Overview of applications for Marketing Authorisations – recent experience in assessment of quality

Presented by: Dr Keith Pugh
Quality Assessor, MHRA, UK
Outline

Quality

• Structure
• Content (CTD)
• Requirements

Quality Requirements

• Guidance

Recent experience
Quality – Content of a dossier

- Legislation (EU Directives and Regulations)
- European Commission – Notice to Applicants (2B) – Presentation and content of the Dossier
- Pharmacopoeias
- Guidelines (ICH or regional specific)
- Additional guidance – Q & As or other formats
Structure of a MA dossier - Quality

CTD Triangle

The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.
Quality part of MA dossier (ICH M4Q (R1))

Module 1 – Product Information

Module 2 - Quality Overall Summary

Module 3

3.2.S DRUG SUBSTANCE

- 3.2.S.1 General Information
  - 3.2.S.1.1 Nomenclature
  - 3.2.S.1.2 Structure
  - 3.2.S.1.3 General Properties
Quality part of MA dossier

3.2.S.2 Manufacture

- 3.2.S.2.1 Manufacturer(s)
- 3.2.S.2.2 Description of Manufacturing Process and Process Controls
- 3.2.S.2.3 Control of Materials
- 3.2.S.2.4 Controls of Critical Steps and Intermediates
- 3.2.S.2.5 Process Validation and/or Evaluation
- 3.2.S.2.6 Manufacturing Process Development

3.2.S.3 Characterisation

- 3.2.S.3.1 Elucidation of Structure and other Characteristics
- 3.2.S.3.2 Impurities
Quality part of MA dossier

3.2.S.4 Control of Drug Substance

- 3.2.S.4.1 Specification
- 3.2.S.4.2 Analytical Procedures
- 3.2.S.4.3 Validation of Analytical Procedures
- 3.2.S.4.4 Batch Analyses
- 3.2.S.4.5 Justification of Specification

3.2.S.5 Reference Standards or Materials

3.2.S.6 Container Closure System

3.2.S.7 Stability

- 3.2.S.7.1 Stability Summary and Conclusions
- 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
- 3.2.S.7.3 Stability Data
Quality part of MA dossier

3.2.P DRUG PRODUCT

- 3.2.P.1 Description and Composition of the Drug Product
- 3.2.P.2 Pharmaceutical Development
  - 3.2.P.2.1 Components of the Drug Product
  - 3.2.P.2.2 Drug Product
  - 3.2.P.2.3 Manufacturing Process Development
  - 3.2.P.2.4 Container Closure System
  - 3.2.P.2.5 Microbiological Attributes
  - 3.2.P.2.6 Compatibility
Quality part of MA dossier

3.2.P.3 Manufacture

- 3.2.P.3.1 Manufacturer(s)
- 3.2.P.3.2 Batch Formula
- 3.2.P.3.3 Description of Manufacturing Process and Process Controls
- 3.2.P.3.4 Controls of Critical Steps and Intermediates
- 3.2.P.3.5 Process Validation and/or Evaluation

3.2.P.4 Control of Excipients

- 3.2.P.4.1 Specifications
- 3.2.P.4.2 Analytical Procedures
- 3.2.P.4.3 Validation of Analytical Procedures
- 3.2.P.4.4 Justification of Specifications
- 3.2.P.4.5 Excipients of Human or Animal Origin
- 3.2.P.4.6 Novel Excipients
Quality part of MA dossier

3.2.P.5 Control of Drug Product

- 3.2.P.5.1 Specification(s)
- 3.2.P.5.2 Analytical Procedures
- 3.2.P.5.3 Validation of Analytical Procedures
- 3.2.P.5.4 Batch Analyses
- 3.2.P.5.5 Characterisation of Impurities
- 3.2.P.5.6 Justification of Specification(s)

3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System

3.2.P.8 Stability

- 3.2.P.8.1 Stability Summary and Conclusion
- 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment
- 3.2.P.8.3 Stability Data
Quality part of MA dossier

3.2.A APPENDICES

- 3.2.A.1 Facilities and Equipment
- 3.2.A.2 Adventitious Agents Safety Evaluation
- 3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

- Product Validation scheme
- Medical device
- Certificates of Suitability

3.3 LITERATURE REFERENCES
Quality – relevant guidance

**ICH M4Q (R1)/ EU - Notice to Applicants (Volume 2B) – location of information**

Module 2 - Quality Overall Summary

Module 3

- text under section titles is intended to be explanatory and illustrative only with where relevant reference to ICH guidelines/EU Guidelines (high level)

