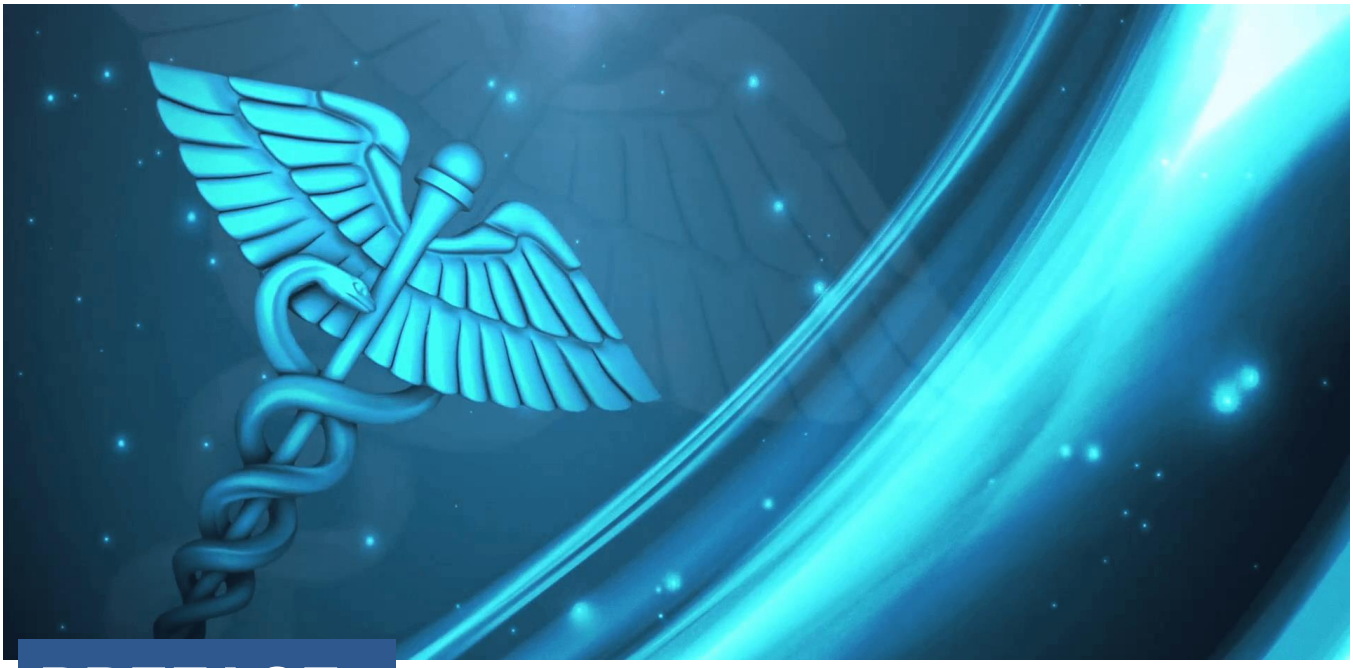
Focus on First Cycle Approval of ANDAs

Regulatory Best Practices

CONTENTS



PREFACE

The IPA launched its Quality Forum (QF) in April 2015 to help Indian pharmaceutical manufacturers achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices.

The QF focused on several priority areas in the last four years, viz., Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of guidelines for several of these topics. In this document, we focus on the best regulatory practices specifically focused on the first cycle approval of Abbreviated New Drug Applications (ANDAs). This document also highlights the key major sections of an ANDA application that, if appropriately and scientifically addressed at the time of the original ANDA submission, leads to an increase in the percentage of first cycle approvals, a decrease in the number of deficiency points in the complete response letter (CRL), and help in finding ways to avoid 'Major' category CRLs. In addition, this document identifies certain key areas of an ANDA application which needs to be continuously monitored and communicated via suitable regulatory strategies, in order to obtain timely approval of and ANDA application.

