Health Canada Santé Canada

Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits de santé et des aliments

QOS Issues Update
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Canada

QOS Issues Update
Overview

- What is a QOS?
- Why?
- Current Status of QOS
- Future Use of the QOS and Ramifications of Integrated Review Process
- Applying Risk Management Criteria to Reviews
- Future Developments

QOS Issues Update
What is a QOS?

- Purpose of QOS
  - Summarize the submission data in a precise manner
  - Standardizes the data package from all companies
  - Standardizes the review for Reviewers
  - Provides prompts to both Industry and Reviewers regarding regulatory requirements
  - Eliminates the reproduction of submission data by the Reviewer
- Value of QOS
  - Provides efficiencies to the review process
  - Provides a global view of the submission in a concise manner

QOS Issues Update
Why?

- Health Canada experience
  - Initially, the QOS impeded the review process, we had to teach industry (still doing it, for example, DIA tutorial in October 2007)
  - Teaching the Reviewer and this meant changing the culture of review and mindset
  - Errors by the Companies in transcribing or summarizing data from the submission volumes created delays in the review process, Reviewers spent too much time in chasing down data
  - Since 1995, Generic Drug Industry in Canada has used the QOS to their advantage in other regulatory environments and as a result, we have continuously received improved documents where the QOS has demonstrated its utility

QOS Issues Update

Why?

- Health Canada experience (cont.)
- Pros and Cons...
  - Objectivity versus subjectivity
  - Can result in mediocrity in some complacent Reviewers
  - Teaching tool for both Industry and Reviewers
  - Document size can be a problem as some Companies have decided to reproduce the whole submission in the QOS
  - Review efficiency
  - Software issues
  - Issues of overwriting of data (protection of tombstone data)

QOS Issues Update
Why? How does this relate to the CPID?

- Certified Product Information Document (CPID)
  - Executive summary of the QOS but it incorporates agreed upon amendments, revisions, deletions and/or commitments such as stability protocol, to the data presented in the Abbreviated New Drug Submission or Supplemental ANDS.
  - Valuable document as it provides data to the Reviewer or Manager in a summarized fashion which facilitates the review of any Supplemental Submission or amendment (Notifiable Change).
- Compliance/Inspection
  - HPFB Inspectorate is now utilizing this document to monitor post approval activities and drug product surveillance (for example, Ontario and Quebec Regions have notified TPD/BPS of unapproved changes).

Current Status of the QOS
Solid Oral Drug Products – Chemistry Issues

- Common Issues for Drug Substances:
  - Drug Master Files
  - Compliance to Identical Medicinal Ingredient policy
  - Characterization of the drug substance
  - Specifications to qualify the drug substance
  - Validation of Analytical Methods
  - Reference Standards
  - Utilization of Stability Data from DMF's

Current Status of the QOS
Solid Oral Drug Products – Chemistry Issues

- Drug Master Files
  - Process issues
  - Route of synthesis concerning the starting material
  - Same issues as the previous slide
  - Characterization of the drug substance
  - Specifications to qualify the drug substance
  - Validation of Analytical Methods
  - Reference Standards for analytical work
  - Stability Data

- Compliance to Identical Medicinal Ingredient
  - Enalapril maleate versus Enalapril Sodium

Current Status of the QOS
Solid Oral Drug Products – Chemistry Issues

- Characterization of the drug substance
  - Issues regarding polymorphism and particle sizes/distribution
  - Unique properties
- Specifications to qualify the drug substance
  - Impurity limits which exceeds the ICH qualification limits
  - How to handle impurity limits for semi-synthetic compounds
- Validation of Analytical Methods
  - Encountering problems with validation strategies from companies outside the ICH regions
  - Interpretation of validation data

Current Status of the QOS
Solid Oral Drug Products – Chemistry Issues

- Reference Standards
  - Validation of Non-compendial Reference Standards

- Utilization of Stability Data from DMF's...
  - The issue of validation and verification of stability data Utilization of Stability Data from DMF's which generic drug companies use to determine a Re-test period

