Quality Overall Summary Grounds for Revision

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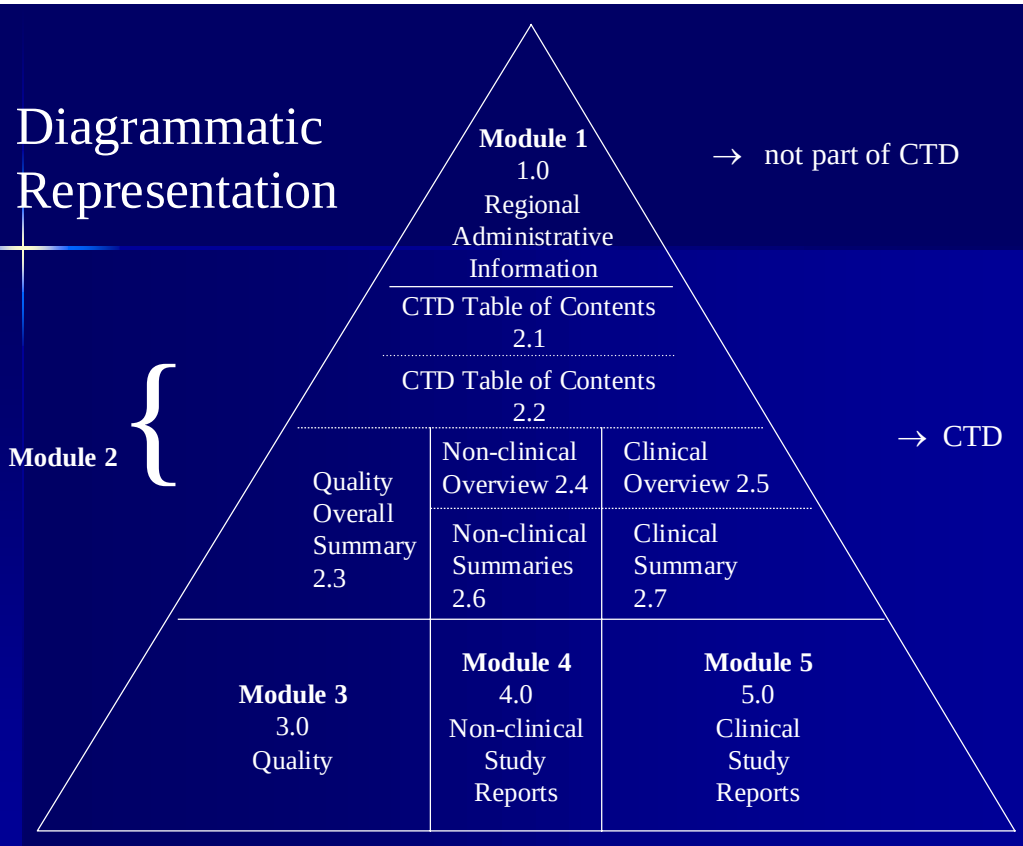
Diagrammatic Representation



Extract from ICH CTD – QOS (1)

- *The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.*

Extract from ICH CTD – QOS (2)

- *The QOS should include sufficient information from each section to provide the Quality reviewer with an overview of Module 3. The QOS should also emphasise critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S module), including cross-referencing to volume and page number in other Modules.*

Extract from ICH CTD – QOS (3)

- *This QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures).*

QOS current situation

- EU/US:
  - Part of application file
  - True summary
  - Not the main basis for the assessment of the application file for MA, used as introductory document
  - Module 3 is assessed

QOS current situation

- Japan:
  - QOS driven by review process
  - Main basis for the assessment
  - Module 3 is used if more information is required

QOS Informal Working Group 4 June 2006

- Objective:

  To identify the future utility of the QOS

QOS Revision: Agreement (1)

- Objective of the proposed revision:

  To use QOS as a principal assessment tool;
  placing key information into QOS.

QOS Revision: Agreement (2)

- Should be prepared in such a way that it facilitates scientific risk-based assessment and that the need to look into Module 3 is minimised.
- A well prepared QOS will present all the information necessary to make an approval decision resulting in stream-lining of the approval process, i.e. benefits depend on the quality of the document.
- Scope: NCEs and Biotech products
- Current Initiative is moving towards the direction of the present use of the Japanese QOS approach.
- The revision of QOS may facilitate harmonisation of the dossier.

QOS Revision: Benefit

- Regulators:
  - concentration on the most important information,
  - better use of resources.
- Industry:
  - will facilitate the submission of a single dossier in the 3 ICH regions.

QOS Revision: further discussion points

- Identification of the type of information necessary in Module 2 (QOS);
  - Guidance document on content needed or
  - Guidance document on format?
- Procedure: EWG versus IWG
- Change of the title QOS ?
- Implications on CTD-Q ?
- Implications on e-CTD (minor impact anticipated)
- Regional consequences:
  Change of legislation? Regional clarification needed.

QOS Revision: Relationship to Module 3 Illustrative Examples (draft proposal)

- **QOS**
  - Drug subs./Drug prod. development/design
  - Drug substance/Drug Product manufacture
  - Impurities profile and qualification
  - Analytical procedures + validation (in tabular form)
  - Stability (in form of figures / tables, commitments)
- **Module 3**

  would contain the supporting information plus studies, experiments.

QOS EU Position

- Can see the advantage of using a QOS as a primary assessment tool.
- Module 3 should still be part of the application dossier for MA.
- Future discussion will be necessary in order to identify the exact implications.

QOS Revision: Future Activities

- Discussion will continue in November 2006
- Clarification of the different issues raised
  - Content or format document
  - Implications on e-CTD
  - Verification of legal implications

Quality Overall Summary

MHLW Reviewer's Experience

Mayumi SHIKANO, Ph.D.

