Best Practices for Post-Approval Chemistry, Manufacturing and Controls (CMC) Changes – Scale Up and Post Approval Changes (SUPAC) Guidance

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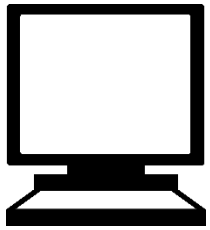
Overview

- Importance of **Pharmaceutical Quality**
- SUPAC Guidance
- Scientific Rationale
- Levels of post-approval Changes
- Types of SUPAC Changes
- Limitations of SUPAC Guidance
- ICH Guidelines to Post Approval Changes
- Conclusion

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user




Drugs are no different.

Pharmaceutical Quality

Pharmaceutical quality is

assuring **every** dose is safe and effective, free of contamination and defects

It is what gives patients confidence in their next dose of medicine

SUPAC Guidance

Approved New Drug Application (NDA)

SCALE-UP

Large Batch Size

Generic Drug Product

Bioequivalent to the FDA reference listed drug

Approved ANDA or AADA

SCALE-UP

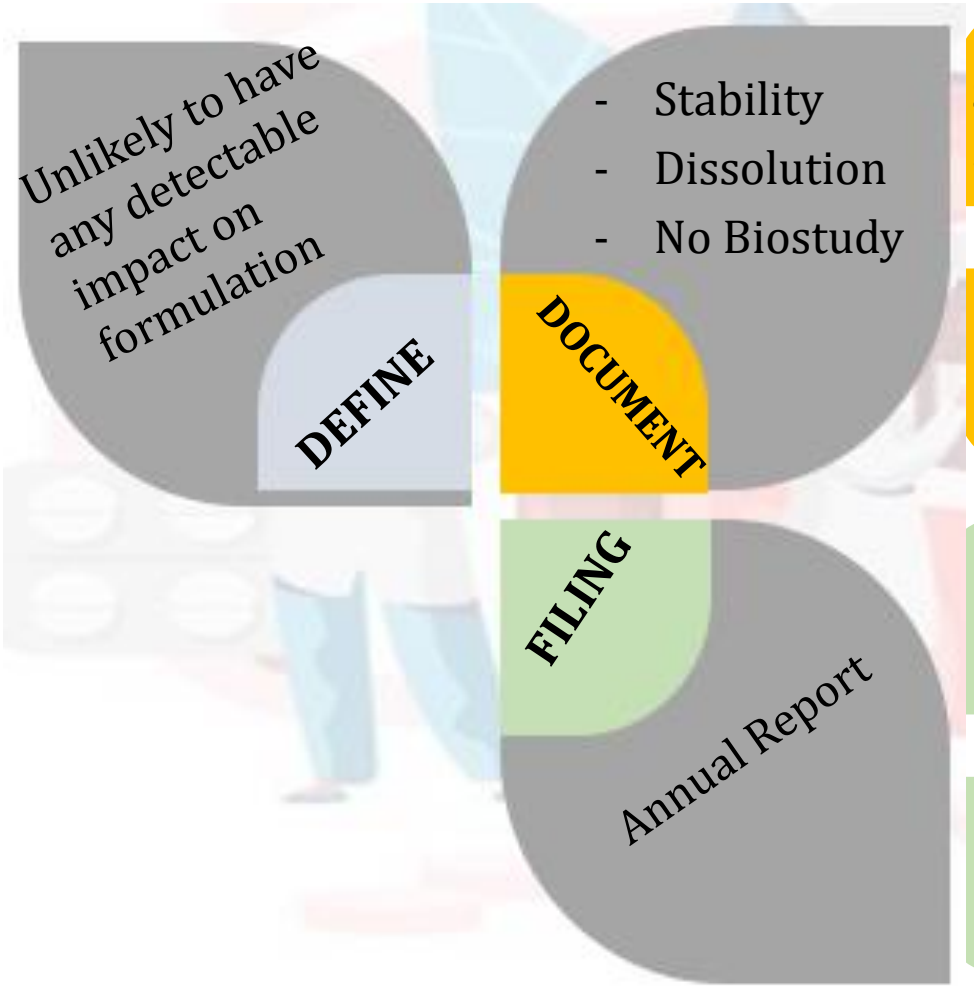
Scientific Rationale

- Provide recommendations and expedite the process of post approval changes in:
  - Drug product Components and Composition
  - The site of manufacture
  - Scale-up/Scale-down of manufacture
  - Manufacturing (process and equipment) of a modified release solid oral dosage form
- FDA can assure their safety and effectiveness
- Reduce the regulatory burden by making post approval CMC changes more predictable and efficient while maintaining formation quality and therapeutic product performance