Current Status of the QOS
Solid Oral Drug Products – Manufacturing Issues

- Common Issues for Manufacturing:
  - GMP Compliance ratings for companies in non-ICH regions
  - Developmental Pharmaceutics
  - Manufacturing issues
  - Process Validation Issues
  - Specifications for release and shelf life testing
  - Stability data

Current Status of the QOS
Solid Oral Drug Products – Manufacturing Issues

- GMP Compliance ratings for companies in non-ICH regions
  - Globalization of generic drug product manufacturing
  - How to deal with companies in India and China
- Developmental Pharmaceutics
  - Analysis of developmental pharmaceutics data
  - Determination of Pharmaceutical Equivalence
  - How to promote the principles of ICH Q8
  - Issues with design space for generic drug product manufacturers

Current Status of the QOS
Solid Oral Drug Products – Manufacturing Issues

- Manufacturing issues
  - Batch size, is it representative of full scale production?
  - Appropriate In-process Controls
  - Manufacturing process changes
  - Formulation process changes
- Process Validation Issues
  - Relevance or validity of the proposed Process Validation Protocol
  - Prospective versus concurrent process validation, generic drug companies are starting to request concurrent process validation

Current Status of the QOS
Solid Oral Drug Products – Manufacturing Issues

- Specifications for release and shelf life testing...
  - Release vs. shelf life testing for assay
  - Standards for dissolution testing
  - Impurity limits which exceeds the ICH qualification limits (tox. studies)
- Stability data
  - Validity of pre-market stability studies, encountering stability problems with the drug product post approval
  - Transportation studies

Future Use of the QOS
Ramifications of the Integrated Review Process

- Integrated Review Process combines the review expertise from all disciplines within the Bureau to form a single review team.
- See Health Canada announcement dated October 1, 2007 for greater details on this review initiative which has been discussed in the past at many fora.
- The goal of IRP is to create a more efficient process and facilitate communication between all disciplines at the same time instead of the current “Silo” approach.

Future Use of the QOS
Ramifications of the Integrated Review Process

- Ultimately, this will lead to a stronger and more scientifically sound decision regarding the merits of a submission for acceptance or rejection (NOC vs NON).

- The QOS is an essential tool of the Integrated Review Process as it will be used in the new step identified as “Pre-Evaluation”

- What does “Pre-Evaluation” really mean?
- See Notice (07-122528-863) posted on the Health Canada website for the 11 items used in the pre-evaluation criteria

Future Use of the QOS
Ramifications of the Integrated Review Process

- The QOS will be used by the Integrated Review Team to conduct a “Pre-Evaluation” and the following criteria will be used to allow acceptance into the review process. These criteria are:
  - Drug product that is not considered to be pharmaceutically equivalent (Identical Medicinal Ingredient
  - Clinical or bioequivalence batches not representative of full scale production (formulation and/or manufacturing process)
  - Significant deficiencies on the manufacturing process or controls for the active ingredient (submission or DMF)
  - Insufficient viral safety data or where a TSE risk assessment is required

Future Use of the QOS
Ramifications of the Integrated Review Process

- Criteria cont.:
  - Lack of GMP compliance rating
  - Significant deficiencies on the manufacturing process or controls
  - Insufficient data or studies on impurities, process validation for a sterile product, compatibility studies, stability studies
  - Insufficient safety/toxicological data to qualify a proposed impurity limit
  - Insufficient information from extractables/leachable studies for components in the container closure system (e.g., USP <87>/<88>

Future Use of the QOS
Applying Risk Management Criteria to Review

- Risk Management Tools:
- Can it be applied to the QOS? Answer is yes!
- Elements of risk management are being used on a day to day basis with the QOS.
  - For example, knowing the strengths and weaknesses of a company in advance of the review
  - The same could be applied internally with the review process
- In the era of doing more with less, we need to ask ourselves, what are the risks as it relates to the QOS?

Future Use of the QOS
Future Developments

- BPS considers the QOS as a dynamic document which is living and will be subjected to revisions wherever warranted.

- BPS is constantly searching for ways to improve the QOS for internal and external use.

- A Pilot Project is underway to combine all Quality review documents into one seamless document which will provide a better basis of understanding to internal staff and to our stakeholders.

Questions?

QOS Issues Update

- Thanks for your attention/Merci pour votre attention.

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