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Regulatory CMC Documentation: A Lessons Learned Perspective

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Abstract

Purpose: This presentation will provide a regulatory CMC lessons learned perspective on several traditional and enhanced developments detailing those items which may impact the Quality Section of the dossier.

Methods: The Quality section of several recent NDA and MAA submissions has been reviewed including the development and manufacturing strategy, the dossier preparation process, the comments received from Health Authorities, and the responses provided.

Results: The preparation of the chemistry and manufacturing controls documentation to support the filing of a commercial dossier could be considered a herculean task by many. Not only does it require coordination of efforts among a number of functions to generate and provide the necessary development and manufacturing information, it also requires an understanding of the global regulatory landscape to ensure that requirements are met to permit a timely review and approval process. Irrespective of whether the submission is an enhanced Quality by Design (QbD) approach, or a traditional development, as long as the provided information demonstrates formulation and process understanding, a risk assessment of quality attributes and a control strategy to ensure that the product quality can be maintained throughout its life cycle, approval requirements can be met.

Conclusions: Health Authority interpretation of ICH Q8, 9 and 10 vary by region, experience with QbD, and is impacted by local regulations. Regardless, it is possible to obtain approval of a global CMC dossier that meets manufacturing requirements and allows for continuous improvement and process verification.

Description of Products

Small Molecules
Pharmacopeia Excipients
Immediate Release Tablets
Conventional Wet Granulation Processes

Knowledge Management

Critical in a number of areas:

- ❑ Supporting development decisions and document rationale.
- ❑ Resource for dossier construction and to answer regulatory questions.
- ❑ Supporting product stewardship though commercial manufacture:
  - ◘ Technology Transfer,
  - ◘ Pre-approval Inspections,
  - ◘ Deviation Investigations,
  - ◘ Post-approval Changes.

Project Scope and Objectives

Influencing and understanding the evolving regulatory environment through Agency interactions, e.g. US, EU, Canada, Japan.

The scope of what could be achieved was predominantly led by the science.

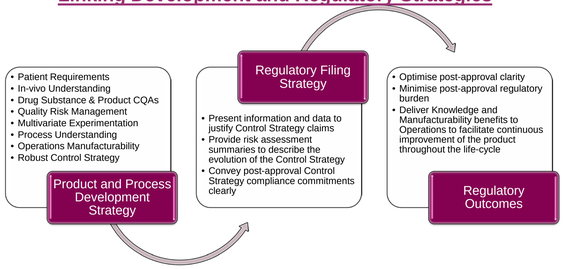
Natural evolution of the Dossier as internal and external knowledge evolved.

Product/Process Robustness:
- ❑ Understand what was important for clinical performance and how to measure it; wanted to avoid issues such as a bioequivalence failure, delay to launch.
- ❑ Ensuring robustness of product supply to patients through scientific understanding :
  - ❑ Robust product and process control strategies.
  - ❑ Right first time; capable manufacturing and analytical testing processes.

To learn about QbD via:
- ❑ Consultations with the US FDA, EMA PAT Team, Canada and Japan; pre-submission meetings for the Dossier were held in an attempt to influence/learn.
- ❑ Wanted to test understanding of ICH Q8, 9 and 10 concepts:
  - ❑ Establish what is meant by QbD and Design Space approaches.
  - ❑ Wanted to 'Push the Boundaries' to challenge/influence Regulatory Agency thinking on QbD.

Reduced Post-Approval Burden:
- ❑ Explore 'boundaries' to achieving reduced post-approval regulatory oversight.
- ❑ Convinced that Design Space was the way to achieve reduced regulatory oversight (as described in ICH Q8).
- ❑ Test the Regulator's appetite in areas that we did not necessarily need.
- ❑ Explore reduction in end-product testing through increased understanding.

Linking Development and Regulatory Strategies



External Environment

QbD is not a mandatory requirement:
- ❑ Expectation to demonstrate assurance of quality through lifecycle is increasing.

The evolving interpretation of ICH Q8, 9, 10 and 11 provides a challenge and makes it difficult to have a complete understanding of Health Authority expectations.

