



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



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Outline

Quality

- Structure
- Content (CTD)
- Requirements

Quality Requirements

- Guidance

Recent experience



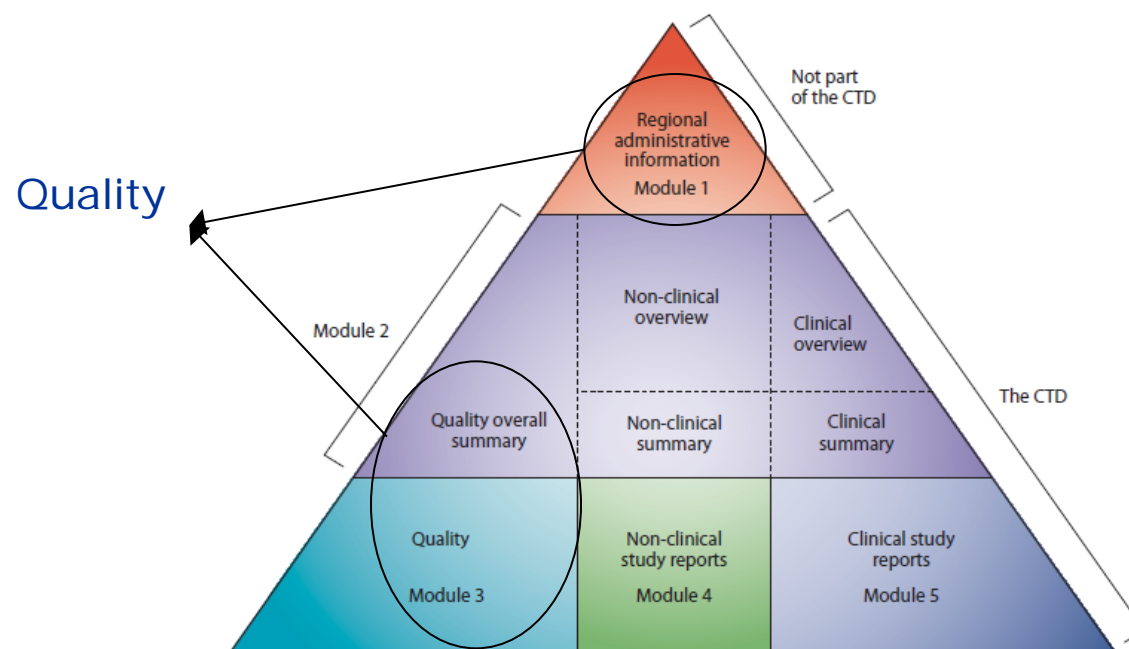
Quality – Content of a dossier

- 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*

- 6 – 3.2.S.7.3 *Stability Data*



Quality part of MA dossier

3.2.P DRUG PRODUCT

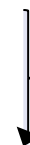
- 3.2.P.1 Description and Composition of the Drug Product
- 3.2.P.2 **Pharmaceutical Development**
 - *3.2.P.2.1 Components of the Drug Product*
 - *3.2.P.2.2 Drug Product*
 - *3.2.P.2.3 Manufacturing Process Development*
 - *3.2.P.2.4 Container Closure System*
 - *3.2.P.2.5 Microbiological Attributes*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

The screenshot shows the European Medicines Agency (EMA) website. The header includes the EMA logo and the text 'EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH'. Below the header is a navigation menu with links for Home, Find medicine, Human regulatory, Veterinary regulatory, Committees, News & events, Partners & networks, and About us. The main content area is titled 'ICH: Quality' and contains a table of contents for quality guidelines. The table of contents lists the following items:

- Stability
- Analytical validation
- Impurities
- Regulatory acceptance
- Quality of biotechnological products
- Specifications
- Good manufacturing practice
- Pharmaceutical development



Quality – EU guidelines

European Medicines Agency - Scientific guidelines - Quality guidelines

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Active Substance
Manufacturing
Impurities
Specifications, analytical procedures and analytical validation
Excipients
Packaging

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Quality guidelines

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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



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- Excipients
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- Specific types of products
- Post approval change management