This document is the outcome of a concerted effort over the last few months by senior managers engaged in the regulatory functions of six IPA member-companies. Mr. Vipul Doshi, Mr. Srinivas Gurram (Srini), Ms. Ranju Nijhawan and Mr. Bhaumik Modi (all in Cadila Healthcare); Mr. Pramod Dahibhate and Mr. Girish Chavan (Lupin); Mr. Dilkesh Shah (Torrent Pharmaceuticals); Mr. G. Srinivas Rao and Mr. S Sri Rama Murthy (Dr Reddy's Laboratories); Mr. P J Deepak (Sun Pharma); and Mr. Ramakant Shukla and Ms. Praveena Manglorkar (Cipla). They shared current practices, benchmarked these with the existing regulatory guidance from the USFDA and developed a robust draft document and got it vetted by leading subject matter experts. The IPA acknowledges their hard work and commitment to the project.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document, to be released at the IPA's 6th India Pharmaceutical Forum 2021, will be hosted on the IPA website - www.ipaindia.org – in order to make it accessible to all manufacturers in India and abroad.

Mumbai
February 2021

This document represents the current thinking of the Indian Pharmaceutical Alliance (IPA) on this topic. It does not establish any rights for any person or persons and is not binding on IPA or the public. An alternative approach may be used as long as it satisfies the requirements of the applicable statutes and regulations.

2 Introduction

- This document is intended to explain to applicants of the generic drug applications about the importance of the First Cycle Approval (FCA) of an original Abbreviated New Drug Application (ANDA) and Prior Approval Supplement (PAS) filed under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

- This document also recommends general and eCTD module specific checkpoints that help in increasing the first cycle approval rate (referred to as FCA hereinafter), decreasing the number of deficiency points in the complete response letter (CRL), and ways to avoid 'Major' category CRLs.

3 Scope

- The recommendations in this document are applicable to the original Abbreviated New Drug Application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). However, it can also be extended to an amendment made in response to Information Requests (IRs), Discipline Review Letters (DRLs), Complete Response Letters (CRLs), post approval supplements, or amendments to supplements as appropriate.

4 Background and Purpose

- The U.S. Food and Drug Administration (FDA) Pharmaceutical Quality for the 21st Century Initiative aims to promote a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight. Over the years, substantial progress has been made toward this vision, including Process Analytical Technology (PAT) (2004), Current Good Manufacturing Practices (CGMPs) for the 21st century (2004), Quality by Design (QbD) (2008 and 2009), Generic Drug User Fee Amendments (GDUFA I) (2012), Continuous Manufacturing (2015), GDUFA reauthorization (GDUFA II) (2017), Emerging Technology (2017), and six sigma pharmaceutical quality (2017).

- In October 2012, with the implementation of Generic Drug User Fee Amendments (GDUFA I), the FDA initiated a program to act on received ANDAs within previously agreed timeframes. To act on an application means the FDA will issue a CRL, an approval letter, a tentative approval letter, or a refuse-to-receive letter.3 As part of this undertaking, the FDA instituted the use of multiple types of letters regarding the review of an application, including complete response letters (CRLs) and IRs.

- While negotiating the reauthorization of GDUFA, it was proposed that applicants be notified of possible deficiencies in an ANDA as early as possible after a discipline review has been completed. It was agreed that at about the mid-point of the review clock, the FDA would (1) issue an IR to request clarification or further information that is needed or would be helpful to allow completion of a discipline review, and/or (2) issue a DRL to convey preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its portion of the pending application at the conclusion of a discipline review.

- US FDA strives to approve the ANDAs in the first review cycle if applicants submit a complete ANDAs consistent with the statutory requirements. It is equally important for the ANDA applicant to respond the IRs and DRLs completely, adequately and within the timeframes requested by FDA, so that FDA can approve ANDAs in the first review cycle. FDA and ANDA applicant's joint efforts can lead to earliest approval of the ANDAs that are potential first generics (i.e., first to file Paragraph IV ANDAs) without forfeiting 180-day exclusivity.

- The purpose behind IRs and DRLs is to improve predictability and transparency of the FDA, promote the efficiency and effectiveness of the FDA review process, minimize the number of review cycles necessary for approval, increase the overall rate of approval of the FDA, and facilitate greater access to generic drug products. The FDA strongly encourages applicants to submit high quality, complete submissions. Generally, the number and significance of deficiencies that the FDA identifies in an application correlates to the number of review cycles. Application quality and applicant responsiveness are key factors in whether IRs and DRLs have maximized value for a particular application.

- If an applicant is unable to completely respond within the time frame requested by the FDA, including any extensions that may be granted by the FDA, then the FDA will generally issue a CRL on goal date.