ICH regions are committed to the QbD initiative and are collaborating in an attempt to harmonize approach through implementation:
- ❑ ICH Implementation Working Group (IWG) publications and workshops;
- ❑ FDA/EMA joint review pilot; PMDA acting as observer;
- ❑ Growing interest in the Emerging Market and Asian Pacific (EMAP) Regions;
- ❑ Expanding more into Biotech and smaller Pharma Companies;
- ❑ Increased expectations for Generic Manufacturers.

Significant challenges remain:
- ❑ Non-harmonized views across multiple Agencies, e.g. FDA, EMA, PDMA lead to potentially differing review outcomes.
- ❑ Differences in regional post approval principles can negate the potential benefits of the QbD approach.
- ❑ Many countries do not follow ICH and have their own regulations and requirements with respect to CMC information.

Pharmaceutical Development Considerations

Linked Critical Quality Attributes (CQAs) of both drug substance and drug product to patient requirements.

Use of Quality Risk Management (QRM) and systematic scientific approaches to achieve an increased understanding of what impacts product quality.

Investigated the impact on all potential CQAs through the use of multivariate experimentation to develop increased understanding of manufacturing processes.

Delivered the most appropriate analytical tools for the control strategies.

Greater evaluation of Process Analytical Technology (PAT) for drug product to increase process understanding.

Exploration of the scale dependency of manufacturing processes through experimentation and risk assessment.

DRUG SUBSTANCE

Emphasis on understanding the formation and fate of impurities, and on drug substance physical properties (polymorphic form and particle size), in order to provide process control.

Investigated using a combination of:

- ❑ Multivariate experimentation to evaluate manufacturing process parameters and establish relationships.
- ❑ Impurity tracking experiments and provocation experiments to understand the capability of the manufacturing process to purge impurities.

DRUG PRODUCT

Emphasis on developing enhanced in-vivo and in-vitro understanding of clinical product performance, in order to provide product & process control.

Investigated using a combination of:

- ❑ Evaluation of the highest risk product and process variants through an in-vivo bioavailability study.
- ❑ Development of in-vitro dissolution tests which could discriminate potentially important product performance failure mechanisms.
- ❑ Multivariate experimentation to evaluate manufacturing process parameters and establish relationships between intermediate product attributes and CQAs.

QbD development approaches have led to enhanced knowledge and understanding of manufacturing processes and product risks.

Continue to adopt QbD development as a way of working:

- ◘ Embedded in business processes.
- ◘ Delivers systematic science and risk based approaches which lead to product and process understanding, robust control strategies, and a quality product that meets patient requirements.
- ◘ Knowledge-rich technology transfer should facilitate post-approval continuous improvement of the product throughout the life-cycle.

The primary goal of QbD development is not necessarily about achieving regulatory flexibility within our dossier commitments.

- ◘ We need to understand and separate development and regulatory strategies.

Design Space Considerations

If projects want to propose a Design Space, there needs to be a very clear and compelling business value and benefit.

In our experience, Agencies' view of Design Space is a multivariate description of demonstrated process parameter ranges. A Holistic Design Space covering an entire process is a concept that is a step too far for the Regulatory Agencies.

Currently, Design Space provides an additional layer of post-approval commitment that we may not need and do not understand.
- ❑ How does a Design Space fit into local legislation and what are the implications for managing change?
- ❑ Design Space changes are potentially more burdensome than parameter changes within current legislations.
- ❑ Design Space should only be submitted when the benefits are clear.
- ❑ Regulatory expectations for Design Space are still evolving and can be inconsistent in different countries.
- ❑ Design Spaces potentially elevate the regulators' level of concern.
- ❑ There are some challenges in managing products with registered Design Spaces as the post-approval variations legislation has not caught up with ICH guidance.

