Assigned AAPS Poster Number
2806

Regulatory Pathways for Managing Post Approval CMC Changes - Comparison of Latest FDA and EMA Guidelines

H. Gutka, B. Mamidipudi, S. Gaddamanugu, P. Nambiar
Syner-G Pharma CMC Consulting LLC

SYNER-G

Purpose

Chemistry, Manufacturing and Controls (CMC) changes are inevitable due to many reasons including changing needs, new findings and continuous improvement. Therefore, regulations require that all changes be evaluated carefully and follow the proper regulatory path for implementation, regardless of whether it is an investigational or a commercial product. Failure to comply with regulatory requirements for post-approval CMC changes can potentially lead to "misbranded or adulterated" status for a given product. This should be taken very seriously for marketed products because of the potential safety/efficacy impact for the vast number of patients as well as legal, regulatory and business impact for the sponsor. In light of QbD paradigm, leveraging the product and process knowledge gained and the use of a risk based approach should allow a sponsor to achieve the best path for post-approval change implementation.

Methods

Main references used for this analysis are the US Code of Federal Regulations (CFR) 21 CFR Part 314.70, EUROPEAN COMMISSION REGULATION (EC) No 1234/2008, and No 712/2012, EMA guidance on Post-authorisation Procedural Advice for Users of the Centralised Procedure, and FDA guidances on Changes to an Approved NDA and ANDA and CMC Post-approval Manufacturing Changes Reportable in Annual Reports (Draft). In addition to regular path, both FDA and EMA provide for managing major CMC changes in a prospective approach via comparability protocol.

Results

This poster will provide a detailed analysis of the current US and European regulations and guidance documents for post-approval CMC change management for small molecules based products. It also provide an analysis of the approaches described in FDA draft guidance on Comparability Protocols —Chemistry, Manufacturing, and Controls EMA draft guidance on Post-approval Change Management protocols.

Conclusion

Knowledge of these similarities and differences will enable the audience to develop the CMC strategy to implement change successfully in US and EU markets.

Types of Post Approval Changes

FDA	EMA
Major Change • Substantial Potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product • Prior Approval Supplement (PAS) • PDUFA V goal date – 4 months	**Type II Variation** • a significant impact on the Quality, Safety or Efficacy of a medicinal pdt • Prior Approval Procedure • Validation + (30, 60, 90)CHMP + 15 days to review and approve
Moderate Change • a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product • CBE 30 – Submission at least 30 days before distribution of the post change pdt • CBE 0 – Distribution can occur when FDA receives the supplement	**Type IB Variation** • minor variation which is neither a Type IA variation nor a Type II variation nor an Extension • Notification Procedure • Validation + 30 days
Minor Change • minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product • Annual Reportable	**Type IA/IA$_{IN}$ Variation** • a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned • Notification Procedure • 30 days

Comparison of FDA and EMA guidance on Post Approval Changes

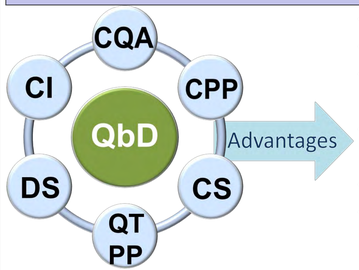
Major Similarities

Changes	FDA	EMA
	Major	**Type II Variation**
Compo-sition	• Additive effect of excipient changes should not change by more than 10%.	• Qualitative or quantitative changes that may have a significant impact on the safety, quality or efficacy of the medicinal product
Mfg Site	• Never inspected by FDA for type of operation being moved • restart of a site that has been discontinued for more than 2 years	• Site which requires an initial or product specific inspection
Mfg Process	• Any fundamental change in the manufacturing process from that currently used by the applicant	• Substantial changes to a manufacturing process
Specifica-tions	• Relaxing an acceptance criterion	• Change outside the approved specifications limits range
	• Deleting any part of a specification	• Deletion of a specification parameter
Container Closure System	• A change in the primary packaging components for any drug product when the primary packaging components control the dose delivered to the patient	• The change which may have a significant impact on the delivery, use, safety or stability of the finished product
	• For sterile drug products, any change that may affect drug product sterility assurance	• Container for Sterile medicinal products and biological/immunological medicinal products
	Moderate Change	**Type IB**
Analytical Procedure	• Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes	• Other changes to a test procedure (including replacement or addition)
	Minor Change	**Type IA Variation**
Batch Size	• Change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch (SUPAC-IR)	• Up to 10-fold compared to the originally approved batch size
Specifica tion	• Tightening of acceptance criteria.	• Tightening of specification limits