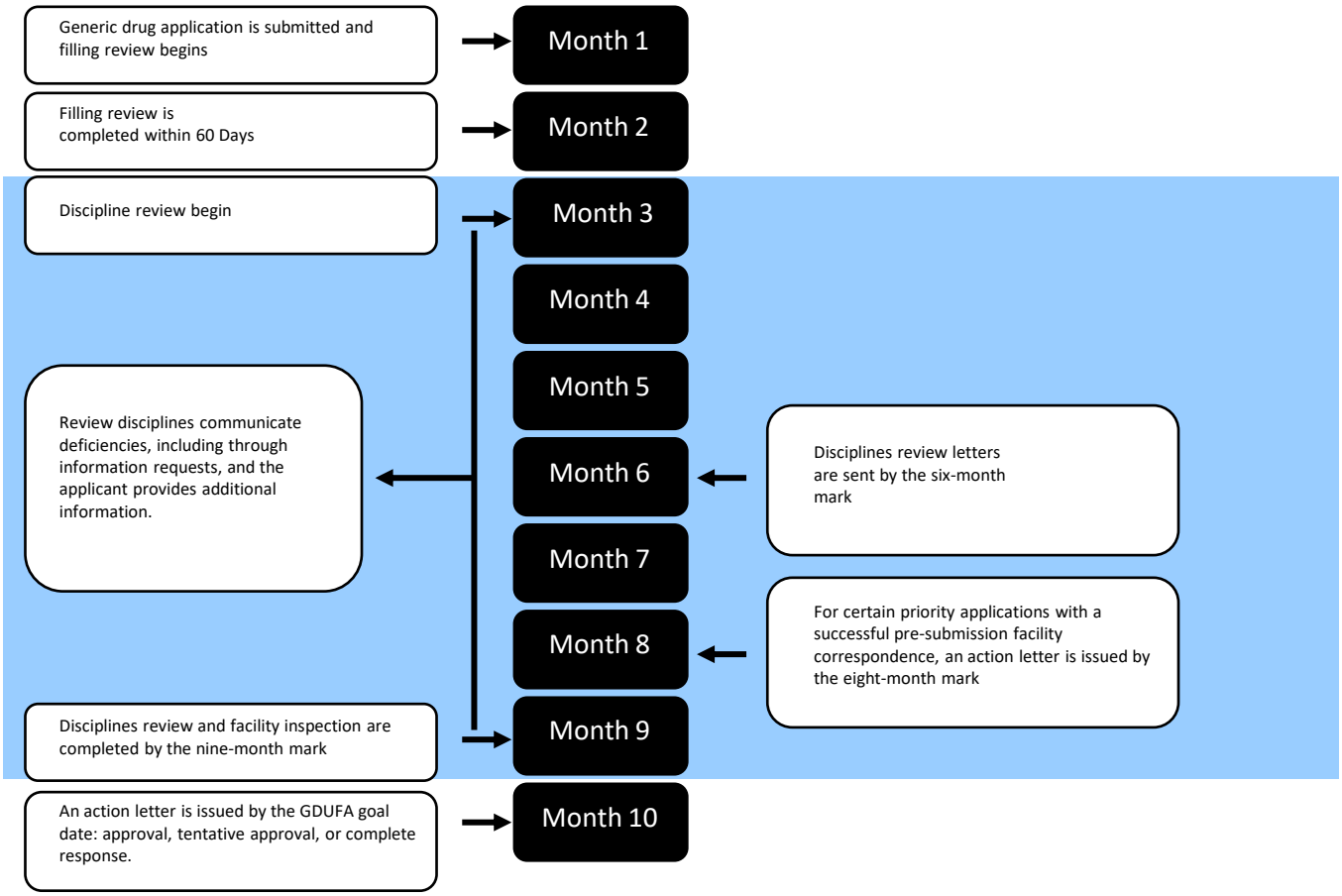


Figure 1: Overview of the FDA timeline and review process for the first review cycle for generic drug applications since the enactment of the Generic Drug User Fee Amendments of 2012 (GDUFA) and its reauthorization in 2017 (GDUFA II).

- The CRL describes all the deficiencies identified in the ANDA that must be satisfactorily addressed before the ANDA can be approved. Issuance of a CRL also completes the ANDA's review cycle, with the next review cycle beginning when the applicant amends the ANDA by submitting a complete response to all deficiencies listed in the CRL.

