 1, then the priority ANDA should be submitted among March 1 (i.e., After 2 months) and April 1 (i.e., After 3 months) of the PFC.
- In case the submitted PFC is vary from the Prior ANDA, e.g., submitted facility information got changed or else the CMO- testing lab info including address, Fax. Those types of differences should be specified in the certification letter, will be include and submit in the Prior ANDA. Agency will regulate whether varies being constitute change. (6)

What Can Industry Do to Assist?

- Submit complete and clear PFCs and ANDAs
- Clearly noted in Pre-Submission Facility Correspondence and ANDA that were requesting a priority goal reviewed
- Clearly noted in ANDA if part of Pre-ANDA Program
- Provide complete and quick responses to IRs (Immediate Response) /DRLs
- Champion your own ANDA
 - Use good contractors (DMFs, etc.)
 - Communicate with contractors (both ways)
 - Consider the timing of changes
 - Update the external changes (RLD, USP, etc.)

Requirements for PFC

- **API/DMF:**
 - DMF CA must be done at the time of PFC submission.
 - DMF LoA
 - Statement from Supplier on facility assessment.
- **Control Manufacturing and Controls (CMC):**
 - Administrative Information
 - Drug substance/Drug Product CMC information
 - Facility Information
 - Process information
 - CFR 820 compliance information for combination product
- **Clinical:**
 - Facility information including analytical Clinical facility
 - Summary report and summary table for studies
- **Planned ANDA:**
 - Should be submitted between the duration of two-three months after PFC submission.
 - Statement in ANDA for not including any facility change from that of submitted in PFC.

ANDA certification clauses

Types of the Submissions for application for ANDA with reference to RLD

Paragraph I	Patent which is not submitted
Paragraph II	Patent has expired
Paragraph III	The date (Duration) of patent will expire
Paragraph IV	Patent is invalid or will not be infringed (8)

Summary

General information for the Planned ANDA, containing information of the manufacturing process, testing CMO information, DS/DP manufacturing information, Process for the PFC expedited approval of ANDA. Manufacturing process for non-drug constituents Parts, BE summary and reports for the generic drug dosage form are provided in submission. Requirements for the PFC and eligibility criteria for the planned ANDA as per FDA agency. The validation reports, Specification of the DP/DS and Excipients and the BE and clinical data with the RLD, the Q1 and Q2 determination in the given submission as per RLD.

Conclusion

For the subjected Finished drug product intended to file the PFC based on number of generics available which is one and availability of one RLD. This Finished drug product falls under the PFC category and all the results of the drug product and drug substance are as per the specification and the drug product is in line with the RLD based on the data, specifications, methods and results we conclude that the drug product is valid for PFC submission. PFC will be used for the prior review to Planned ANDA, where ANDA takes 10 months for the approval, the PFC will Expedited-approval in 8 months. The FDA allows applicant for introduce the New generic drug in to the Market.

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