Pharmaceuticals and Medical Devices Agency

Contents

- Japanese NDA Dossier and QOS
- Current Practice and Experience with QOS in Japan

• Japanese NDA Dossier and QOS

Japanese NDA Dossier

Application Form + **CTD**

Application Form and Approval Matters

- Contents provided in the NDA application form are dealt with as "matters subject to approval."
- Contents described in approval letter are "legal binding" approval matters.
- Contents described in QOS (module 2) and module 3 are not legal binding.

Approval Matters

- General name (for active ingredient)
- Brand name
- Composition
- Dosage and administration
- Manufacturing process, including control of materials
- Indications
- Storage condition and shelf-life
- Specifications and analytical procedures

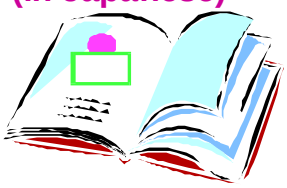
Relationship between Application Form and CTD Documents

Application form (in Japanese)

Analytical procedures (JP style) & acceptance criteria

Manufacturing process

Module 2 (QOS) (in Japanese)



- Specifications
- Analytical procedures
- Pharmaceutical Development
- Manufacturing Process
- batch analyses
- Justification

etc.

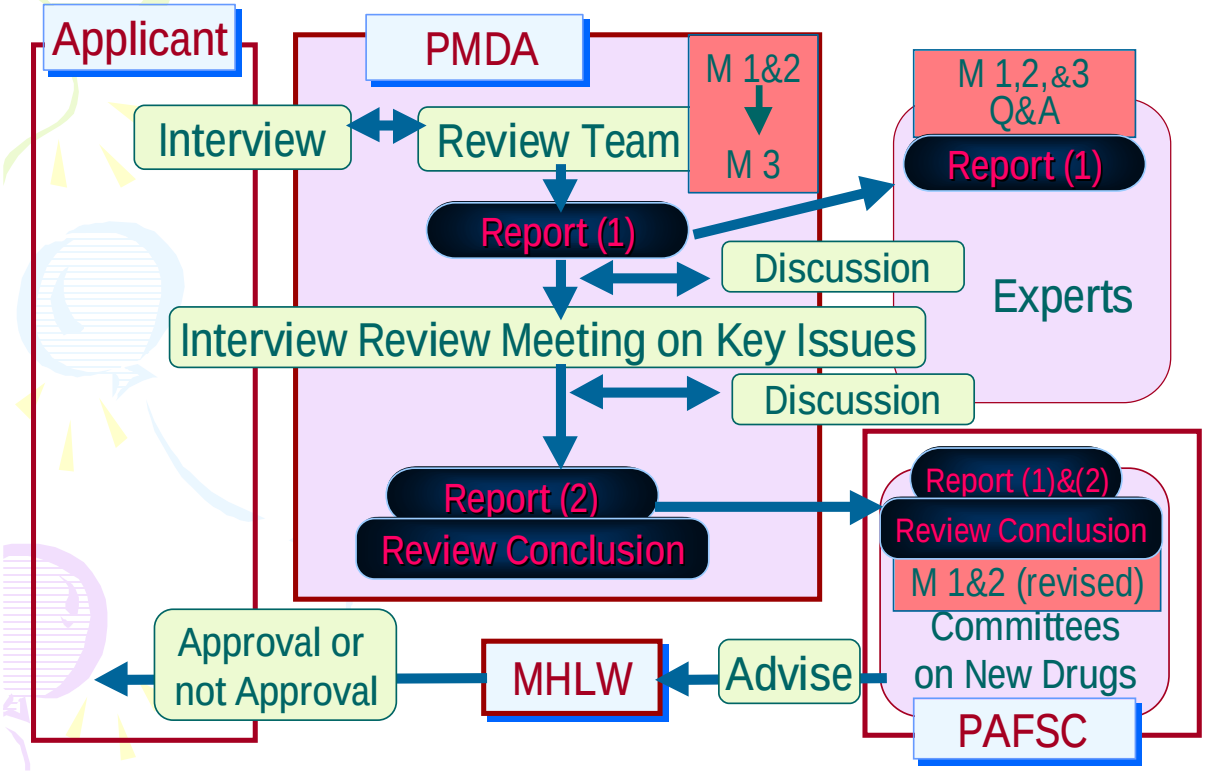
Module 3 (in Japanese or English)

3.2.S4.1 Specification
3.2.S4.2 Analytical procedures
3.2.S4.3 Validation of analytical procedures
3.2.S4.4 Batch analyses
3.2.S4.5 Justification of specification

Raw data

- **Current Practice and Experience with QOS in Japan**

NDA Review Process in Japan



Module 2 as Key Review Documents in Japan

- Without IND, comprehensive QOS helps reviewers to understand quality of the product quickly.
- Reviewers review QOS and then narrow down into Module 3 when they need more detailed information.
- Reviewers require Applicant to revise Application Form reflecting Analytical Procedure and Manufacturing Process described in revised QOS.
- Module 1 and 2 together with review reports written by reviewers are evaluated in Pharmaceutical Affairs and Food Sanitation Council.

Characteristics of Japanese QOS

- Within CTD guideline
- Expected to summarize critical data in module 3 into QOS, along with sufficient discussion on every critical point for ensuring the quality, efficacy and safety of the drug
- Include many figures and tables which summarize critical data
- Include narrative summary and/or discussion
- Should be written in Japanese
  - :Tables & Figures may be in English

Benefits from Japanese QOS

- QOS helps efficient review; reviewers can understand the characteristics of the drug within a short period
- QOS can be a vehicle for knowledge management in regulatory authorities and in industry
- Writing Japanese style QOS takes significant time and energy. BUT it helps the applicant organizations to understand own product and process consistently

We do NOT feel necessity for major change of current Japanese QOS.

