EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

MHRA
Regulating Medicines and Medical Devices

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Quality Assessor, MHRA, UK

Outline

Quality

- Structure
- Content (CTD)
- Requirements

Quality Requirements

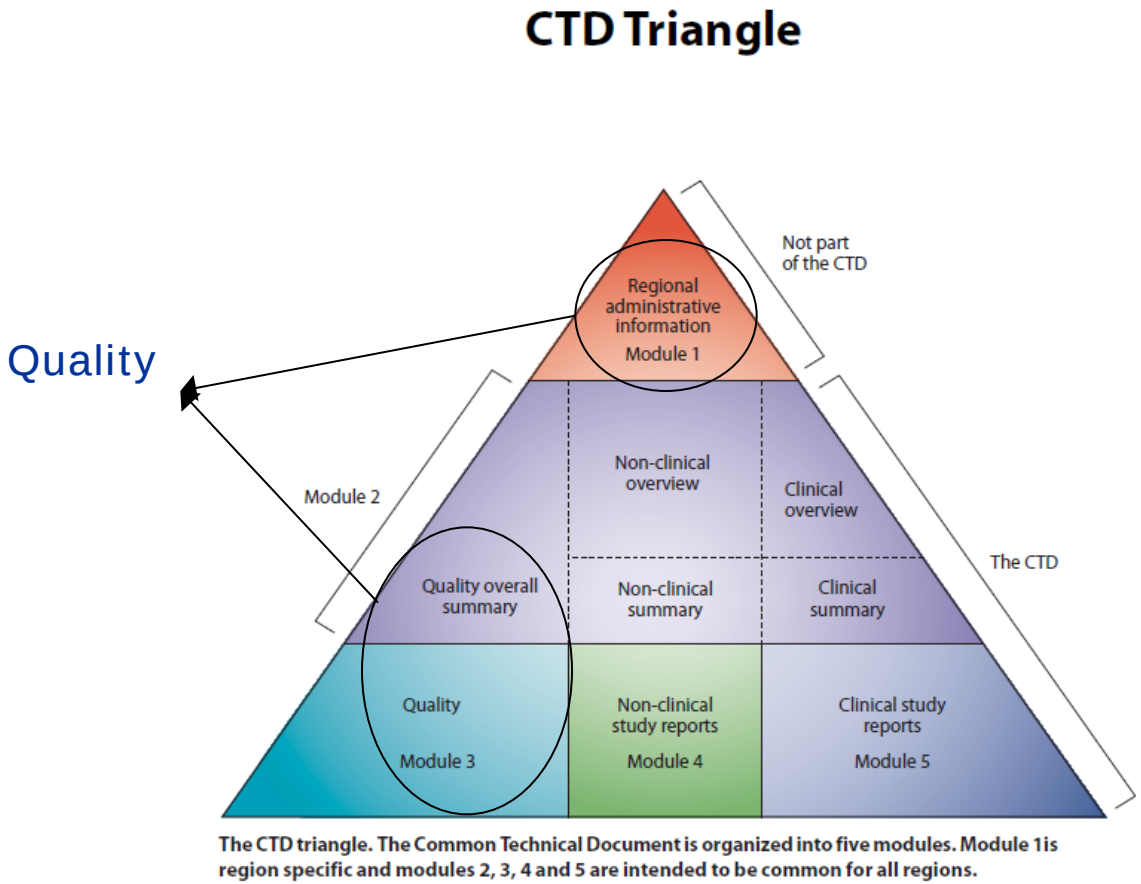
- Guidance

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



The CTD triangle. The Common Technical Document is organized into five modules. Module 1is 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

