Focus on Post Approval Changes and Change Control Evaluation

Regulatory Best Practices

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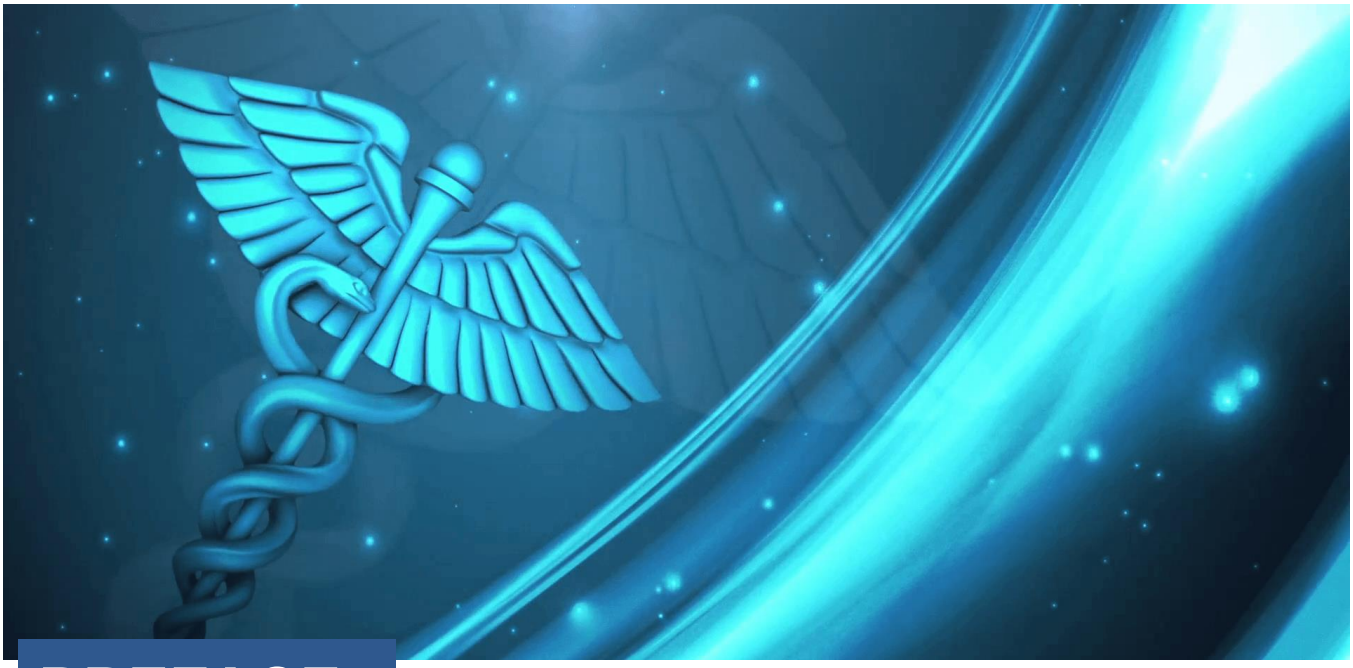

PREFACE

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 Post approval changes (i.e., regulatory reporting category evaluation and regulatory documents requirement for specific changes) & change control evaluation. This document also highlights the key major sections of a sANDA application that, if appropriately and scientifically addressed at the time of the original sANDA submission, leads to decrease in the number of deficiency points in the complete response letter (CRL) and provides ways to avoid 'Major' category CRLs. In addition, this document identifies certain key areas of an sANDA application which needs to be continuously monitored and communicated via suitable regulatory strategies, in order to obtain timely approval of and sANDA 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, Mr. Bhaumik Modi and Mr. Darshan Doshi (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.

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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 and Background

- The document covers recommended reporting categories for post approval changes for drugs other than specified biotechnology and specified synthetic biological products.

- The key objectives of this regulatory best practice document are listed below:

    - This document acts as a Ready Reckoner to determine the post approval submission category as per US FDA's various guidelines;

    - Identification of post approval change submission requirements and intelligence at one place;

    - Precise and easy change control assessment process;

    - For the smooth life cycle management of the post approval changes.

- Various post approval changes have been broadly classified in to following categories. Detailed regulatory requirements for each change is provided below in Annexure 1 of this document.

    - Pharmacopeia Compliance;

    - Type II DMF Notifications;

    - Risk Mitigation Strategies;

    - Increase Productivity or Trouble Shooting;

    - Packaging Material Changes;

    - Cost Improvement.