QOS is main Document for Reviewing NDA in Japan

- Expert team in PMDA reviews NDA using module 2 (QOS) as main review document and referring to module 3, and prepares a review report.
- (Final)QOS and review report are submitted to the Committees on new drugs in the Pharmaceutical Affairs and Food Sanitation Council (PAFSC).
- The committee members discuss quality, efficacy and safety of the drug based on the review report and QOS. (Usually, the committee members do not review module 3.)
- The opinion of the committee is sent to MHLW together with the review report, then the Minister of Health, Labor and Welfare grants the new drug approval to the applicant.

Utilization of the Quality Overall Summary – Health Canada Perspective

Sultan Ghani
Director
Bureau of Pharmaceutical Sciences
Therapeutic Products Directorate (TPD),
Health Canada

June 2006

Outline

- Background
- Utilization of QOS in our Review Process
- Potential Benefits with Health Canada Model
- "QOS Mock-up"
- Experiences/Lessons Learned

Background

- Quality summary first introduced in 1995 to promote efficiencies in the review process.
- Evolve with the experience and introduction of the CTD; modified to be consistent with CTD-Q format/content
- Now available for various application types (CTAs, NDSs, ANDSs, and DINA) including chemical entities and across range of biological products (including biotech, blood products, vaccines)
- Approaches vary: Template Vs. Guidance.
- Encouraged, not mandatory

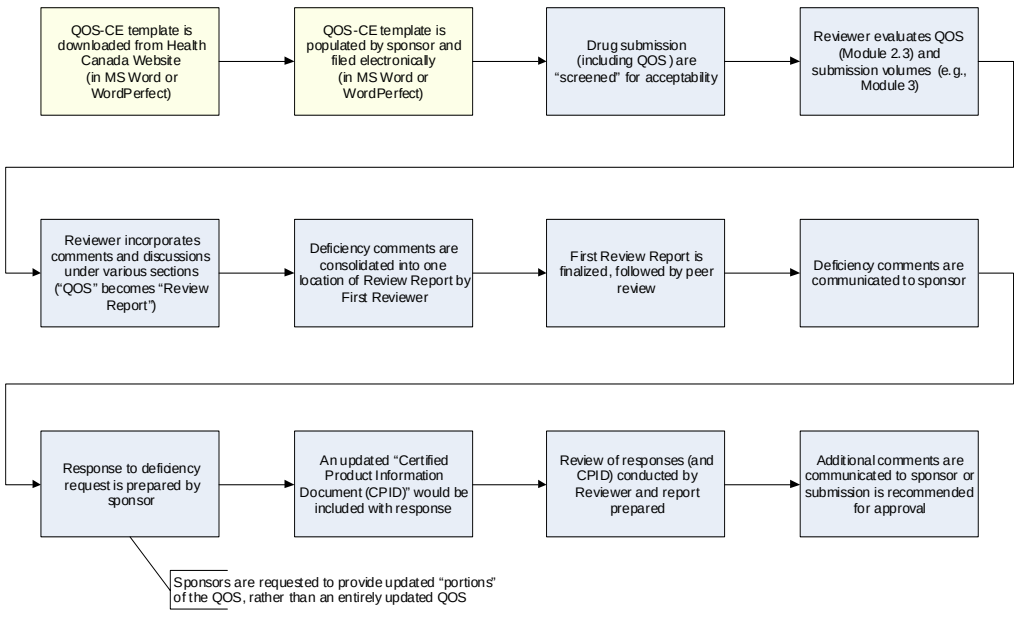
"Quality Overall Summary (QOS)"

- The Quality Overall Summary (QOS):
  - Is part of a drug submission organized according to ICH's Common Technical Document (CTD) Guideline (i.e., Module 2.3)
  - ICH's CTD-Q structure (including the QOS) has been formally adopted by Canada for various drug submission types, e.g.:
    - Clinical Trial Applications (CTAs)
      - Phase I, Phase II/III, BA Studies,
    - New Drug Submissions (NDSs),
    - Abbreviated New Drug Submissions (ANDSs),
    - Drug Master Files (DMFs)
      - Provided the 'Open'/'Closed' portions are submitted in separately bound dossiers.

"Quality Overall Summary – Chemical Entities (QOS-CE)" Template

- **Health Canada's (QOS-CE) Template:**
  - **Was developed to manage the submission workload and to assist sponsors in the preparation of the Quality Summary**
  - **Promotes efficiencies in submission preparation and in the review process**
  - **Available for various submissions types (CTAs x3, NDSs and ANDSs, etc.)**
  - **Entirely compatible with ICH's QOS (e.g., can be considered an acceptable replacement for the QOS as defined by the CTD-Q)**

Process for Utilizing the QOS or QOS-CE



Health Canada Santé Canada
Health Products and Food Branch
Direction générale des produits de santé et des aliments

Benefits of the QOS-CE Templates *for* Industry and Regulators

- **Can Facilitate the Preparation of *Better Quality* Submissions & Expedite the Review Process, e.g.:**
  - Can act as a Quality Control check for sponsors when preparing the dossier (e.g., more prompts, provides further guidance on technical expectations, better understanding of submission requirements)
  - Elicits discussions of data (e.g., batch analyses, differences between clinical and commercial formulations, stability data)
  - Greater consistency from different sponsors (and from the same sponsor!)
  - Evaluator does not need to manually summarize data (e.g., specifications, formulation, manufacturing process)
  - Promotes more consistency in the internal review process (e.g., consistent application of requirements)
  - Electronic QOS serves as basis for the review report

An illustrative example…

- **Health Canada's QOS-CE Template:**

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (name, manufacturer)

2.3.S.1.1 Nomenclature (name, manufacturer)

(a) Recommended International Non-proprietary Name (INN):

(b) Compendial Name, if relevant:

(c) Chemical Name(s):

(d) Company or Laboratory code:

(e) Other Non-Proprietary Name(s) (e.g., national name, USAN, BAN):

(f) Chemical Abstracts Service (CAS) registry number:

2.3.S.1.2 Structure (name, manufacturer)

(a) Structural Formula, including relative and absolute stereochemistry:

(b) etc.