Home > Human regulatory > Scientific guidelines > Quality > Manufacturing

Quality: Manufacturing

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Topic	Documents	Reference number	Publication date	Effective date	Remarks
Process validation	Overview of comments Adopted guideline Draft guideline Concept paper	EMA/CHMP/CV MP/QWP/7027 8/2012 Rev. 1	February 2014	June 2014	
Process validation	Adopted guideline	CPMP/QWP/84 8/96	Feb 2001	Sep 2001	
Annex II: Process Validation - Non-Standard Processes	Adopted guideline	CPMP/QWP/20 54/03	Jul 2004	Jan 2005	
Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products	Adopted guideline	CPMP/QWP/15 9/01	Mar 2001	Apr 2001	
Manufacture of the finished dosage form	Draft concept paper Adopted guideline	EMA/CHMP/Q WP/324350/20 13	July 2013		End of consultation 31 December 2013
Annex: Start of Shelf-Life of the Finished Dosage Form	Adopted guideline	CPMP/QWP/07 2/96	May 2001	Dec 2001	
The use of Ionizing Radiation in the Manufacture of Medicinal Products	Adopted guideline	3AQ4A	Dec 1991	Jul 1992	



Quality – EU guidelines

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Quality: Specifications, analytical procedures and analytical validation

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Topic	Documents	Reference number	Publication date	Effective date	Remarks
Real Time Release Testing	Overview of comments Adopted guideline Draft guideline Concept paper	EMA/CHMP/Q WP/811210/2009	Apr 2012	Oct 2012	
ICH Topic Q8, Q9 and Q10 Quality Implementation Working Group Questions and Answers	Adopted guideline	CHMP/ICH/265 145/09	Dec 2009	Dec 2009	
Q 4B Annex 11 Capillary Electrophoresis General Chapter	Draft guideline	CHMP/ICH/730 028/09	Release for consultation Dec 2009		Deadline for comments Feb 2010


Use of Near Infrared Spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations	Draft guideline	EMA/CHMP/C VMP/QWP/177 60/2009 Rev 2	Release for consultation Jan 2012		Deadline for comments 31 May 2012
Use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations revision 1	Overview of comments Draft guideline Concept paper	EMA/CHMP/C VMP/QWP/177 60/2009 Rev 1	Release for consultation Feb 2009		Deadline for comments 31 Aug 2009

← Adopted and will be published shortly




Quality – EU – Q&As

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Quality of medicines questions and answers: Part 1

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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

In March 2011, the Agency and the United States (US) Food and Drug Administration (FDA) launched a **three-year pilot programme for the parallel assessment** of sections of applications that are relevant to quality by design.

The pilot programme is open to selected procedures, including applications for initial marketing authorisations, type-II variations and **scientific advice**. Its objectives are to:

- ▶ share knowledge;
- ▶ facilitate consistent implementation of international guidelines;
- ▶ promote the availability of medicines of consistent quality throughout the European Union (EU) and the United States.

Participation in the pilot is voluntary. Interested applicants and sponsors should notify both agencies **three months prior to submission** of an application.

Both agencies assess the parts of the applications relevant to quality by design, such as development, design space and real-time release testing. The evaluation is performed separately by each agency, with regular communication and consultation throughout the review. The aim is a common [list of questions](#) to the applicants and harmonised evaluation of their responses.

The agencies publish question-and-answer documents below reflecting the conclusions reached.

With the agreement of the applicants, experts from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) participate as observers in the programme.

PAT team

The Agency set up a **process analytical technology (PAT) team** in November 2003 to support PAT and quality-by-design activities in the EU.

PAT is a system of controlling manufacturing through timely measurements of critical quality attributes of raw and in-process materials. It is often used as part of a quality-by-design approach.

The PAT team reviews the implications of quality by design and ensures that the European regulatory network is prepared for the evaluations of submissions including quality by design.



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Quality by design

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The European Medicines Agency welcomes applications that include quality by design. Quality by design is an approach that aims to ensure the quality of medicines by employing 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 measures. 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 methods 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 continuous improvement of products and processes.

The concepts behind quality by design were introduced in **international guidelines** intended for the pharmaceutical industry between 2009 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 dossiers.





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 feed back 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](http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10.html)

Q&As

General/Design Space/Real Time Release Testing/Control Strategy/Pharmaceutical Quality System/Inspection practices/Knowledge Management/Software solutions

<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>

Points to consider

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

<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>



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)

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Joint European Medicines Agency/Parenteral Drug Association quality-by-design workshop

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Title	Joint European Medicines Agency/Parenteral Drug Association quality-by-design workshop
Date	28/01/2014 - 29/01/2014
Location	European Medicines Agency, London, UK
Summary	The EMA and the Parenteral Drug Association (PDA) organised the workshop to promote a common understanding of quality by design (QbD) and to share the experience gained since the first workshop organised in 2009 on the topic.