- **How much is the worth to the generic world of a first cycle review ANDA approval?**

- Generic drugs, which are essentially copies of approved brand-name drugs, can provide substantial cost savings for patients and third-party payers, including government health programs. According to industry estimates, in 2018 generic drugs accounted for nearly 90 percent of prescriptions filled in the United States.

- In 2016 it is reported that, on average, generic drugs have retail prices that are 75 to 90 percent lower than the retail prices of their brand-name counterparts, and new research indicates that the gap between brand-name and generic drugs may be widening. While estimates vary, studies have found that generic drugs have collectively saved patients and third-party payers billions of dollars. Such cost savings have resulted in widespread national interest in facilitating the quick approval of generic drugs; however, the interest in quick approvals must be balanced by the need for safety and efficacy.

- The timely approval of safe generic drugs in the first review cycle of the FDA can provide substantial cost savings to patients and third-party payers. Since the enactment of GDUFA, the FDA has taken steps to help applicants submit stronger generic drug applications and correct deficiencies within the first review cycle.

- **What is the first cycle approval rate?**

- United States Government Accountability Office (GAO) found that 12 percent of the 2,030 generic drug applications reviewed by the FDA from fiscal years 2015 through 2017 were approved in the first review cycle. In contrast, an NDA is now approved on the first cycle review approximately 95 percent of the time.

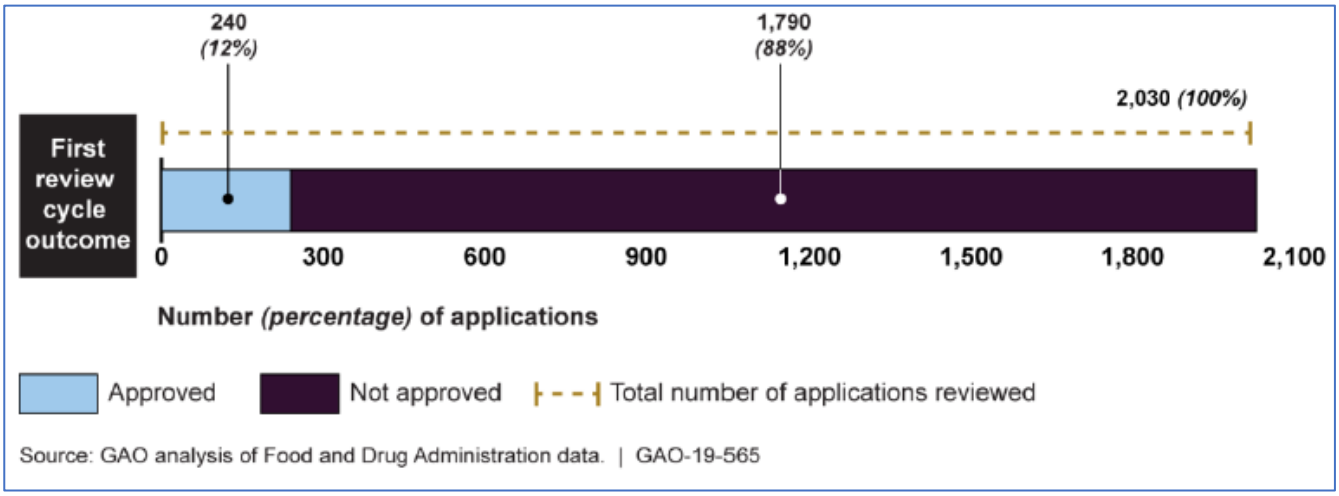


Figure 2: Number and percentage of generic drug applications approved in the First Review Cycle, Fiscal Years 2015–2017.

- According to the FDA, in recent years (fiscal years 2013–2017) it took an average of three review cycles for a generic drug application to reach approval; this process can take years, including the time it takes for the applicant to make changes to the application in response to FDA's comments and the time it takes for the FDA to review the changes.

- **Factors that may affect approval rates in the first review cycle**
- There are several factors, including certain characteristics of generic drug applications that may contribute to whether an application receives approval in the first review cycle, including the sufficiency of the application, deficiencies in drug quality, the type of drug reviewed, and priority status of the application.

- **Factors under control of Agency (US FDA):**
- According to a GAO (Government Accountability Office) report (2019), the following two are the major factors that the Agency should fix to achieve the first cycle approval:

- Inconsistency in written comments to generic drug applicants—including the clarity of writing and the content of comments—among reviewers, and

- The timing of brand-name companies' drug labeling changes.