"QOS-CE Mock-up"

- **Requests have been received for a sample completed QOS (similar to those previously issued with the templates released in 1995 and 1998)**
- **A 'model' QOS has been prepared:**
  - QOS-CE template used as the basis for the Mock-up
  - Drug substance:
    - "ambrosol" as "ambrosol hydrochloride"
    - not "highly soluble" according to dose/solubility volume
  - Drug product:
    - enteric-coated tablets: 25 mg, 50 mg, and 75 mg (of base)
    - has undergone a number of formulation changes during PD
  - A copy is available upon request.

"Certified Product Information Document (CPID)"

- **Provides a *condensed summary* of the critical Quality information and an accurate record of technical data in the drug submission at the time of approval:**
  - DS: API manufacturer(s), DS specs, Container Closure system, Re-test period
  - DP: Composition, Manufacturer(s), Manufacturing process, DP specs, Container Closure system, Shelf life
  - Summary of Protocols/Commitments
- **A number of valuable uses:**
  - Assessment for Post-approval Changes
  - By Inspection Staff
  - By Canadian Provinces
- **As an illustrative example ... a QOS may be ~75-100+ pages, whereas the "CPID" may be ~10-15 pages**

Experiences with QOSs / QOS-CEs

- **Observations/Experiences:**
  - Initially, evaluators had the option of: (1) using the completed QOS as the basis of the Review Report, or (2) preparing a separate Review Report to be placed "on top" of the QOS ... Now, all Evaluators use the first option to maximize the potential review efficiencies
  - A properly prepared QOS can reduce the frequency of going to Module 3 information
  - Analytical methods and validation reports are not adequately summarized (templates would be useful)
  - Lack of cross references in QOS makes it difficult to locate information in Module 3 (more time spent searching for data)
  - Some QOSs prepared globally do not provide same level of detail or discussions as when prepared with Health Canada's QOS template

Considerations

- **Health Canada supports the concept of developing a *Global* QOS that could serve as a *Primary Review Tool***
- **Considerations for developing such document:**
  - Utility as review tool would be highly dependent on the quality of the QOS received – certain sections (e.g. stability) more challenging than others
  - More robust QOS would address some short comings in the current QOS (including Health Canada's template version)
  - Need to achieve the right balance to define the level of detail and contents that would be adequate within the QOS for it to be useful.

Considerations … *contd..*

- **CTD/eCTD Implementation Issues:**
  - Potential impact on CTD guideline would need to be assessed.
  - Implications respecting eCTD should be considered in parallel
  - Benefits of receiving an electronic copy of QOS (e.g., in an editable format) in parallel with paper submission
  - Archiving, retrieval and updating of document

Conclusion

- Health Canada's model with the QOS-CE template has become an integral part of our review process and, if completed properly, can:
  - facilitate the preparation of submissions
  - expedite the review process …
- Continue our commitment to the adoption of ICH guidelines
- Develop and/or update any domestic (Canadian) Guidance documents, where necessary
- Continue internal and external communications, including dialogue with other Regulatory Agencies, Industry, and Pharmacopoeia
- Global QOS may facilitate harmonization of the contents of submission documents

Thank you

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TPD Website: www.hc-sc.gc.ca/dhp-mps/prodpharma/index_e.html

Quality Guidelines: www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/index_e.html

QOS-CE Templates: www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/templates-modeles/index_e.html

Japanese Experience

- Benefits of Quality Gaiyo -

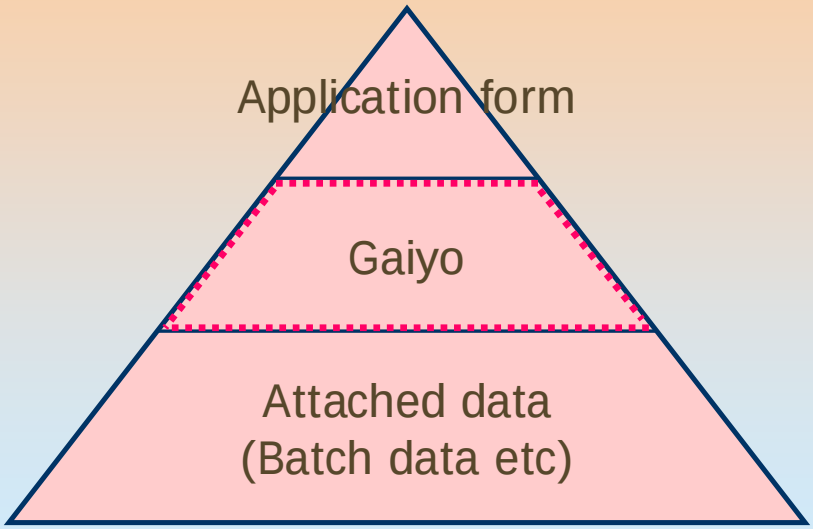
Tsuneo Okubo, Ph.D.
Shionogi & Co., Ltd.
Japan Pharmaceutical Manufacturers Association

June 9, 2006

Today's presentation

- What is quality gaiyo?
- Gaiyo to J-QOS; Update
- Revised J-PAL
- Desired state of QOS

What is Quality Gaiyo?



What is Quality Gaiyo?