SUPAC Guidance

1995	SUPAC-IR
1997	SUPAC-IR & ANSWERS
1997	SUPAC-SS
1997	SUPAC-MR
1999	SUPAC-IR/MR: Manufacturing Equipment Addendum
2014	SUPAC: Manufacturing Equipment Addendum

Level I Changes



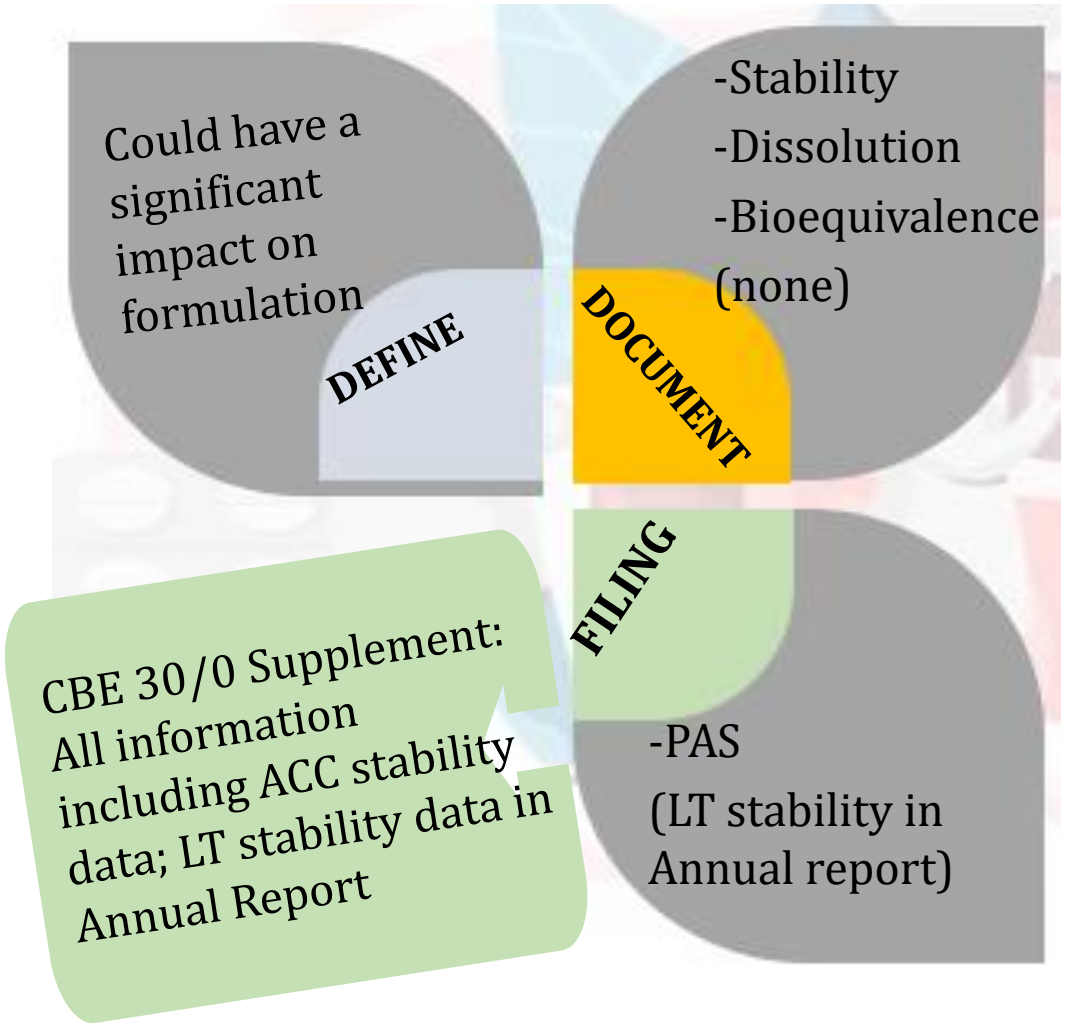
Stability: 1st Production batch on LT stability data in annual report