- Several steps already taken by the Agency will further evaluate methods to improve the clarity and content of primary reviewer comments by providing training and work aids on written communication.

- Moreover, the FDA will identify and access examples of the application in which the brand name drug company submitted a supplemental application for a labeling change that impacted the timeline of the generic drug approval.

- **Factors under control of the Generic Industry:**
- The generic industry has a very high stake in ensuring first cycle approval. Although the industry has implemented many of the FDA's 21st Century Initiatives for Pharmaceutical Quality in the generic submissions, opportunities still exist to enhance industrywide submission practices for higher first cycle approvals.

- In order to increase the first cycle approval rate, critical and major non-exhaustive general check points and eCTD module specific checkpoints have been compiled and presented in the Annexure 1 of this document, which can be utilized along with the guidance documents of the FDA.

- Although important, but not always necessary for the ANDA applicants to ensure FCA checklist compliance. Circumstances may exist where ANDA applicants can waive of some of the requirements by providing sound scientific justification and / or risk assessment. The risk assessment generally takes into account the drug product's desired launch timelines based on intellectual property scenario (i.e., patent/exclusivity status) or business model on case by case basis. Risk assessment also takes into account the evaluation of sound regulatory strategies for managing post approval changes involving minimal resources utilization (mainly cost and time) and maximum benefit without impacting the commercial supply continuity after FCA. For example, if product launch is planed immediately after ANDA approval, then all aspects provided in the FCA checklist should be considered. However, on the other hand, if product launch date is not immediately after ANDA approval, then certain points given in the FCA checklist shall be relooked at the time of original ANDA submission or during ANDA review cycle.

5 Definitions

- **Act on an application:**
- This means that the FDA will either issue a complete response letter, an approval, a tentative approval, or a refuse-to-receive action.

- **Complete Response Letter (CRL):**
- This refers to a written communication to an applicant or DMF holder from the FDA usually describing all of the deficiencies that the agency has identified in an abbreviated application (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. Complete response letters will reflect a complete review which includes an application-related facilities assessment and will require a complete response from industry to restart the clock. Refer to 21 CFR 314.110 for additional details. When a citizen petition may impact the approvability of the ANDA, the FDA will strive to address, where possible, valid issues raised in a relevant citizen petition in the complete response letter. If a citizen petition raises an issue that would delay only a part of a complete response, a response that addresses all other issues will be considered a complete response.

- **Complete Review:**
- This refers to a full division—level review from all relevant review disciplines, including inspections, and includes other matters relating to the ANDAs and associated DMFs as well as consultations with other agency components.

- **Discipline Review Letter (DRL):**
- This means a letter used to convey preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its portion of the pending application at the conclusion of the discipline review.

- Timeline for DRL response is 30 calendar days.

- The Agency provides their preliminary thoughts on possible deficiencies to the applicant before a complete review of the entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter, these possible deficiencies do not reflect a complete review of the ANDA application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. It should be noted that deficiencies may be modified or additional deficiencies may be identified as the Agency completes their review of the entire application.

- Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if the FDA's review of the response has been deferred or if the FDA has outstanding concerns after review of the response.

- The FDA will strive to review the DRL response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of DRL response may be deferred. When the FDA defers review of DRL response, it will be reviewed during the next review cycle for the application.

- **Information Request (IR):**
- This means a letter that is sent to an applicant during a review to request further information or clarification that is needed or would be helpful to allow completion of the discipline review.

- Timeline for IR response is 30 calendar days.

- **First Cycle Approval (FCA):**
- As per FDA Reauthorization Act of 2017, the term 'First Cycle Approval' means the approval or tentative approval of a generic drug application after the FDA's complete review of the application and without issuance of one or more complete response letters.

- **Major:**
- This means a major amendment as described in CDER's December 2001 Guidance for Industry: Major, Minor and Telephone Amendments to Abbreviated New Drug Applications.

- **Prior Approval Supplements (PAS):**
- A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change.