- Integrated summary of data
- Primary review documents
- Bridges NDA Application Form and Attached Data
- Contain all(?) necessary information
- Contain sufficient discussion on critical point

<Guideline for Gaiyo format>
March 31, 1992

Guideline for Gaiyo format

- Must be described in Japanese
- Total 200 pages (Q, S, E)
- Tabulated summary basis
- CMC section: 2 parts
  - Physicochemical properties and Specifications: 30 pages
  - Stability study: 20 pages

Content of Quality Gaiyo

- **Physicochemical properties and Specifications**
  - Elucidation of Structure
    - Brief outline of manufacturing process (synthetic route)
    - Spectral analyses
  - physicochemical and other relevant properties
  - Specifications
    - Specifications
    - Analytical procedures
    - Batch analysis
    - Analytical validation
    - Justification of specifications
    - Reference standard
  - Formulation development

Content of Quality Gaiyo

- **Stability study**
  - Storage condition and shelf-life
  - Long-term test
  - Accelerated test
  - Stress test
  - Forced degradation test
  - Compatibility of co-administered drugs

Gaiyo system

- Has greatly contributed to accelerating review process of limited review human resources
- Applicants are expected to summarize critical data in a lot of attached paper files into Gaiyo, along with a sufficient discussion on every critical point for ensuring the quality, efficacy and safety of the drug
- Gaiyo makes it possible for reviewers to understand the characteristics of the drug within a short time, and to review the NDA application efficiently

Today's presentation

- What is quality gaiyo?
- Gaiyo to J-QOS; Update
- Revised J-PAL
- Desired state of QOS

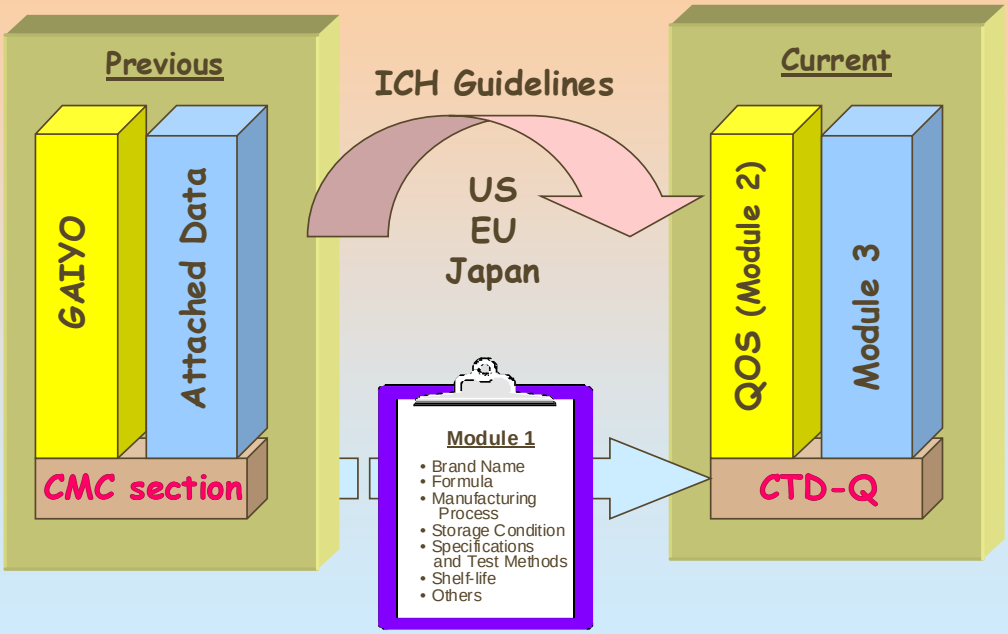
Gaiyo to QOS

- **Vision of CTD**
  - Common standards/formats for well-structured applications across the ICH regions
  - Standard terminology across regions (and internally)
  - Greater efficiency of document production
  - Facilitates electronic submission
  - Simplifies regulatory reviews and communication
  - With companies
  - With other regulatory agencies
  - Worldwide harmonized label
  - Patients get medicines sooner

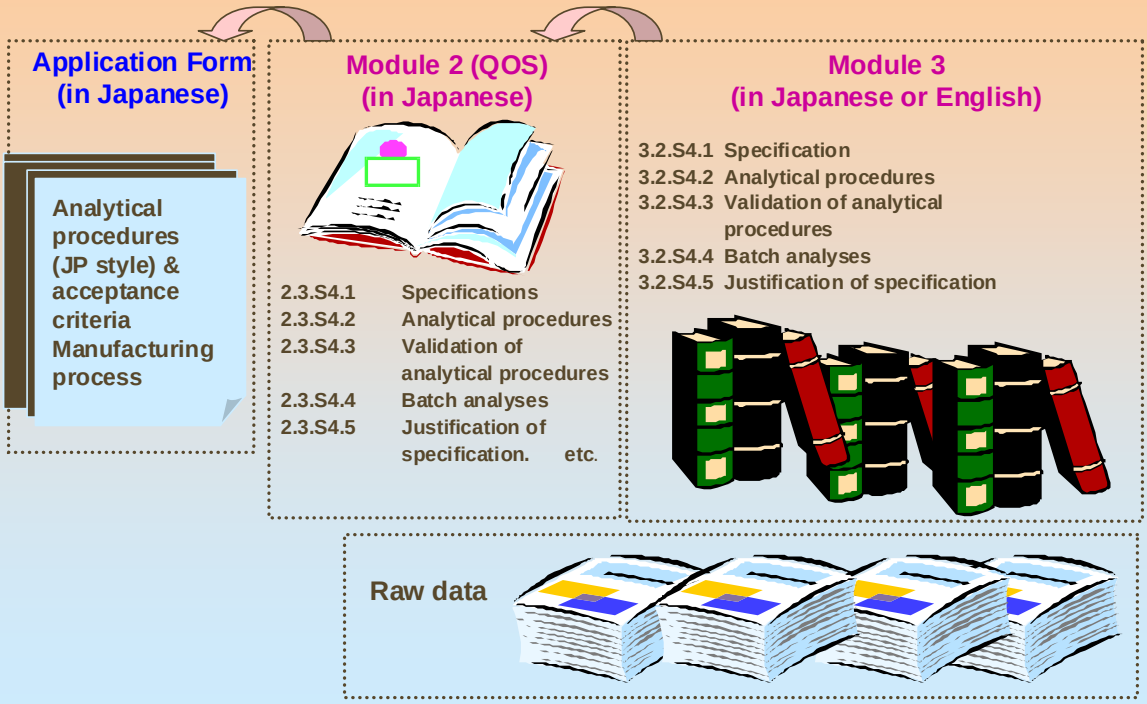
Gaiyo to QOS

- Common Technical Document does not mean a common content:
  - New data accumulate between staggered filings
  - Company files for different indications in different regions
  - Regional requirements for registration differ
- Much of the same content can practically be used
  - Many ICH Quality guidelines have already been harmonized
  - Accept the CTD format from July 1st, 2003
  - Implemented in the ICH regions; US, EU, Japan