- Neither type nor extent of supporting data addressed (may depend upon regional guidance)

ICH Implementation Working Group - Q&As
Quality – relevant guidance

EU - Notice to Applicants (Volume 2B)

Annex to Module 3

A- List of references to quality guidelines

References to EU guidelines are provided to assist applicants when compiling the chemical, pharmaceutical and biological part of the application. However, *it remains the applicants’ responsibility* to ensure that all relevant legislation and guidelines are taken into account in the preparation of each part of their dossier.
Quality – relevant guidelines (ICH)

Stability Q1A - Q1F

Analytical Validation Q2

Impurities Q3A - Q3D

Pharmacopoeias Q4 - Q4B

Quality of Biotechnological Products Q5A - Q5E

Specifications Q6A- Q6B

Good Manufacturing Practice Q7
Quality – EU guidelines

This section includes the European Medicines Agency’s guidelines on the quality of medicines.

The Agency’s Committee for Medicinal Products for Human Use (CHMP) prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing-authorisation applications for human medicines.

Guidelines provide a basis for practical harmonisation of how the EU Member States and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy that are in the Community directives.

The Agency strongly encourages applicants and marketing-authorisation holders to follow these guidelines. Applicants need to justify deviations from guidelines fully in their applications at the time of submission. The Agency advises applicants to discuss any proposed deviations with EU regulators during medicine development through scientific advice.

Quality guidelines are provided for:
- Active substance
- Manufacturing
- Impurities
- Specifications, analytical procedures and analytical validation
- Excipients
- Packaging
- Stability
- Pharmaceutical development
### Quality – EU guidelines

#### Quality: Manufacturing

If you have comments on a document which is open for consultation, please use the Form for submission of comments on scientific guidelines.

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<th>Topic</th>
<th>Documents</th>
<th>Reference number</th>
<th>Publication date</th>
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Quality – EU guidelines

Adopted and will be published shortly

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Use of Near Infrared Spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations

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Quality of medicines questions and answers: Part 1

These questions and answers address a number of questions that have been brought to the attention of the Joint Committee for Medicinal Products for Human Use / Committee for Medicinal Products for Veterinary Use Quality Working Party (QWP) by marketing-authorisation holders (MAHs) or European Economic Area (EEA) competent authorities, on matters related to the quality of medicines. They have been developed and are maintained by the QWP.

They provide the EEA's harmonised position on issues that can be subject to different interpretation or require clarification, typically arising from discussions or correspondence during assessment procedures.

If a question is not addressed, marketing-authorisation holders are encouraged to contact the European Medicines Agency for further information at qwp@ema.europa.eu.

These questions have been produced to provide clarification or additional information, and should be read in conjunction with the European Pharmacopoeia, quality guidelines and other guidance documents.

Key:
- H: applicable to medicinal products for human use
- V: applicable to veterinary medicinal products

Table of contents
- Active Substance - Active-substance-master-file procedure
- Active substance - Declaration by the qualified person on the good-manufacturing-practice status of the active substance manufacturer
- Active Substance - Good-manufacturing-practice compliance for sterilisation of an active substance
- Active Substance - Starting materials of herbal origin
Quality – relevant guidance (ICH)

Pharmaceutical Development Q8

Quality Risk Management Q9

Pharmaceutical Quality System Q10

Development and Manufacture of Drug Substances Q11

Cross-cutting Topics

Parallel assessment with the United States

Quality by design

The European Medicines Agency welcome applications that include quality by design. Quality by design is an approach that integrates the quality of medicines by using statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines.

One of the goals of quality by design is to ensure that all sources of variability affecting a process are identified, explained and managed by appropriate means. This enables the finished medicine to consistently meet its predefined characteristics from the start – so that it is "right first time".

Quality by design centres on the use of multivariate analysis, often in combination with modern process analytical chemistry tools and knowledge management tools to enhance the identification and understanding of critical attributes of materials and critical parameters of the manufacturing process. This enhanced understanding of product and process is used to build quality into manufacturing and provide the basis for continued improvement of products and processes.

The concepts behind quality by design were introduced in international guidelines interested in the pharmaceutical industry between 2000 and 2012.

Applications including quality by design

The Agency welcomes applications that include quality by design aspects. These can include applications for marketing authorisation, variations to existing marketing authorisations and scientific advice.