- A major change is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

Annexure 1 : Checklist for First Cycle Approval

Section	Sub Section	Critical Points
General Points	----------	1. Submit substantially complete ANDA, meeting the requirements of all relevant guidance. 2. Completely address the deficiencies received through Discipline Review Letter (DRL) within the stipulated timeframe. 3. Avoid providing any commitments in response to DRL/Information Request (IR). 4. Proposal on specifications/control strategy should be based on scientific justification and based on batch analysis data. 5. Continuously monitor updates for Labeling, United States Pharmacopeia – National Formulary (USP-NF), OGD dissolution database, Citizen Petition, solicited DMF updates, and product specific guidance. 6. Ensure all exclusivities and patents listed in the electronic OB are addressed and updated in the application along with subsequent legal documents and relevant updates related to court findings. Revision in OB status needs to be submitted to the FDA at the earliest. 7. The labeling of the test product should be identical to that of the RLD except for the changes due to formulation difference and text omitted due to patent/exclusivity. 8. Avoid submission of unsolicited amendments for DMF and ANDA during the review period. 9. Monitor the compliance status of facilities referred in application for manufacturing and testing of drug substances intermediates, drug substance and Drug Product, and CRO/Clinical Sites. Limit the facilities used for ANDA (i.e., submit ANDA with single manufacturing facility, single or no contract testing lab). All the facilities mentioned in the ANDA should be judiciously tracked for upcoming audits; in case of any adverse outcome, the site can be withdrawn well in time. 10. Submit Pre-facility Correspondence (PFC) wherever applicable in order to obtain the shorter goal date for priority submissions. Additionally, pre-ANDA development meeting and pre-ANDA submission meeting for complex products should be planned to avoid major deficiencies or unaddressed development aspects during the review cycle. 11. Goal date should be communicated to DMF holder so that it can be ensured that query responses are submitted 90 days before goal date. 12. Make sure to build own deficiency database to implement the learnings in new filings proactively. 13. Make sure to work closely with FDA and other stake holders on REMS.

Section	Sub Section	Critical Points
General Points	----------	14. Adequate evaluation of impurities (genotoxic impurities and literature-based impurities), elemental impurities (ICHQ3D) and polymorphism (method capabilities for the undesired polymorphic forms). 15. Provide FDA recommended impurity tables. 16. Evaluate the presence of NDMA (N-Nitrosodimethylamine) and other N-nitrosamine impurities in drug substance. 17. Difference between physico-chemical properties if any (viz., polymorphism, solubility, pKa, pH etc., disclosed in the RLD PI) of the RLD API and Test Product API shall be justified in the original ANDA. 18. For API sensitive to heat, humidity or light, storage and handling procedure at the drug product manufacturer's end shall be explained in 'Module 3.2.S.6'. 19. Starting material shall be appropriately defined in the DMF.
Module 3 – DP	3.2.P.1	1. All components including solvents and processing aids with their functions should be listed, and the amount of inactive ingredients should be as per Inactive Ingredient Database (IID). If outside the IID database, it should be adequately justified. Control Correspondence with the FDA is recommended during development if excipients quantity exceeds IID database. 2. Physical description of the product should be comparable to Reference Listed Drug (RLD) including functional score. 3. Justification of overages/overfill (if any) should be provided. 4. Daily elemental iron calculation or statement of adherence to 21 CFR 73.1200 must be ensured. 5. The shape and size of the test product should comply with the related FDA guidance or else it may call for a reformulation.

Section	Sub Section	Critical Points
Module 3 – DP	3.2.P.2	1. A comprehensive product development report should be provided, including Reference Product characterization, Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs) drug-excipient compatibility studies, summary of Pilot BE Studies, dissolution discrimination power studies (although USP/OGD conditions adopted for MR products), other scientific studies (DOE study, Taste Masking studies, tablet split study, extractable-leachable study, Milliard reaction, oxidation induced degradation study, elemental risk assessment for FP, etc.), shipment study (for chewable/ODT products), summary of development and optimization studies, control strategy, etc.. 2. Product Development Report should be limited to relevant experimental/trail data. Sequential and simple language should be used for providing easy understanding for the reviewers.

Section	Sub Section	Critical Points
Module 3 – DP	3.2.P.3	1. Identify and list all the facilities used for manufacturing, release and stability testing of drug substance and drug product. The listed facilities should have satisfactory cGMP status. 2. Manufacturing process flowchart should include all input materials, unit operations, in-process controls and in-process tests. 3. Proposed commercial batch size should not be more than 10 times the standard exhibit batch size and the proposed commercial batch size should be same as that of the exhibit batch size, if it is not of the standard process or the process is complex. 4. All proposed process controls/tests should be justified. 5. Stratified CU/ASTM details to be included (if applicable).
Module 3 – DP	3.2.P.4	1. Complete tested COAs should be provided for all the components used in exhibit batches. 2. Differences in results between vendor's COA and Drug Product manufacturer COAs (if any) should be addressed appropriately. 3. For non-compendial or in-house analytical methods, validation data must be provided. 4. For compendial methods (e.g., quantitative determination method), verification data must be provided. 5. Provide ICH Q3D compliance statement wherever possible.