CTD-Q for J-NDA



Relationship between Application Form and CTD Documents



Slide by Dr. Y. Hiyama

QOS: Main Review Document for J-NDA

- Replaces GAIYO (Summary)
  - PMDA officers mainly review the QOS in the J-NDA review process
- QOS must be described in Japanese
  - Tables and Figures are accepted in English
- 2002, MHLW and pharmaceutical industries jointly published “Mock-up” J-QOS
- Potentially gives reviewers easier access to the original data if necessary

QOS: Main Review Document for J-NDA

- ICH Guidelines are the basis for NDA review
- There are some domestic guides for those not covered by ICH Guidelines
- The Japanese Pharmacopoeia (JP) is also the basis for setting specifications and acceptance criteria of drug substances and drug products

  "General methods described in the JP, and internationally harmonized methods are considered to be validated."

Slide by Dr. Y. Hiyama

Characteristics of QOS for J-NDA

- Within CTD guideline
- Include lots of figures and tables which summarize critical data
- Include narrative summary and/or discussion on data
- Should be written in Japanese

The Mock-up of Japanese QOS (J-QOS mock)

- Need to prepare a model for smooth implementation in Japan
- Published by The Pharmaceutical Manufacturers Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Health Science Foundation
- Merely shows an example of description for each section and just a reference for an applicant to prepare QOS
- Not covers all information required for each NDA nor shows acceptance criteria for each categories

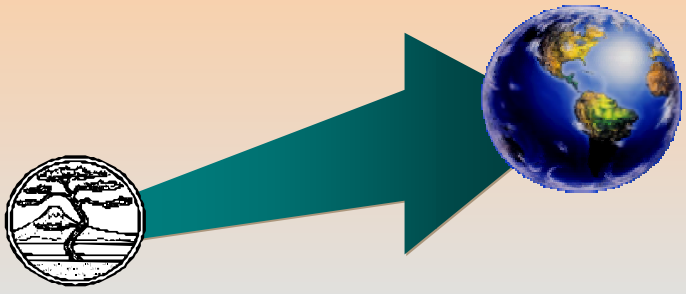
The Mock-up of Japanese QOS (J-QOS mock)

- Reference information
  - GAIYO model
    - Prepared by Osaka Pharmaceutical Manufacturers Association, 2000
- Principle
  - Covers both NCE and Biotech
  - Following CTD guideline
  - Following GAIYO description
  - Create additional information/data
    - manufacturing information
    - container/closure
    - Pharmaceutical development

Today's presentation

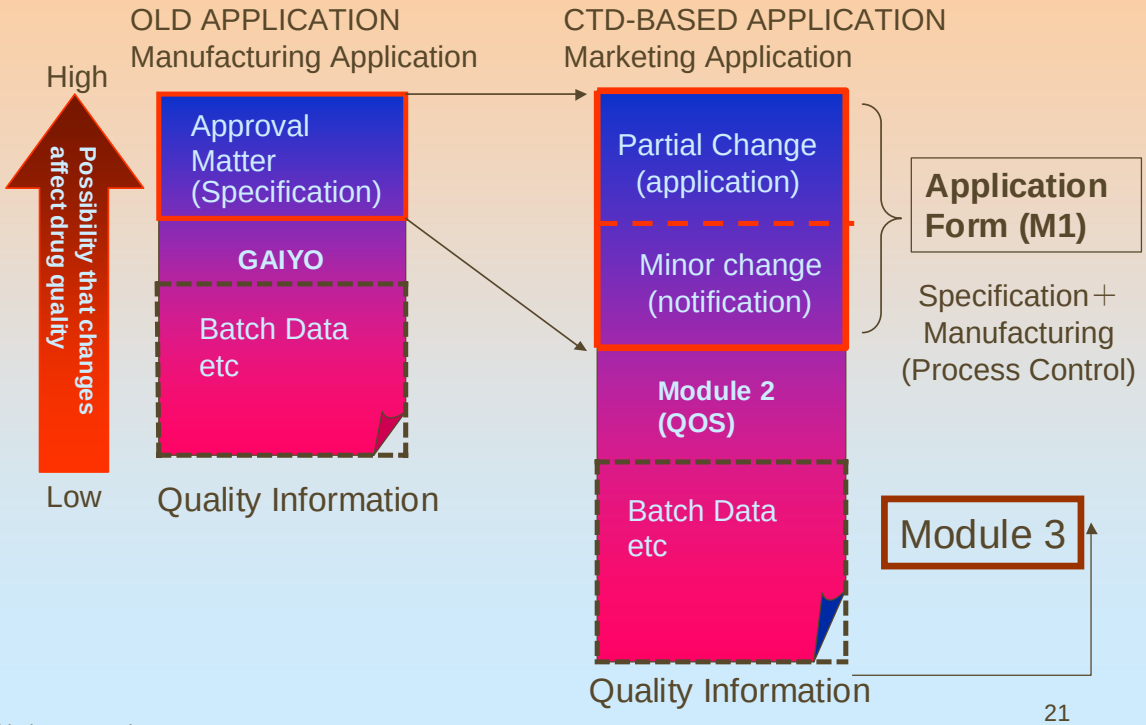
- What is quality gaiyo?
- Gaiyo to J-QOS; Update
- Revised J-PAL
- Desired state of QOS

Revision of Pharmaceutical Affairs Law (PAL), effective April 2005



Previous PAL	**Revised PAL**
Approval System focusing on	Approval System focusing on
Manufacturing Function	Marketing Activities
Product Manufacturing Approval	**Product Marketing Authorization**