Applicants wishing to make use quality by design should read the guidance documents below. These include guidelines Q8, Q9, Q10 and Q11 from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). They explain how aspects related to quality by design should be presented and explained in application documents.
ICH Q8: Approaches to Pharmaceutical Development

**Minimal approach (traditional)**
- Empirical development
- One variable at the time
- Fixed manufacturing process
- Focus on reproducibility
- Off-line analysis
- Quality assurance by testing
- Reactive lifecycle management (corrective actions)

**Enhanced, QbD, approach (*)**
- Systematic approach to development
- Multivariate experiments, DoE
- Manufacturing process (and quantitative formulation) adjustable within the design space
- Focus on control strategy and robustness of the process
- PAT tools used for feed forward and feedback process control
- Risk based control strategy & potentially Real Time Release
- Preventive lifecycle management and continuous improvement

(*) Optional approach. Parts may be applied.
ICH - Implementation WG on Q8, Q9, Q10 (November 2007)

Training

Unique training programme for industry and regulators (assessors and inspectors) in the three regions during 2010 (Tallin, Washington and Tokyo)

http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10.html

Q&As


Points to consider

Criticality/Control strategy/Level of documentation/Manufacturing process description/Models/Design Space

ICH Q11 Approaches to Pharmaceutical Development – drug substances

Main sections

• Manufacturing process development
• Description of manufacturing process and controls
• Selection of starting materials and source materials
• Control strategy
• Process validation/evaluation
• Submission of information in CTD format
• Lifecycle management
• Illustrative examples
QbD - Regulators/Industry learning (EU)
EMA/PDA - Joint Regulator/Industry QbD Workshop
(28/29 January 2014)

Scope

Workshop based on real cases (5 chemical & 1 biological)
Survey of what has been achieved so far
Experience gained so far
Promotion of common understanding
Identify bottlenecks/obstacles to QbD
Identify next steps
International harmonisation: participation of FDA/MHLW- PMDA
QbD - Regulators/Industry learning (EU)
EMA/PDA - Joint Regulator/Industry QbD Workshop
(28/29 January 2014)
Recent experience

Classification of points raised

- Potential *serious* risks to public health *(Major)*
- For clarification

Level and number of points generally reflect the overall quality of the submission

How points are addressed

- amending/updating something
- providing additional supporting information/justification (may require additional studies to be carried out)
General Overview of MA Applications by SMEs

2011, 2012 and 2013

AVERAGE Number of Major Objections:

- 7 for Positive MAAs
- 13 for Negative/Withdrawn MAAs
- 6 for MAAs of Medicines containing Chemical Entities (positive and negative)
- 18 for MAAs of Medicines containing Biological Entities (positive and negative)

Scope of the Major Objections (Biol.+Chem.)

- 43% Quality
- 38% Clinical Efficacy
- 12% Clinical Safety
- 7% Non-Clinical

Scope of the Major Objections (Chemical Entities)

- 40% Quality
- 44% Clinical Efficacy
- 13% Clinical Safety
- 3% Non-Clinical
Major Objections for SME dossiers containing Chemical Entities

2011, 2012 and 2013

Medicines containing Chemical Entities (29)

- 20 Positive Opinions
- 9 Withdrawn/Negative Opinions

Average number of MO for Medicines containing Chemical Entities: 6

Average number of MO for Positive MAAs: 5
Average number of MO for Negative/Withdrawn: 9
Major Objections in Quality Aspects for SME dossiers containing Chemical Entities

2011, 2012 and 2013 (by descending order of frequency)

- Manufacturing Process Validation Incomplete 14.3%
- Stability or Compatibility data lacking/ Shelf life 12.9%
- Issues on the Pharmaceutical Development 11.4%
- Setting of Specifications to be Justified 10%
- Lack on the Control and/or Characterization data of Drug Substance/Drug Product 10%
- Issues on the Manufacturing Process Development/Control Strategy\(^1\) 10%
- Lack of evidence of consistency between Batch-to-Batch 7.1%
- High level of Impurities or Related Substances Profile 5.7%

\(^1\) The Control Strategy of the manufacturing processes for Drug Substance or Drug Product.
Major Objections in Quality Aspects for SME dossiers containing Chemical Entities

2 new categories of MO not identified in previous analysis:

**Devices** (4.29%) and **Starting Materials Issues** (5.71%)
Recent experience

Points for clarification

*Qualified Person declarations* - Confirmation that drug substances (anything from the designated starting material onwards) are manufactured in compliance with the detailed guidelines on GMP for starting materials. Need to include the basis for the declarations (i.e. audit, date of audit and the professional capacity of the auditors).

*Product information*

SmPC - Section 6.3, compliance with the Note for guidance on the maximum shelf life for sterile products for human use after first opening or following dilution (CPMP/QWP/159/96 corr).
Thank you for your attention!