Section	Sub Section	Critical Points
Module 3 – DP	3.2.P.5	1. Proposed specification should be supported by exhibit batches data and RLD (wherever applicable). Wherever possible, the limits should be tightened on the basis of 6-months stability data in order to avoid FDA deficiency asking for tightening. 2. Full validation/method equivalency of in-house methods should be provided along with method transfer if the release testing site is different from the validation site. 3. All proposed process controls/tests should be justified and provide FDA recommended impurity table adequately. 4. Provide data for force degradation and mass balance study for Assay and Degradation Product method. 5. Provide FDA recommended impurity tables. 6. For compendial methods provide the verification data. 7. Provide adequate data of impurity qualification, if it is above ICH recommendations.

Section	Sub Section	Critical Points
Module 3 – DP	3.2.P.6	1. Characterization data of all reference/working standards should be provided having adequate potency/purity.
Module 3 – DP	3.2.P.7	1. Provide summary on container closure system of primary and secondary packing material (wherever applicable) including information on resin and colorant. 2. Provide complete data on each packaging component like technical drawings/diagrams, child resistant compliance statement, certifications in accordance with relevant USP General chapters and CFR, extractable/leachable study report and control strategy (wherever applicable), different lots of primary packaging materials (wherever applicable). E.g., for nasal/transdermal dosage form having complex dose delivery controlled by packing material, multiple lots of the primary packaging material must be used in the registration batches. 3. Provide in-process packaging tests, frequency and acceptance criteria.
Module 3 – DP	3.2.P.8	1. Provide stability summary and proposal on expiration period. 2. Provide intermediate stability data if there is any failure or significant change at accelerated condition. 3. One-time stability studies in support of labeling instructions (reconstitution, in-use study, etc.) should be provided.

Section	Sub Section	Critical Points
Module 3 – DP	3.2.P.8	4. Stability commitment for validation batches/commercial batches should be in line with ICH Q1A guideline. 5. Provide for photo stability study (wherever applicable). 6. Control of NDMA or other nitrosoamine impurities shall be evaluated if it is relevant to the formulation manufacturing process and sensitive to the storage condition over a period of time (viz. Ranitidine formulation).
Module 3	3.2.R	1. Executed batch records should include equipment numbers used for batch manufacturing and packing, batch reconciliation and label reconciliation in tabular format. 2. Provide data for justification of low yield and CAPA if applicable. 3. Exhibit batches should be manufactured with identical composition, process, equipment's design and principle, packing material and packaging process (manual vs. automatic) as proposed for the commercial batches.
Module 5	--	1. All clinical study reports conducted on proposed formulation should be submitted by using eCTD Study Tagging File for each study. 2. Statistical outlier should not be included in statistical analysis for confirmation of BE. 3. Deviation from the PSG design shall be adequately justified if applicable. 4. Provide data for additional in-vitro BE study data relevant to the dosage form, e.g. in-vitro permeation test, adhesion study, skin irritation/sensitization study, etc.

Revision History

Effective Date	Revision Number	Revisions
Jun 2020	01	1. Provision for priority request is included under 'General Points'. 2. Requirement for evaluation of Nitroso impurities is included under 'Module 3-DS' and 'Module 3-DP' 3. Difference between Physico chemical properties to be justified under 'Module 3.2.S' 4. Storage and handling precaution for the sensitive API at the FP manufacturer's end shall be explained in original ANDA under 'Module 3.2.S'. 5. Starting material shall be appropriately defined in the DMF in 'Module 3.2.S' 6. Additional editorial changes providing better clarity with examples.
Aug 2020	02	Details pertaining to the determination of the FCA benefits Vs. Commercial/supply continuity benefits included under "Factors under control of the Generic Industry". 1. Point number 11 included in the Annexure as "Goal date should be communicated to DMF holder so that it can be assured that they submit query response before 90 days of goal date."

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