3 Scope

- This document provides recommendations to holders of Abbreviated New Drug Applications (ANDAs) who intend to make post approval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and § 314.70 (21 CFR 314.70).

4 Definitions

- **Prior Approval Supplement (PAS):**

- 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. A major change requires the submission of a supplement and approval by the FDA prior to distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a Prior Approval Supplement (§ 314.70(b)).

- **Changes Being Effected in 30 Days (CBE-30) and Changes Being Effected (CBE) Supplement:**

- A moderate change is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. There are two types of moderate change. One type requires the submission of a supplement to the FDA at least 30 days before the distribution of the drug product is made using the change. This type of supplement is called, and should be clearly labeled, a Supplement - Changes Being Effected in 30 Days (§ 314.70(c)(3)). In the second type, the FDA may identify certain moderate changes for which distribution can occur when the FDA receives the supplement (§ 314.70(c)(6)). This type of supplement is called, and should be clearly labeled, a Supplement - Changes Being Effected.

- **Annual Report:**

- A minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next Annual Report (§ 314.70(d)).

Annexure 1

Checklist for post approval changes & change control evaluation

Sr. No.	Area	Type of Change	Change Proposal Evaluation Documents	Regulatory Documents Required at the Time of PAF (Post approval Filing)	Reporting categories
Pharmacopeia Compliance					
1	API/DP	Relaxation of acceptance criteria and change in dissolution method.	• Stability trend data (if applicable). • Method verification (if applicable). • Impact of relaxation in API spec over DP spec or vice versa (if applicable).	• Specification. • STP (if applicable). • Certificate of Analysis (COA). • Method verification (if applicable). • Updated stability data. • Dissolution Profile • Dissolution Method discrimination (if applicable).	CBE-30
2		Deletion of test (if test is CMA, the FDA may not approve the Supplement).	• Evidence/justification that removal is not adversely impacting the identity, strength, quality, purity, or potency of the API/DP.	• Specification. • Standard test procedure.	
3		Addition of test	• Method verification/ equivalency/validation (as applicable). • Impact of addition of test in API spec over DP spec or vice versa (if applicable).	• Specification. • STP. • COA. • Method verification/validation/equivalency (as applicable). • Updated stability data.	CBE

Sr. No.	Area	Type of Change	Change Proposal Evaluation Documents	Regulatory Documents Required at the Time of PAF (Post approval Filing)	Reporting categories
Type II DMF Notification					
1	API	Change/addition in intermediate source.	• 1 lot API COA with new source analysed by the DP manufacturer. • cGMP compliance • 3 lots API equivalency data with old source API.	• 1 lot API COA with new source. • New source's cGMP certificate and debarment certificate. • 3 lots API comparison/equivalency data.	**PAS** **[If mfg. process, specification of intermediate/final API remains same or similar then the change may be submitted under CBE-30 reporting category]**
2		Change/additional of KSM source (other than source material change for natural product).	• Not applicable	• DMF holder's notification letter.	**Annual reportable** **[Generally, this information is not disclosed by the DMF holder to the ANDA applicant; hence no supplement filing is warranted].**
3		Change in the process (after final intermediate processing step). (Subject to no change is ROS and/or impurity profile)	• 1 lot API COA. • 3 lots API equivalency data with old process API.	• 1 lot API COA tested by DP manufacturer. • 3 lots API equivalency data with old process API.	**PAS**
4		Change in process (before final stage/after final intermediate processing step) that results into change in the ROS and/or impurity profile.	• 1 lot API COA • 1 batch DP COA • FP accelerated and long term stability data (it will be required if there is change in degradation impurities due to change in process). • FP forced degradation study report. • API and FP related substance method validation.	• 1 lot API COA analysed by DP manufacturer. • 1 batch DP COA. • DP accelerated and long term stability data. • DP forced degradation study report (if applicable). • API and DP related substance method validation (if applicable).	**PAS**