Major Differences

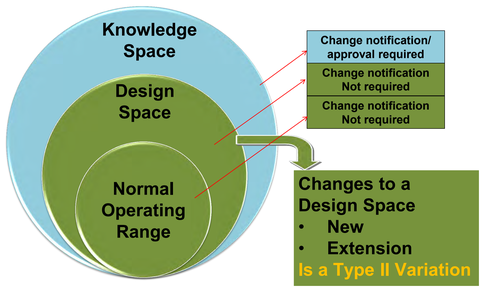
Changes	FDA	EMA
Mfg Site	**Major Change** • Transfer of aseptically processed Sterile DS or DP to : 1. a newly constructed or refurbished facility, 2. to an existing facility that does not manufacture similar approved drug products	**Type IB** • Site where any manufacturing operation(s) take place, that are aseptically manufactured excluding biological/immunological medicinal products
	Moderate Change • Transfer to a site not covered by a Major Change	
	Moderate Change (CBE 30) • A move to a different manufacturing site for the primary packaging : 1. That is not a major change and 2. modified-release solid oral dosage form DP	**Type IA IN** • Replacement or addition of Primary Packaging site
	Minor Change • A move to a different Secondary Packaging site	**Type IA IN** • Replacement or addition of Secondary Packaging site
Container Closure System	**Major Change** • For liquid and semisolid dosage forms : 1. a change to or in polymeric materials of primary packaging components, 2. when the changed composition has never been used in a CDER-approved same drug product	**Type IB** • Change in immediate packaging of semi-solid and non-sterile liquid pharmaceuticals
	Moderate Change(CBE 0) • A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms without a change from one container closure system to another	**Type IA** • Change in shape or dimensions of the container or closure for Non-sterile medicinal products
Stability	**Major Change** • Change in a approved stability protocol	**Type IA** • Change in a approved stability protocol
	Moderate Change (CBE 30) • Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product.	**Type IA IN** • Reduction of the shelf life of the finished product

Post Approval Changes in QbD Paradigm – FDA and EMA approach (ICH Q8[R2])



QTPP – Quality target product profile; CQA – Critical Quality Attributes;
CPP – Critical Process Parameters; CI – Continuous Improvement; CS – Control Strategy; DS – Design Space.

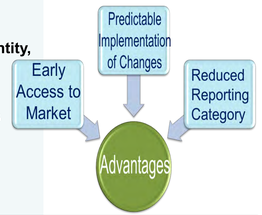
- Reduced Regulatory Burden
- Less supplements for managing Post Approval Changes
- Risk based Scientific Approaches facilitate a better dialogue with the Agency
- Control of the Drug Product Quality through knowledge gained during the Development stages
- Continuous Process Improvement
- Faster access to the market-
  - Reduced End Product Testing and
  - Reliance on Real Time Release Testing(RTRT)



Comparability Protocol to manage Post Approval Changes

A Comparability Protocol is
- well defined, detailed, written plan
- for assessing the effect of specific changes on the identity, strength, quality, purity and potency of a specific drug product

A Comparability Protocol prospectively specifies
- Tests and Studies to be performed
- Analytical procedure to be used
- Acceptance criteria to be achieved



FDA	EMA
• To Be submitted as a PAS. • PDUFA Goal date – 4 months	• To be submitted as a Type II Variation • 60 day Time table

Changes to Approved Comparability Protocol

• PAS - Major Changes	• Type II Variation - Major changes • Type IB - Minor changes

Reference

- Guidance for Industry CMC Post Approval Manufacturing Changes Reportable in Annual Reports
- Guidance for Industry Changes to an Approved NDA or ANDA
- Guidance for Industry Comparability Protocols – Chemistry, Manufacturing and Controls Information
- EUROPEAN COMMISSION REGULATION (EC) No 2013/C 223/01, No 1234/2008, and No 712/2012,
- EMA guidance on Post-Authorisation Procedural Advice for Users of the Centralised Procedure
- Questiona and Answers on Post Approval Change Management Protocols
- EMA-FDA pilot program for parallel assessment of Quality by Design applications

FDA + EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

Highlights -
- Design Space development, including Scale-Up
- Development, Verification and Lifecycle management of different models in QbD
- Approaches for implementing RTRT
- Design Space based on clinical relevance
- Post-approval regulatory flexibility including
  - How data is presented in the application
  - Type and Extent of Data to be provided

Scope -
- NDA/MAA
- PAS(sNDA)/Type II Variation
- CMC Formal meeting/Scientific Advice

Evaluation -
- Parallel Evaluation
- Consultative Advice

This Program ends in April 2014