Dissolution Documentation: None beyond application/compendial requirements

Bioequivalence documentation: None

Annual Report: All information including LT Stability data

Level II Changes

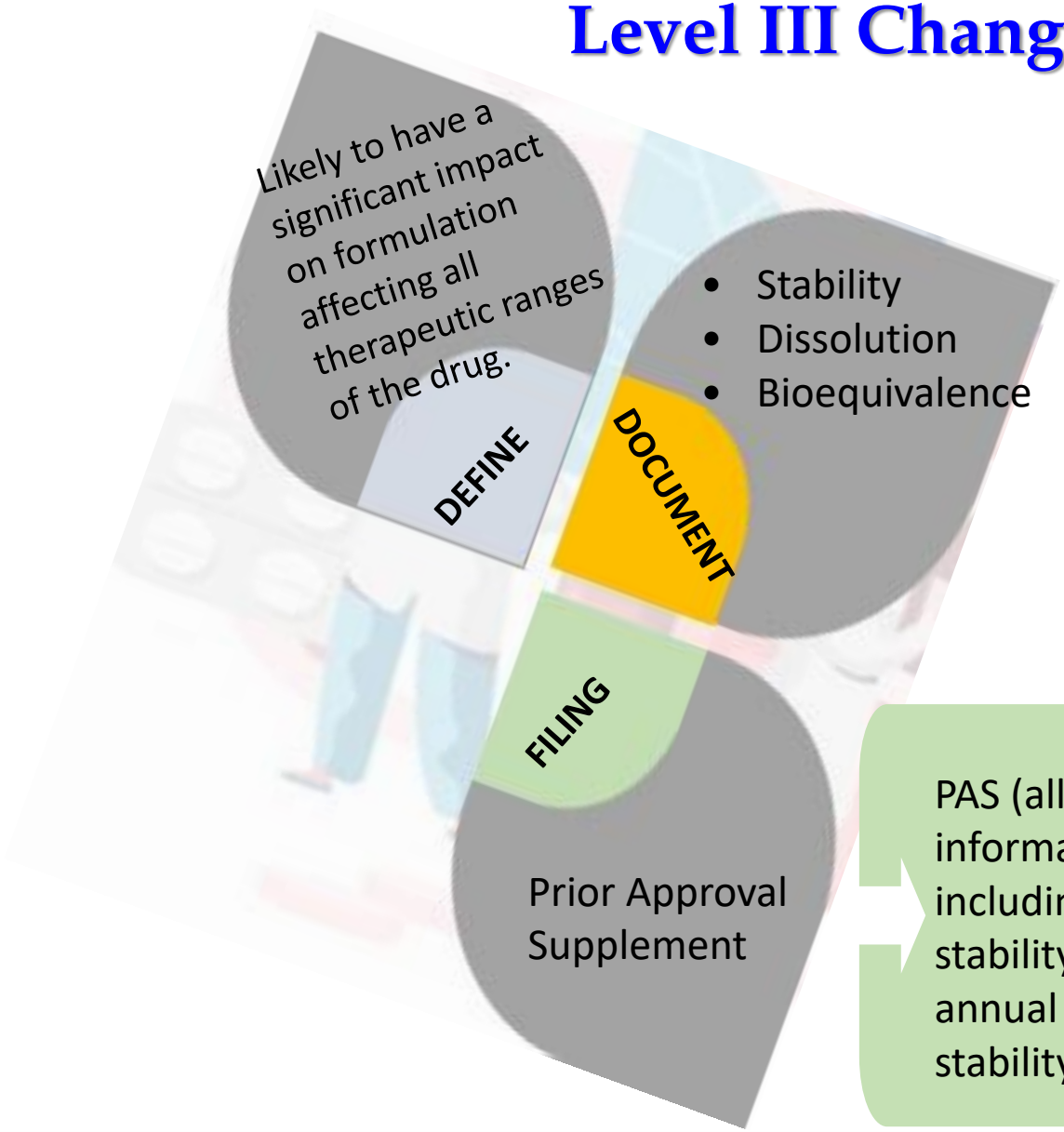


Dissolution

Extended Release:
Application/compendial release requirements + Multipoint dissolution profiles in 3 other media between biobatch/pre- and post-change batches

Delayed Release:
Application/compendial release requirements + Dissolution test in acid stage, buffer stage under standard test conditions and two additional agitation speeds using apparatus I and II

Level III Changes



Stability: 3 batches with 3 months' ACC stability data

Dissolution: Same as in level II

Bioequivalence: A single-dose BE study . The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation

PAS (all information including ACC stability data); annual report (LT stability data).