Dossier Authoring Considerations

The amount of information and data presented in the dossier should convey justification to support the Control Strategy claims:
- ❑ Story-boarding can help in gaining wider agreement of strategies.
- ❑ The complexity or non-standard nature of the control strategy claims could impact the scope and size of S2 and P2 sections, e.g. Real Time Release (RTR) elements.
- ❑ Harmonize the presentation of Control Strategy across the drug substance & drug product modules; linked to the delivery of CQAs.
- ❑ Need a clear understanding of the level of detail presented in the dossier versus the implications for post-approval compliance and change, e.g. process descriptions, specifications, analytical procedures and stability.

Consistent approaches to the presentation of risk assessments:
- ❑ Ensure that the tools and methods are described adequately.
- ❑ Integration of risk assessment summaries to describe the evolution of the Control Strategy.

In the absence of Design Space claims, do not include descriptions of post-approval change management as this may cause confusion during the review.

Regulatory Dossier Filing Considerations

The primary goal of a QbD development is not about achieving regulatory flexibility with a minimal dossier where our compliance commitments are unclear.

Reduced commitments are not achieved by filing minimal information, fewer details may likely lead to higher number of questions.

Assessment scrutiny is linked to the impact on product quality. We need to understand and separate development and regulatory strategies.

QbD is an ICH concept which doesn't change national regulatory requirements. If claims are made in a submission, need to ensure cross-functional understanding of what these mean and how to manage them during the product lifecycle.

Predominantly, regulatory commitments are linked to Control Strategy. Need a clear understanding of Operations requirements to develop a clear regulatory filing strategy.

Need an understanding of global submission strategy and timings to feed into the regulatory filing strategy, with a view to optimizing and proactively managing the number of dossier variants.

Need to clearly lay out compliance commitments in the dossier to deliver benefits to Operations (optimize post-approval clarity and minimize post-approval regulatory burden).

Should not file commitments that may not be needed or used. This can lead to post-approval commitments that are difficult to manage, e.g. RTR elements for drug product, registering manufacturing sites (maintenance commitment) and flexible quantitative formulation composition.

Use of non-ICH terminology is not recommended due to confusion on it's interpretation both by the Regulators and ourselves.

Regulatory Interactions - Review and Approval

Some Examples

Risk Assessment	• Integration of risk assessments to describe the evolution of the control strategy was seen as positive and transparent. • Presentation of 'Traffic Light' risk assessment summaries led to questions about risk tools/scoring and basis for our conclusions around low risk outcomes.
CQAs and CPPs	• Linking the drug substance and drug product CQAs to the control strategy aided review. • Use of 'non-ICH' terminology e.g. 'Key Parameters' was not considered helpful to reviewers.
Design Space	• Summary of process development studies used to support proposed design space facilitated review. • 'End to End' holistic design space spanning an entire manufacturing process is not acceptable. Unit Operation Design Spaces are more likely to succeed. • The expectation is that any proposed Design Space will have been proven experimentally. • Shared understanding of ICH Q8 interpretation of design space, e.g. expectation that input process parameters are included in a design space, and the difference between design space and PARs.
Control Strategy	• Reduced compliance commitments are not achieved by including minimal information in process descriptions. Less information in the dossier is likely to lead to more questions. • Wider process parameter ranges and specification limits can be achieved based on process understanding and downstream quality requirements. • Reduced end product testing is achievable; however, comprehensive supporting data is required.
LCM/ Continuous Improvement	• Inclusion of information relating to the management of post-approval changes was interpreted differently by the major agencies. • The level of risk associated with a process parameter does not preclude its inclusion in the process description but rather impacts the required reporting levels associated with post-approval parameter changes.

Post-Approval Experiences

When writing the dossier, understand the different and varied post-approval legislation underpinning commitments.

The assessment of changes is not straightforward when product has a design space.
- ❑ Understanding of compliance commitments versus design space is challenging.
- ❑ US post-approval legislation is risk-based, EU and Canada category-based.

Consider ease of post-approval change when making dossier claims; variations could already be easy without a design space
- ❑ Changes in design space are currently a higher filing category.
- ❑ For example, batch size is an easy post-approval variation.

The use of 'non-ICH' terminology could make it more difficult to interpret commitments in the lifecycle of the product.

Inclusion of change management statements in the dossier should be avoided as they could conflict with national variations guidance.