Sr. No.	Area	Type of Change	Change Proposal Evaluation Documents	Regulatory Documents Required at the Time of PAF (Post approval Filing)	Reporting categories
Type II DMF Notification					
5		Change in ROS or change in API source.	• 1 DP batch per strength (if same impurity profile). • API spec and STP. • API COA. • DP COAs. • DP Accelerated and long-term stability data. • DP dissolution profile.	• API spec and STP. • API COA. • DP dissolution profile similarity. • DP COAs. • 3 M Accelerated and long-term stability data of DP. • DP executed BMR.	PAS
6		Final API Spec/STP change due to change in manufacturing process (i.e., addition or deletion of residual solvents).	• 1 lot API COA with changed manufacturing process. • 3 lots equivalency data with old process API.	• 1 lot API COA with changed manufacturing process. • 3 lots equivalency data with old process API. • DP COA.	CBE-30
7		API mfg./testing site addition/change (Subject to site is US FDA audited, no change in manufacturing process / API Spec/ROS and site is currently in GMP compliance).	• cGMP status. • cGMP and debarment certificate. • 1 lot API COA. • 3 lots equivalency data with old API mfg. site.	• cGMP and debarment certificates. • 1 lot API COA. • 3 lots equivalency data with old API mfg. site.	CBE-30
8		API mfg/testing site addition/change if the site is not US FDA audited and/or there is change in manufacturing process and/or ROS.	• cGMP status. • cGMP and debarment certificate. • 1 lot API COA. • 3 lots equivalency data with old API. • 1 batch DP COA. • 1 DP batch stability data (Accelerated and long-term).	• cGMP and debarment certificate. • 1 lot API COA. • 3 lots equivalency data with old API mfg. site. • 1 batch DP COA. • 3 M Accelerated and long-term stability data of DP.	PAS

Sr. No.	Area	Type of Change	Change Proposal Evaluation Documents	Regulatory Documents Required at the Time of PAF (Post approval Filing)	Reporting categories
Risk Mitigation					
1	DP	**Drug product manufacturing site change:**			
		For solid oral IR dosage forms: The new site has either never been inspected OR with no satisfactory cGMP status for the type of operation being moved OR transfer causes a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.	cGMP certification, Debarment Certification, GDUFA fees payment Receipt, LOA, US agent Details, site details and Contact details, Functions details and Inspection details, 356h form, retest data.	• DP dissolution profile similarity. • 3 M Accelerated and long-term stability data for one batch for all strengths.	**PAS**
		For solid oral IR dosage forms: The new site has been inspected for the type of operation being moved.		• DP dissolution profile similarity. • 3 M Accelerated and long-term stability data for one batch for all strengths.	**CBE 30**
2		**FP spec/STP change**			
		Reduction in shelf life	• Long-term stability data up to the proposed shelf life. • Intermediate condition stability data (if applicable). • Root cause for the reduction in the shelf life. • Intended stability protocols.	• Long-term stability data up to the proposed shelf life. • Intermediate condition stability data (if applicable). • Revised expiration dating period certification. • Revised BMR and BPRs. • Intended stability protocols.	**CBE-30**

Sr. No.	Area	Type of Change	Change Proposal Evaluation Documents	Regulatory Documents Required at the Time of PAF (Post approval Filing)	Reporting categories
3	DP	Extension in shelf life	Based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application, or (2) full shelf life data on pilot scale batches using an approved protocol.		PAS
			• Exhibit stability protocols. • Intended stability protocols. • Long-term stability data up to the proposed shelf life.	• Exhibit stability protocols. • Intended stability protocols. • Updated long-term stability data up to the proposed shelf life. • Pilot scale batch BMRs and BPRs. • Intended BMRs and BPRs. • Expiration dating period certifications.	
			An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application.		Annual Report
			• Long-term stability data up to the proposed shelf life.	• Intended stability protocols. • Updated long-term stability data up to the proposed shelf life. • Intended BMRs and BPRs. • Expiration dating period certifications.	

Sr. No.	Area	Type of Change	Change Proposal Evaluation Documents	Regulatory Documents Required at the Time of PAF (Post approval Filing)	Reporting categories
4	Excipients	Alternative hard gelatin capsules supplier.	No change in capsule composition or appearance		Annual Report
			• Capsule shell composition. • Vendor COA. • TSE-BSE certification. • Residual solvent declaration. • Vendor letter of authorization.	• Capsule shell composition. • Vendor and DP manufacturer's COA. • TSE-BSE certification. • Residual solvent declaration. • Intended BMR. • Specification and STP of capsule shell. • Finished product specification, STP and COA. • Exhibit BMR. • Stability data. • Vendor letter of authorization.	
			Any change in capsule composition or appearance, including change in size, color or dye, or a change from gelatin to non-gelatin alternative.		PAS
			• Capsule shell composition. • Vendor COA. • TSE-BSE certification. • Residual solvent declaration. • Vendor letter of authorization.	• Capsule shell composition. • Vendor and DP manufacturer's COA. • TSE-BSE certification. • Residual solvent declaration. • Intended BMR. • Specification and STP of capsule shell. • Finished product specification, STP and COA. • Exhibit BMR. • Stability data. • Vendor letter of authorization. • Dissolution profile may be required.	