Application Form after the Enforcement of Revised PAL



Slide by Dr. Y. Hiyama

Revised J-PAL: Major/minor change definition and introduction of Target/Set Value concept

- **Application Form (Module 1)**
  - Manufacturing Description – COMMITMENT
  - Clear definition of major change (need post approval review process)/minor changes (notification without review) of manufacturing process parameters-describe in application form in advance for future changes
  - Introduction of Target/set values concept for process parameters to enable industry to operate with flexibility

Revised J-PAL: Major/minor change definition and introduction of Target/Set Value concept

- **J-QOS as main review document**
  - Manufacturing description of Application form to be reflected in the corresponding section's descriptions in J-QOS

Today's presentation

- What is quality gaiyo?
- Gaiyo to J-QOS; Update
- Revised J-PAL
- Desired state of QOS

Desired State of QOS in EU and US

- Recently there are a few activities related to QOS in conjunction with the Q8 “Design Space” and P2
  - EFPIA has been working on Pharmaceutical Development section’s Mock-up (P2 Mock) as an example to stimulate science based discussion-communicating with regulators
  - FDA initiated “Products Quality Assessment” pilot program with Comprehensive QOS last year

Will need further discussion at ICH to evaluate/to incorporate all the examples including J-QOS in order to obtain global consensus

Desired State of QOS in Japan

- May need some changes in J-QOS mock to accommodate Q8 concept , particularly P2 section
- Need to update in J-QOS mock, especially manufacturing section (S2 and P3) to accommodate “revised” Application Form

We are ready to work with PMDA/NIHS

Desired State of QOS in Japan

As conclusion and message from Japanese Industry

- Single concise QOS (Content) for ICH regions
  - This is an ultimate goal…long-way?
- QOS could be a powerful tool for Regulators and Industry as primary regulatory review document and knowledge management

Thank you for your attention!

Comprehensive Quality Overall Summary (CQOS) - An FDA Perspective

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PQF/ISPE Symposium
Yokohama, Japan
June 9, 2006

Contents

- Background and Utility of QOS in the US
- What is a Comprehensive Quality Overall Summary (CQOS)?
- Potential benefits of CQOS
- Content and essential elements of CQOS
- Benefits of incorporating sponsor's assessment/ analysis in CQOS
- Relationship to Module 3
- Formatting options
- International Harmonization
- Conclusions

Background: ICH

- ICH Guidance
  - Organization and format; Five Modules
- Module 1: Administrative
- Module 2: Summaries and Overviews
  - **Module 2.3: Quality overall summary (QOS)**
  - Module 2.4: Non clinical overview
  - Module 2.5: Clinical overview
  - Module 2.6: Non clinical summary
  - Module 2.7: Clinical summary
- **Module 3: Quality**
- Module 4: Non clinical
- Module 5: Clinical

What is a Comprehensive Quality Overall Summary (CQOS)?

- A comprehensive summary of information, knowledge, and understanding of the drug substance and drug product, from development to commercialization, emphasizing what is critical for a robust manufacturing process and appropriate product quality

What is a Comprehensive Quality Overall Summary (CQOS)?

- A guide to present relevant CMC information in M3 in a more concise and organized manner
- A venue to present applicant's
  - Overall approach to acquiring product/process knowledge
  - Explanation of its thought process for decision making, using scientific, risk-based rationales
  - Risk assessment results and mitigation activities
- A means to concisely demonstrate knowledge/ understanding factors critical to product quality

Potential benefits of CQOS

- A properly constructed and developed QOS will guide applicants in gathering, organizing, and presenting critical CMC information essential to regulatory decision making
  - Focuses presentation on scientific rationales for established design space, leading to higher quality submissions and reviews
  - Facilitates introduction and incorporation of new pharmaceutical development concepts (QbD)

Potential benefits of CQOS

- A properly constructed and developed QOS can improve the efficiency of regulatory process
  - Assists in early identification of potential issues of disagreement for quick resolution to achieve first cycle approval
  - Facilitates a more relevant and focused scientific dialogue between reviewer and applicant
  - Provides an easy access to an organized, critical reference document, facilitating post-approval change evaluation and inspections
  - Guides and facilitates Pre-approval Inspection (PAI)
  - Facilitates development of potential "CMC regulatory agreement"

Content and essential elements of CQOS

- Summary of expanded P2 (CTD) type of information on both DS and DP illustrating:
  - Product knowledge, QbD, identification and justification of critical manufacturing steps, process understanding, CPP, in-process controls, etc.
- Demonstration of design space, e.g., product and manufacturing process design, process operating parameters, control strategies, trend analyses
- Organized by unit operation to facilitate review

Content and essential elements of CQOS

- Demonstration of process understanding from pilot scale to manufacturing scale
- Inclusion of risk analysis, assessment and management information that assure product quality
- Quality attributes and process parameters
- Summary of the information in Module 3 through effective use of tables, figures, graphs, charts, etc.
- Scientific assessment and analysis of all critical

Benefits of incorporating sponsor's assessment and analysis in CQOS

- Summary of data in Module 3 is insufficient to achieve desired outcome of CQOS
- Enhances applicant's ability to demonstrate product knowledge, and process understanding
- Provides insight into applicant's scientific rationale and thought process and conclusions
- Minimizes the need for reviewer's assumptions
- Contributes to a more relevant and focused scientific dialogue between reviewer and applicant
- Facilitates critical assessment by reviewer, and expedites regulatory decision making and approval

Relationship to Module 3

- CQOS provides a comprehensive summary of data, justifications, assessments, conclusions, resulting in a "complete story"; while M3 provides details and access to relevant data
- The use of CQOS as a potential primary review document will depend on its quality and content

Expanded Introduction – "The Whole Story"