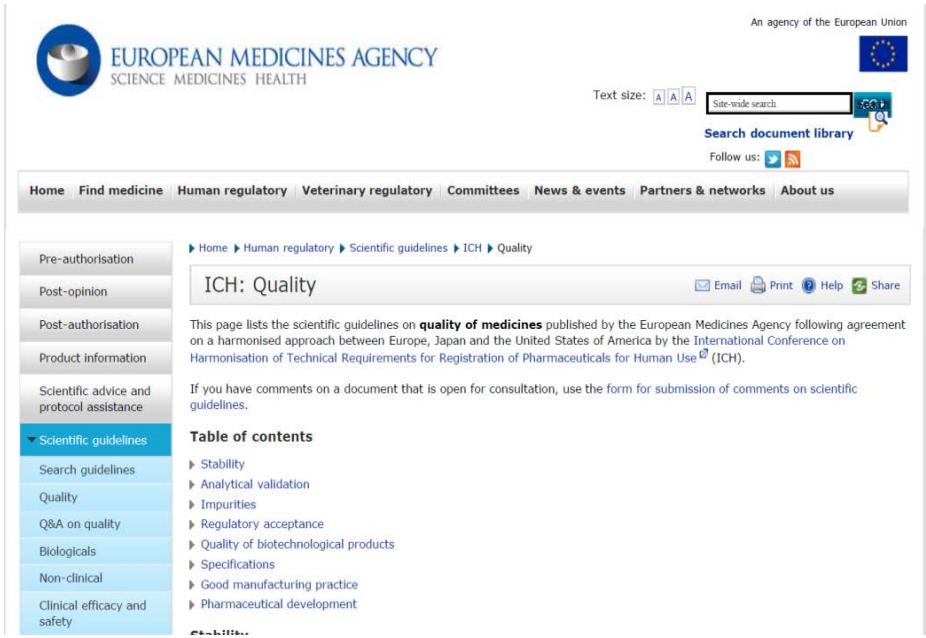
Impurities Q3A - Q3D

Pharmacopoeias Q4 - Q4B

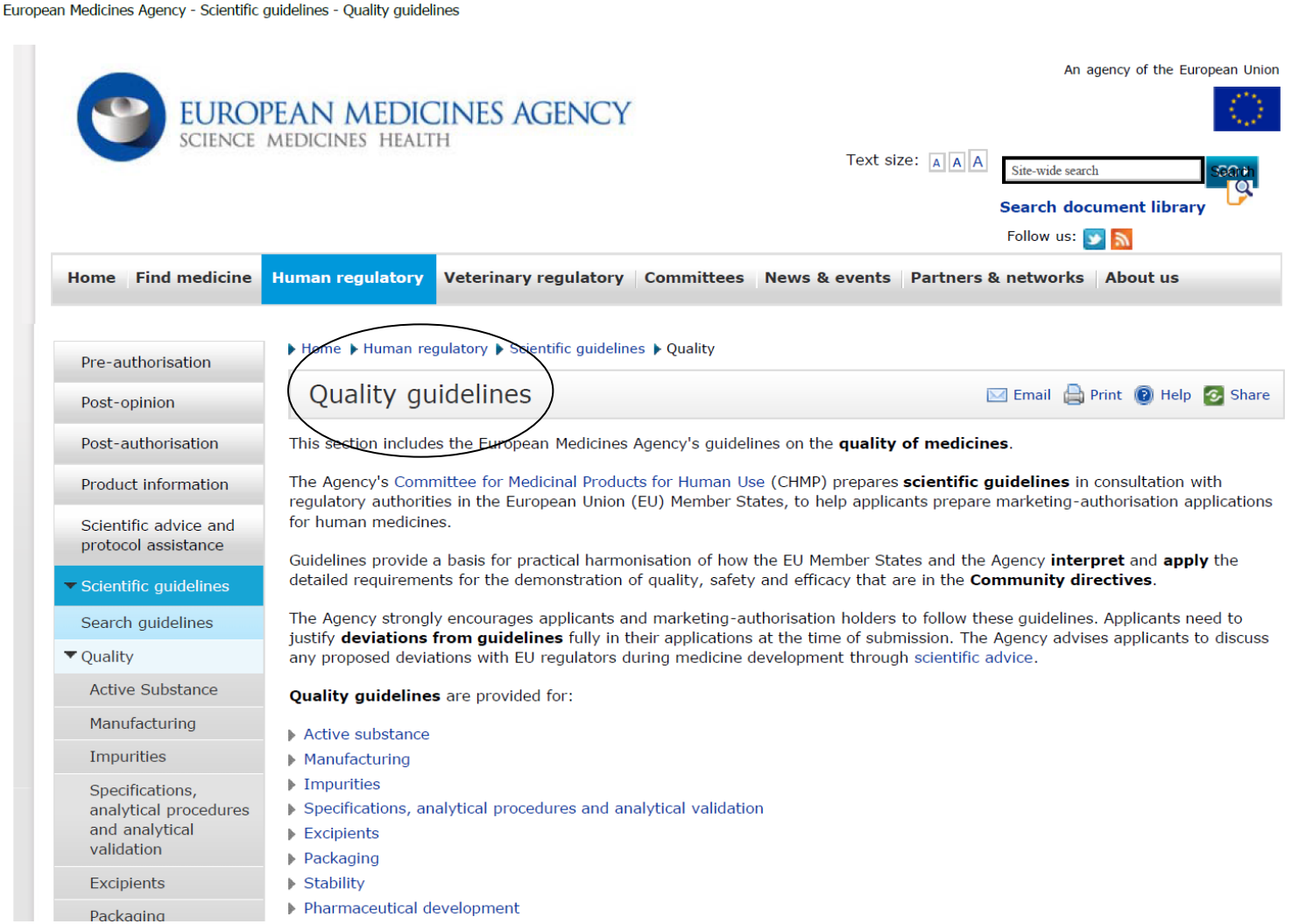
Quality of Biotechnological Products Q5A - Q5E