COMPONENTS AND COMPOSITION

- **SUPAC-IR:** Focus on changes in amount of excipients in the drug product
- **SUPAC-MR:** Functionality of each excipient should be identified. The criticality of changes to excipients is based on whether the excipients
  - Control the release of the drug product –Release controlling excipient
  - Does not control the drug release - Non-release controlling
- Sponsor should provide appropriate justifications for claiming any excipient(s) as a non-release controlling or release controlling in the formulation
- **SUPAC – SS:** Changes in preservatives

Case Study 1

An Applicant would like to include an **alternate source** for the excipient Anhydrous Dibasic Calcium Phosphate (DCP) for its IR Tablet which is manufactured by direct compression. The proposed source of DCP is **granular powder** while the approved source is **coarse powder** The drug product contains MCC and Anhydrous Dibasic Calcium Phosphate as co-diluents.

This supplement should be submitted as:

A. In the Annual Report

B. Changes Being Effected

C. PAS

Answer: A change in the technical grade of the excipient (from coarse to granular) is a SUPAC-IR Level 2, due to differences in particle size and bulk density and must be submitted as a PAS

NONRELEASE CONTROLLING EXCIPIENTS

Level	Classification	Documents	Filing Category
Level I	✓ Deletion or partial deletion of ingredient that affects color or flavor ✓ ≤5% w/w change based on total excipient contents	✓ LT Stability ✓ Compendial product release ✓ No biostudy	Annual Report
Level II	✓ Change in technical grade and/or specifications ✓ ≤10% w/w change based on total excipient contents	-Updated records -Stability -Dissolution documentation -Extended Release -Delayed Release -No biostudy	Prior approval supplement
Level III	>10% w/w change based on total excipient contents	- All Level II requirements - Single-dose BE Study	Prior approval supplement

RELEASE CONTROLLING EXCIPIENTS

Level	Classification	Therapeutic Range	Test Documentation	Filing Category
Level I	≤5% w/w change based on total excipient contents	All drugs	-Stability -Compendial requirements -No biostudy	Annual report
Level II	Change in technical grade and/or specifications. ≤10% w/w change based on total excipient contents	Non-narrow	- 1 exhibit batch with 3 months ACC Stability -Dissolution documentation -Extended Release -Delayed Release - No biostudy	Prior Approval Supplement
		Narrow Prior approval supplement	- 3 exhibit batches with 3 months ACC stability - Same dissolution - Single-dose BE study	Prior Approval Supplement
Level III	>10% w/w change based on total excipient contents	All drugs	- 3 exhibit batches & 3 months ACC and LT stability - Dissolution for ER and DR - Single-dose BE study	Prior Approval Supplement

Case Study 2

Company A submits a CBE 30 to revise the theoretical weight gain of Drug Loaded Pellets and Functional Coated Pellets at functional coating stage of its approved Extended-Release drug product as shown below.

Should this supplement be granted CBE 30 or elevated to PAS based on section IV.C (Level 3) of the SUPAC-MR Guidance?

Stage	Approved Acceptance Criteria	Proposed Acceptance Criteria
Theoretical Coating Weight gain of Drug Loaded Pellets	Target: 108.50 kg (Range 100.90 kg – 108.50 kg)	Target: 108.50 kg (Range: 97.65 -108.50 kg)
Theoretical Coating Weight Gain of Functional Coated Pellets	Target: 50.03 kg (Range: 47.66 kg – 50.03 kg)	Target: 50.03 kg Range: 39.30 kg – 50.03

Case Study 2 (Cont'd)

Drug Loaded Pellets, kg*	Functional (Extended-Release) Coated Pellets			
	Target wt. gain, kg / %		Approved wt. gain lower limit, kg / %	Proposed wt. gain lower limit, kg / %
294.285	50.03 17.0%		47.53 16.2%	39.30 13.4%
ER coating batch formula contains*				
Ethyl Cellulose NF 20 cps, kg	37.021	74.0%	35.17	29.08
Net change, kg			-6.09	
% NET CHANGE			**-16.5%**	
ER coating layer unit dose contains**				
Ethyl Cellulose NF 20 cps, mg	20.775	74.0%	19.74	16.32
Net change, mg			-3.42	
% NET CHANGE			**-16.5%**	
Hypromellose USP (Methocel E5), mg	3.538			
Hypromellose USP (Methocel E15), mg	2.358			
Polyethylene Glycol 8000 NF, mg	1.403			
Total, mg	**28.07**			

Conclusion: *Proposed change resulted in a >10% w/w change in the total release-controlling excipient content in the formulation (Level 3) and was elevated to PAS*