- Existing QOS does not tie the "story" together
- An expanded introduction describing the applicant's QbD approach to product and process designs in a succinct manner could be very useful
  - Background information ⇒ DP performance ⇒ DP design ⇒ DP process design ⇒ DS design ⇒ DS process design ⇒ DS and DP quality assurance strategy ⇒ DS and DP stability
  - Including critical quality attributes (CQAs), critical steps, critical process parameters (CPPs)

Formatting Option

- Location (CTD)
  - Module 2: to replace current QOS
- Format
  - Maintain same format and sequence of Module 3, but with expanded Introduction
- Direct cross references or hyperlinks to pertinent sections of M3

ICH Harmonization

- Mitigates differences among companies and regions
- Consistent presentation of information to each regional regulatory authority
- Move US and EU closer to the Japanese regulatory approach
- Facilitates the introduction of new QbD development concepts across the three regions
- Better utilization of resources thus allowing more focus on enhancing quality of submission and review

ICH Harmonization

- Provides a common base for the international process for drug regulation, application and approval
- Facilitates drug approval process in the three regions
- Progress made:
  - Informal discussions, October 2005 in Chicago
  - Informal Working Group (IFW) meeting, June 2006, Yokohama
  - Concept paper to be developed

Conclusions

- A comprehensive QOS:
  - Rich in Knowledge and tells the “Whole Story”
  - Includes applicant’s analysis/assessment/justifications
  - Its utility as a main assessment tool will depend on its quality and contents
  - Module 3 will continue to be submitted
- Additional challenges and concerns
  - Implementation challenges for FDA and industry
  - Inclusion and utilization of the applicant’s self assessment and analysis
  - Additional work for the applicant
  - Harmonization challenges (resources and agreement on content)

The QOS

An EFPIA and PhRMA view on its revision

John Berridge – EFPIA
Robert Baum - PhRMA

PQF Yokohama June 2006

What is our primary goal?

- Bring important, life-saving medicines to patients faster
  - Improved efficiency – allow everyone to do 'more with the same resources'
  - Optimisation and better understanding of manufacturing processes

EFPIA & PhRMA Overview

- We agree that revision of guidance on QOS would be beneficial
  - Needs to address content
- The Japanese QOS model and review approach has merits
- Support the revision as an ICH topic
  - It should facilitate one QOS that is acceptable in the 3 ICH regions

Benefits of Revision

- Improve the overall efficiency of the review process
- Opportunities for global alignment (generally moving in the direction of the Japanese model)
- Should not be viewed as de-regulation

QOS - Guiding Principles

- Enable a single global submission (harmonized content)
- Enable review and approval in the three regions without the need to use Module 3
- Should promote QbD submissions
- No redundancies between Mod 2 and Mod 3
- Focus on attributes and parameters that are critical to quality
- Increases efficiency of submission, review and post-approval maintenance
- Current CTD format, impact on eCTD ???

Scope and purpose of the new QOS

Scope

- Applicable to all submissions
  - Initial MAA, line extensions,
- All molecular types
  - NCE and biotech
- Applicable to all regions

Purpose

- The primary review document
- Present to assessor all they need to know to make an approval decision
- Present a compelling description and critique of the Quality component of the dossier
  - Information and knowledge rich.

Isn't it different for Biotech?

- No
- Same data for all Drug Substances will be submitted
- Biotech emphasis is different for viral safety and manufacturing of the drug substance.

The new QOS should be

- Comprehensive summary of knowledge of the API & product from development to market
  - emphasizing what is critical for a robust, reproducible process and consistent, reliable product quality
- Mechanism to present briefly applicant's approach to acquiring product & process knowledge
  - science and risk based rationales for decision making
- A means to demonstrate concisely knowledge & understanding of factors critical to quality
  - And related control strategies;
- A formal template to present relevant CMC information

What is in Module 2?

- Discussion of the critical elements of the DS & DP development studies performed (e.g. P2)
- DS & DP Manufacturing Processes & Controls
- DS & DP Specs and summary of justification
- Summary of analytical procedures and their validation (summary)
- Summary of stability
- Summary of basis for post approval change

A compelling 'story'

The Compelling Story

- Rationale for the product design
- Comprehensive summary with a critique of the knowledge gained during the development of the product and components (API, excpients)
  - Optionally with focus on the proposed design space.
- Summary leads to identification of critical API and product attributes and process parameters (Design Space or ranges) affecting purity, manufacturability, performance and consistency of the product.
- Discussion of Quality Risk Management and risk mitigation
- From this discussion follows the list of elements subject to change control.

What happens to Module 3?

- It should contain the data that supports Module 2
  - There should be no repetition/duplication of Module 2 and Module 3 content
  - Module 3 could be the data that would primarily support GMP inspections, containing validation data, plant info stability tables.
    - Much of this is not required for approval.
- Module 3 could be left at the site for inspection – it may not be required for submission

Points we wish to discuss (1)

- How to describe change in purpose
  - Tell a compelling scientific story so Assessor can understand what applicant did and why
- Need clarity on where to locate Design Space(s)
- How to minimise data and maximise knowledge
- How to avoid
  - Summaries of summaries from Mod 3
  - Repetition
  - Too much detail, so that it is no longer a summary
  - Requirement for established products.
- Agree on what (if any) of the QOS is compliance
  - Manufacturing instructions, specifications, composition etc
    - These could be part of a 'Regulatory Agreement' located elsewhere (e.g. Module 1)

Points we wish to discuss (2)

- The impact on e-CTD should be evaluated prior to finalization of a modified QOS
  - Format/contents of QOS will be different
  - Format/contents of Module 3 will be different
- We need to prioritise QOS against potential revision of Q6a and the API development guideline
- A robust template and content guidance applicable to all regions should be provided
- Are regulators ready for the change from a data review to a knowledge review?
  - With potential for increased regulatory flexibility?

Conclusions

- We support revision of guidance on QOS
  - Needs to address content
- The Japanese QOS model and review approach has merits
- It should facilitate one QOS that is acceptable in the 3 ICH regions