Note: The presentation on 'Learning and best practices from the case studies' will be published at a later stage.



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)



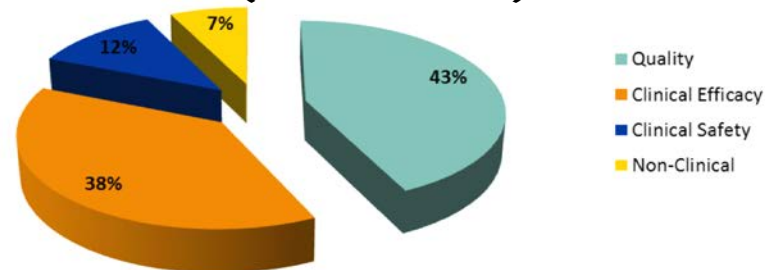
General Overview of MA Applications by SMEs

2011, 2012 and 2013

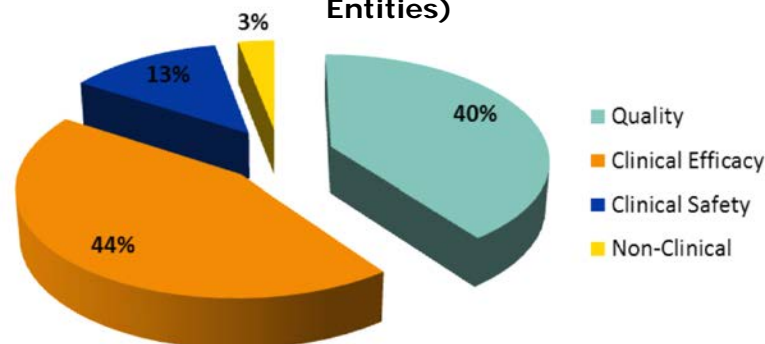
AVERAGE Number of Major Objections:

- 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.)



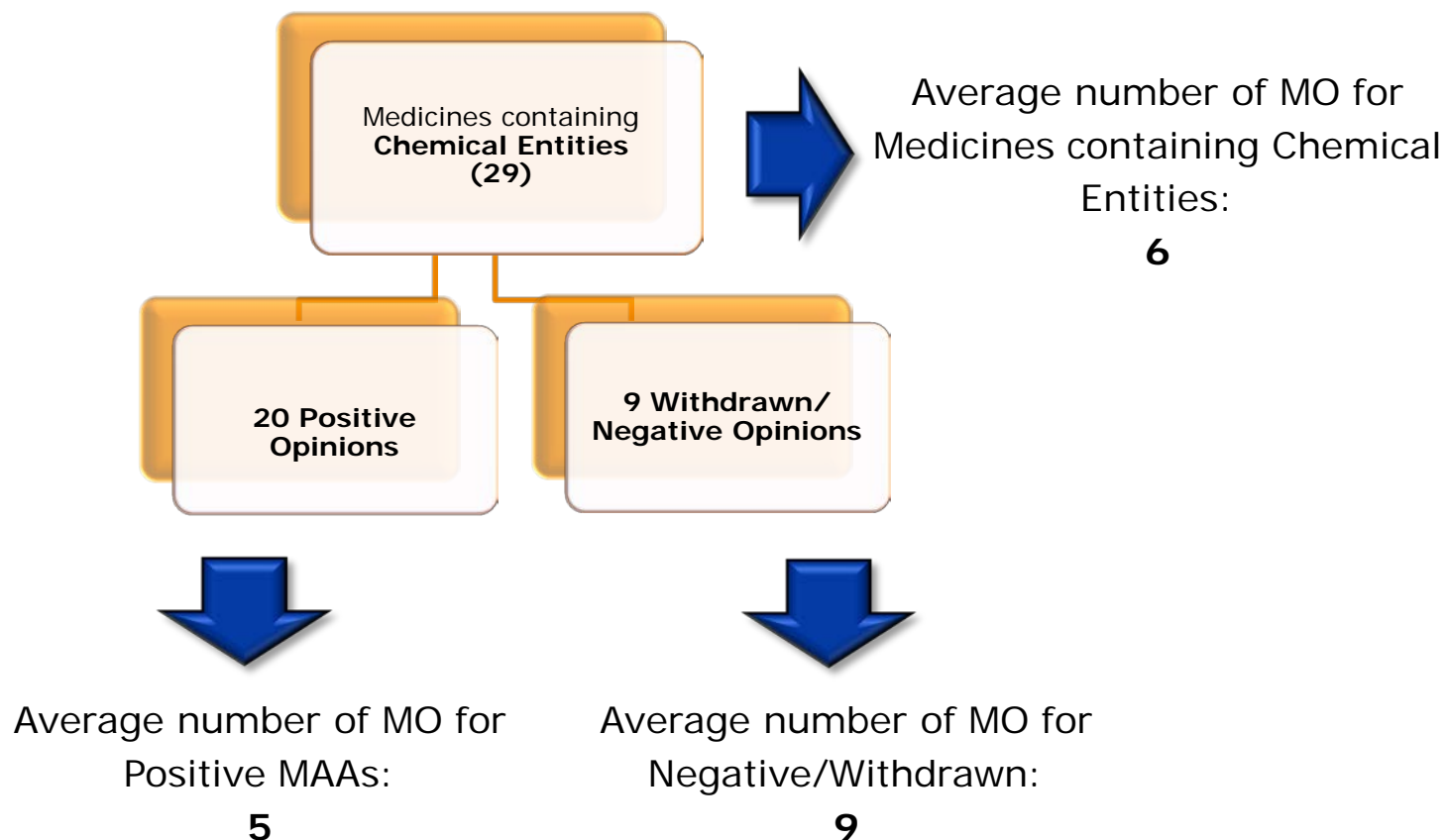
Scope of the Major Objections (Chemical Entities)