MANUFACTURING SITE CHANGES

Level	Classification	Test Documentation	Filing Category
Level I	-Single Facility -Common Personnel -No other changes	-Compendial requirements -No Biostudy	Annual report
LEVEL II	-Same contiguous campus -Common personnel -No other changes	-Identification and description of site change, and updated batch record -Notification of site change -Dissolution documentation (Extended Release & Delayed Release Requirements)	Changes Being Effected
LEVEL III	-Different campus -Different personnel	-Notification of site change -Updated batch record -Stability -application/compendial requirements -Biostudy	Prior approval supplement

BATCH SIZE – SCALE UP/SCALE DOWN

LEVEL	CLASSIFIACTION	CHANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	• Scale-up of bio-batches or pivotal clinical batch(s) • No other changes	≤10X	• Updated batch record • Stability • Application/Compendial requirements • No Biostudy	Annual report
II	• Scale-up of bio-batches or pivotal clinical batch(s) • No other changes	>10X	• Updated batch record • Stability • Dissolution documentation -Extended release -Delayed release • Bioequivalence documentation	Changed being Effected supplement

MANUFACTURING EQUIPMENT CHANGES

LEVEL	CLASSIFIACTION	CHANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	• Equipment change(s) • No other changes	• Alternate equipment of same design and principle • Nonautomated/non mechanical to Automated/Mechanical equipment	• Updated batch record • Stability • Application/Compendial requirements • No Biostudy	Annual report
II	• Equipment change(s) • No other changes	• Change in equipment of different design and operating principle.	• Updated batch record • Stability • Dissolution documentation -Extended release -Delayed release • Bioequivalence documentation	Changed Being Effected Supplement

MANUFACTURING PROCESS CHANGES

LEVEL I	LEVEL II	LEVEL III
Classification • Adjustment of equipment operating conditions within approved ranges	**Classification** • Adjustment of equipment operating conditions outside approved ranges	**Classification** Change in the Manufacturing Process e.g. Wet granulation to direct compression
Test Documentation • Updated batch records • Application/ compendial requirements • No biostudy	**Test Documentation** • Stability • Dissolution documentation -Extended release -Delayed release • No Biostudy	• **Test Documentation** • Updated batch record • Stability • Application/Compendial requirements • Biostudy
Annual Report	**Changes Being Effected**	**PAS**

Limitations of SUPAC Guidance

- As more generic drugs get approved by FDA, clarity regarding the lifecycle management of these products becomes dire
- Has not been updated (1995/97 for main guides; 1997/2014 for manufacturing/ Equipment Addenda)
- Does not discuss multiple changes
- Does not directly cover same class and different subclass for equipment changes
- Does not cover modified equipment
- Must be used in conjunction with other references, e.g. excipient handbook

ICH Guidelines to Post-Approval Changes

- ✓ Provide opportunity for science- and risk-based approaches to drug product development and regulatory decisions
- ✓ Provide valuable information in assessment of CMC changes across product lifecycle

Q8(R2) *Early stage of product lifecycle*

Q9 *Quality Risk management*

Q10

Q11 *Focus: Early stage of product (DS) lifecycle*

Q12

Q14

Focus: Commercial phase of product lifecycle

- ✓ Complement and add flexibility to regulatory approaches to post-approval CMC changes described in Q8 & Q10
- ✓ Provides a harmonized framework to facilitate management of post-approval CMC changes more predictably
- ✓ Defines categorization of post-approval changes to CMC, Established Conditions (EC), Post-Approval Change Management Protocols (PACMP) and Product Lifecycle Management (PLCM) concepts

ICH Q12 – Established Conditions (EC)