Sr. No.	Area	Type of Change	Change Proposal Evaluation Documents	Regulatory Documents Required at the Time of PAF (Post approval Filing)	Reporting categories
Increase Productivity or Trouble Shooting					
1	DP	Increase in Batch size >10X of pilot/bio batch.	For IR products: Based on (1) equipment used to produce the test batch(es) may vary in capacity, but are of the same design and operating principles; (2) batch(es) is manufactured in full compliance with cGMPs, and (3) same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).	• Intended BMR. • 1 In-process COA. • 1 DP-COA. • 1 DP batch stability data (3 M Accelerated and long-term). • 1 batch executed BMR & BPR. • 1 batch dissolution profile similarity.	CBE (if proposed equipment does not have same design and/or principle, then filing category will be either CBE-30/PAS supplement based on data evaluation).
			For MR products: Based on (1) equipment used to produce the test batch(es) may vary in capacity, but are of the same design and operating principles; (2) batch(es) is manufactured in full compliance with cGMPs, and (3) same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).	• Intended BMR. • 1 In-process COA. • 1 DP-COA. • 1 DP batch stability data (3 M Accelerated and long-term). • 1 batch executed BMR & BPR. • 1 batch dissolution profile similarity. • Multimedia dissolution profiles similarity.	
		Increase in batch size within 10X of pilot/bio batch.	Based on (1) equipment used to produce the test batch(es) may vary in capacity, but are of the same design and operating principles, (2) batch(es) is manufactured in full compliance with cGMPs, and (3) same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).	• Intended BMR • 1 In process COA • 1 DP COA • 1 batch DP stability data (Long-term) • Intended BMR	Annual Report (if proposed equipment does not have same design and/or principle, then filing category will be either CBE-30/PAS supplement based on data evaluation).

Packaging Material Change				
1	DP	Packaging components (primary/secondary) change <u>for solid orals/ topical/ parenteral</u> if already used in the CDER Approved drug product or the container closure system is already approved in the same ANDA for other strengths of the drug product.	• 3M Accelerated and long-term stability data in new packaging. • Packaging material equivalency data. • Batch packaging record. • Packaging material Certificate of Analysis. • Packaging material LOA and food grade certification. • DP COA. • E/L study (if topical/parenteral products)	Annual Report
2		Packaging components (primary/secondary) change <u>for solid orals/ topical/ parenteral</u> if not previously approved in other CDER products		PAS
3		Addition or deletion of filler in approved pack to avoid brakeage of the drug product during transportation.	• 3 M accelerated and long-term stability data. • Batch packaging record. • Packaging material Certificate of Analysis. • Packaging material LOA and food grade certification. • FP COA.	CBE
4		Deletion/addition of desiccant.		CBE
		Change in type of desiccant.		CBE
5		Reduction in quantity of desiccant.		CBE

Sr. No.	Area	Type of Change	Change Proposal Evaluation Documents	Regulatory Documents Required at the Time of PAF (Post approval Filing)		Reporting categories
Cost Improvement						
1	API	Drug Substance - specification reduced testing frequency.	Trend data to be evaluated	Consecutive batches trend data.		**CBE-30 or being cGMP related practice, Agency may not review such proposal for API.**
2	DP	Drug Product - in process specification reduced testing frequency.	Trend data to be evaluated	Consecutive batches trend data.		**CBE-30**
		Stability bracketing/matrixing (Without pre-approved protocol).	Trend data to be evaluated	Consecutive batches trend data.		**PAS**

Important Note:

- **The reporting category, change evaluation/assessment data, and filing category may vary on case-to-case basis, depending on various factors, such as physico-chemical properties of the molecule and/or drug product characteristics, availability of significant body of information, product and process understanding, whether change is within or outside the established design space, GMP compliance history, potential to impact the identity, strength, quality, purity, or potency of a drug product based on the supportive data generated with proposed change, etc.**
- **Many more profound post approval changes will be included in this check list, viz. complex dosage forms (Ophthalmic, TDS, Nasal), device component part change, labelling changes, design space, etc.**
- **Covid -19 pandemic and post approval change management**
  - **Depending on the need of API and/or drug product under Covid-19 situation (Public Health Emergency or Drug Shortage), there may be change/s in the post approval change evaluation requirements (e.g., batches, stability data at the time of filing, exhaustive characterization of API and / or DP, BCS based bio waiver approach etc.), filing category and review classification (standard/ priority) etc. It is advised to consult the US FDA review discipline and/or drug shortage staff well in advance of any such submissions.**

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