Major Objections for SME dossiers containing Chemical Entities

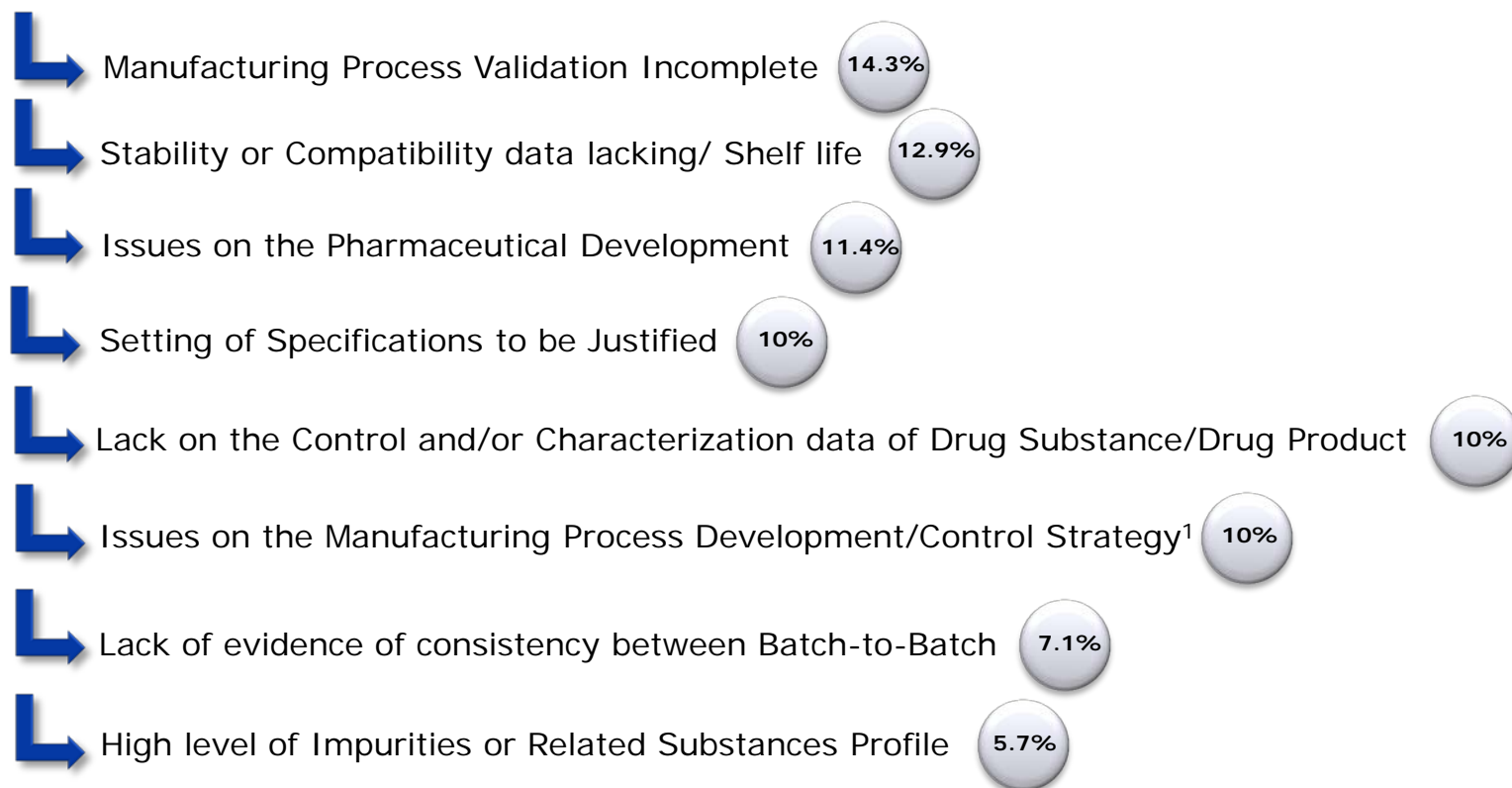
2011, 2012 and 2013





Major Objections in Quality Aspects for SME dossiers