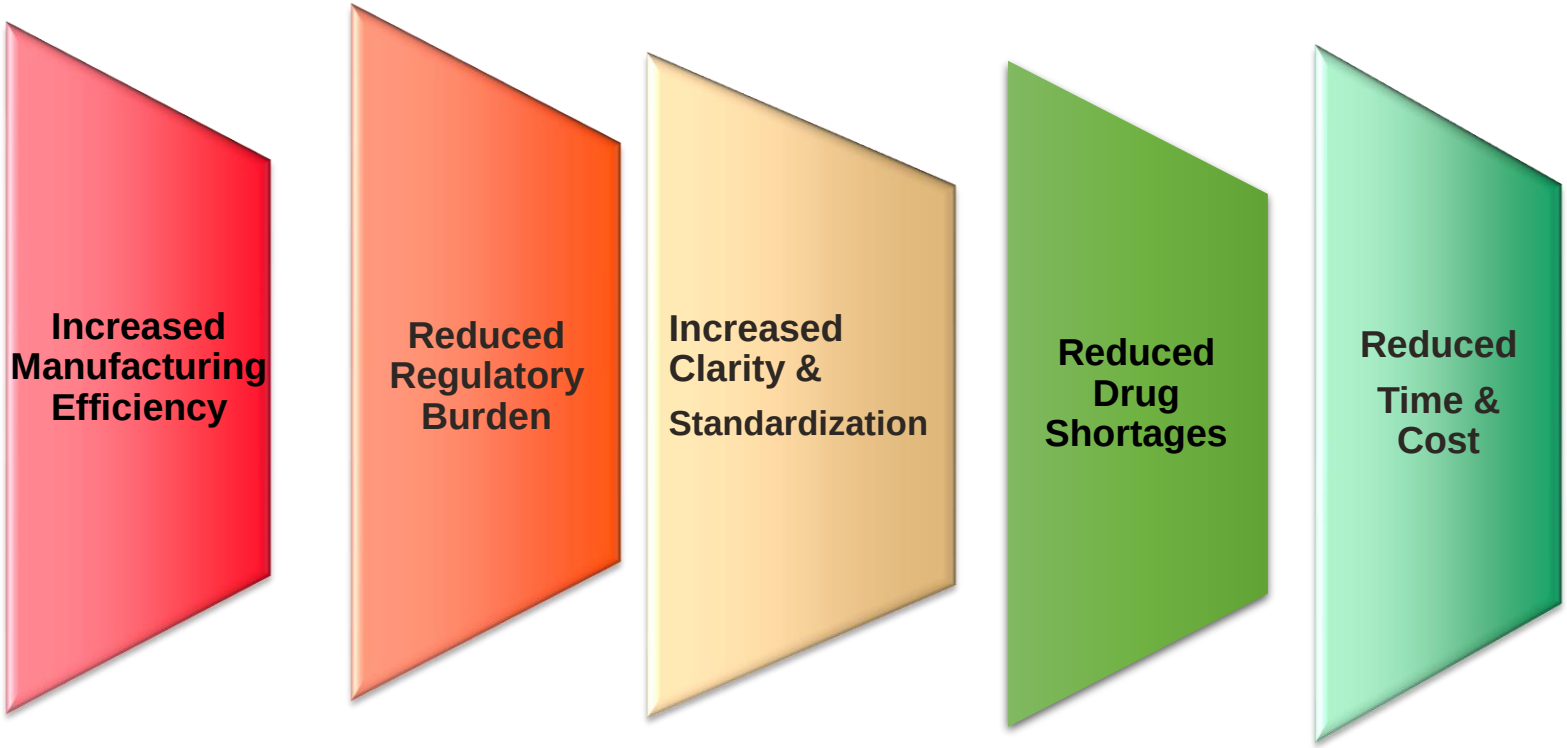
- Elements of the control strategy in an application (i.e., product and process parameters, specifications and associated methods and frequency of monitoring and control) facility and equipment operating conditions, in-process controls, finished product that are necessary to assure process performance and product quality.
  - If any EC is changed, it requires a (post approval) regulatory submission
  - Supportive information does not require regulatory submission, if changed
- The extent (number and how narrowly defined) of ECs varies based on
  - Product and process understanding
  - Characterization
  - Firm's development approach
  - Potential risk to product quality
- Product and process understanding can come from development studies, platform knowledge and/or commercial experience

Post-Approval Change Management Protocol (PACMP)

- Provides predictability and transparency regarding the information required to support a CMC change and the submission required for the change
- Referred to as **Comparability Protocol** in the US
- May be submitted with original application or as a stand-alone submission (PAS)
- Can be submitted to address one or more changes for a single product or may address one or more changes to be applied to multiple products

 A CMC change that would require supportive efficacy, safety (clinical or non-clinical) or human PK/PD data IS NOT suitable for inclusion in a PACMP

Advantages


Increased Manufacturing Efficiency
Reduced Regulatory Burden
Increased Clarity & Standardization
Reduced Drug Shortages
Reduced Time & Cost

Conclusion

- It is Applicant's responsibility to improve the quality of submission by using science-based and risk-based approach to assess the impact of proposed change(s) on product quality
- Demonstrate good product and process understanding in your supplement
  - Adopt modern quality techniques with focus on sound science for assessing and mitigating risks of poor product and process quality(e.g., QbD, CQA, CPP, CMA and Control strategy)

Thank you