containing Chemical Entities

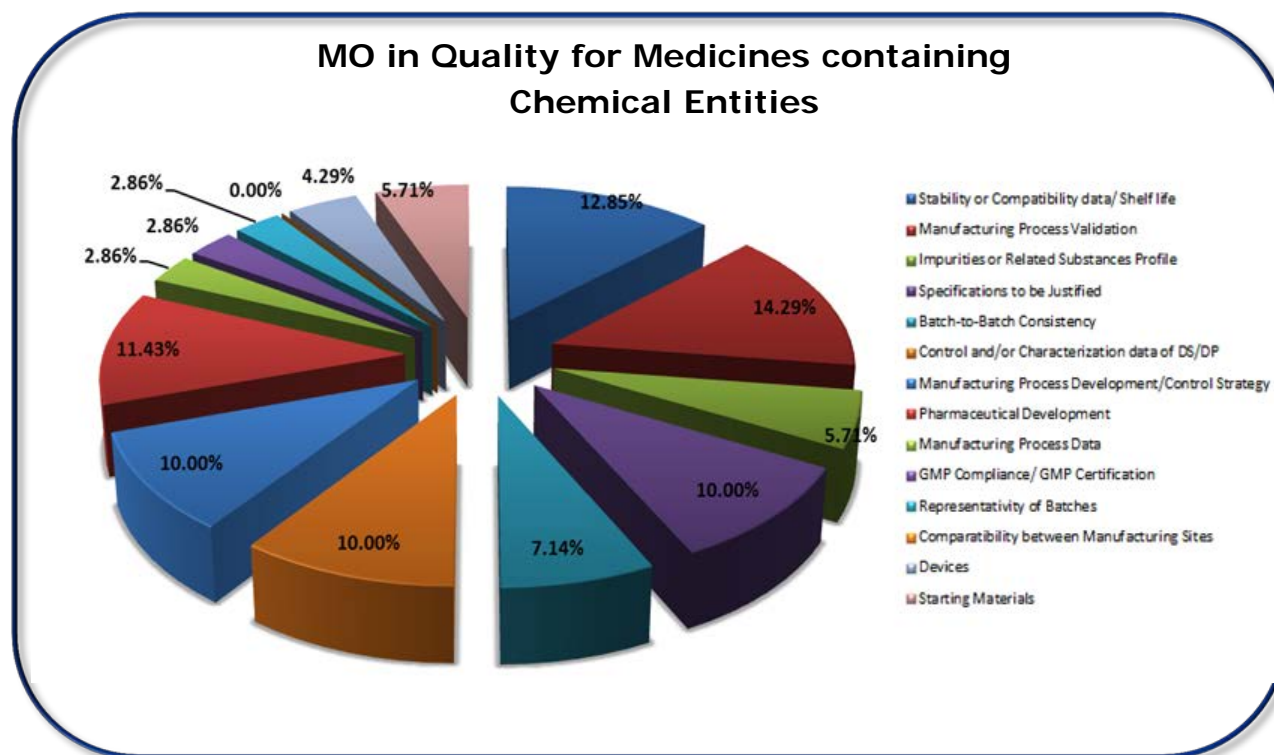
2011, 2012 and 2013 (by descending order of frequency)



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!