Specifications Q6A- Q6B

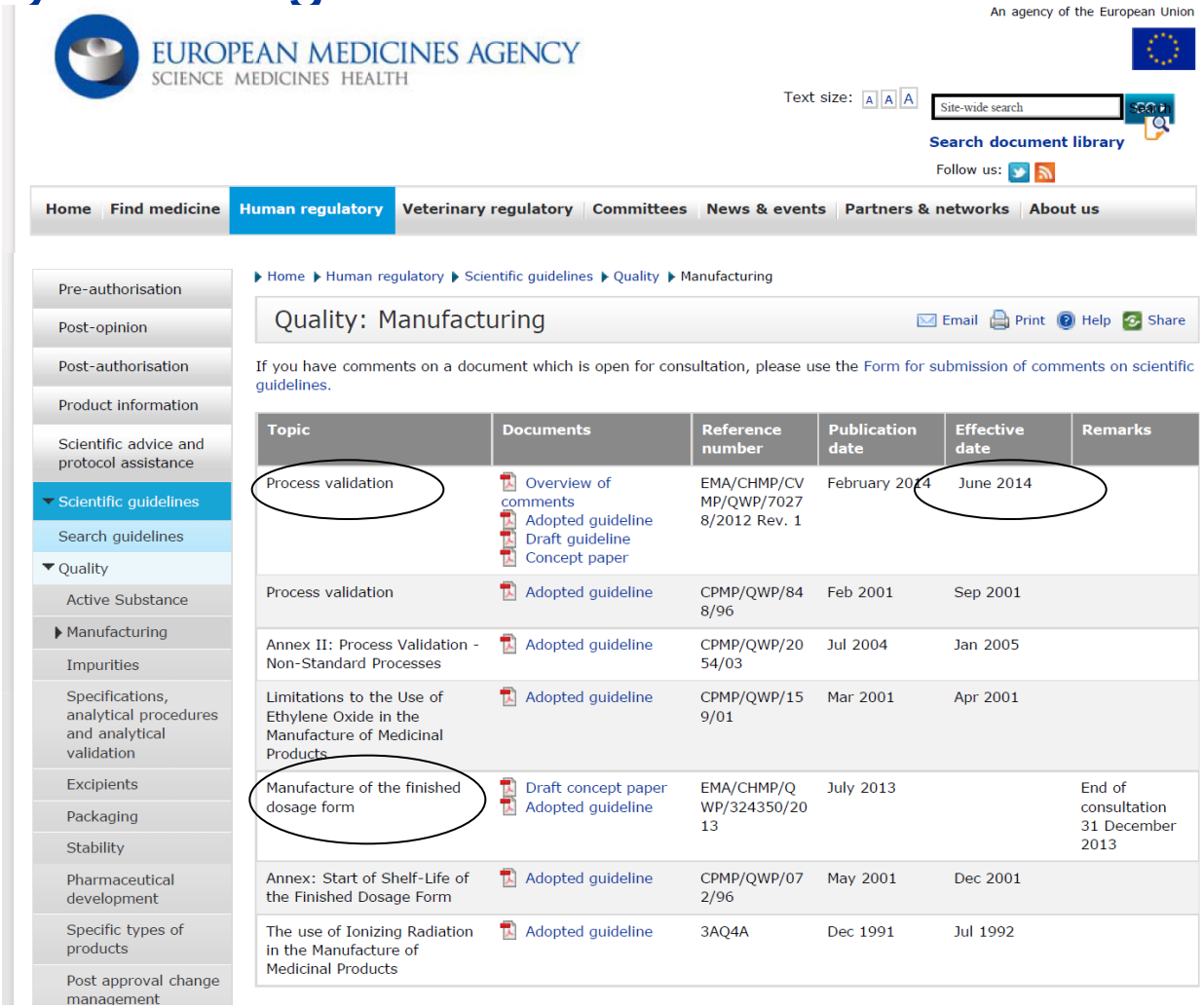
Good Manufacturing Practice Q7



Quality – EU guidelines



Quality – EU guidelines



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Quality: Manufacturing

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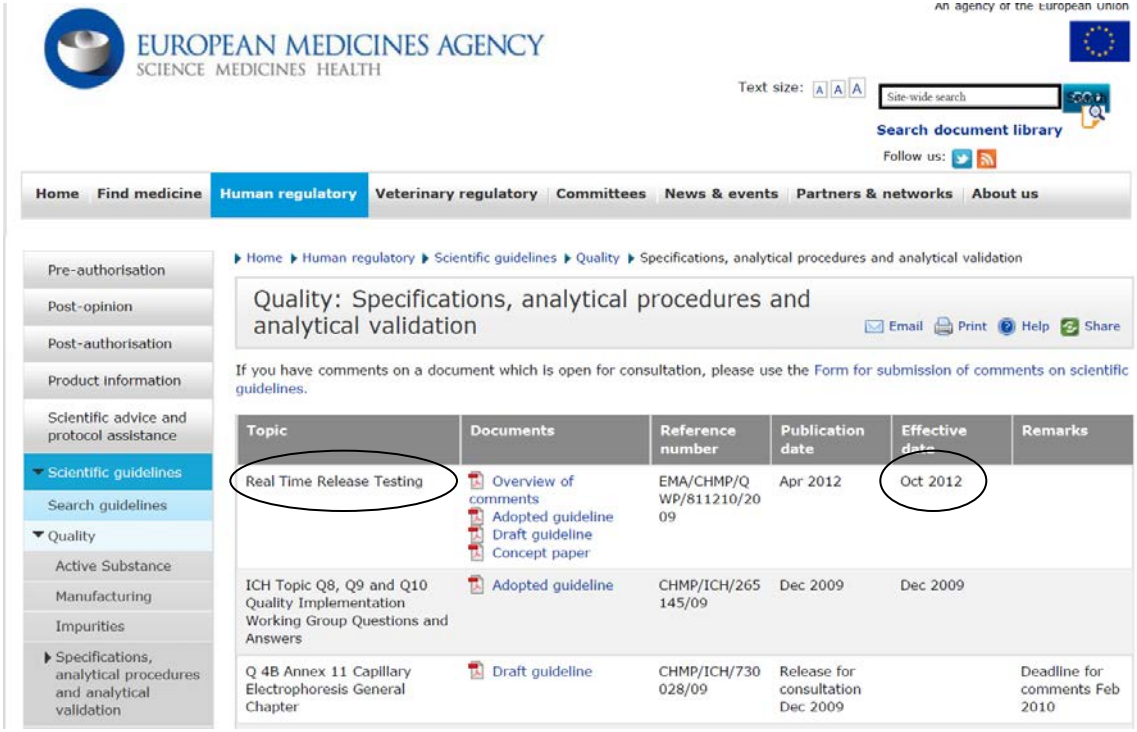
If you have comments on a document which is open for consultation, please use the Form for submission of comments on scientific guidelines.

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Process validation	Overview of comments Adopted guideline Draft guideline Concept paper	EMA/CHMP/CVMP/QWP/70278/2012 Rev. 1	February 2014	June 2014	
Process validation	Adopted guideline	CPMP/QWP/848/96	Feb 2001	Sep 2001	
Annex II: Process Validation - Non-Standard Processes	Adopted guideline	CPMP/QWP/2054/03	Jul 2004	Jan 2005	
Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products	Adopted guideline	CPMP/QWP/159/01	Mar 2001	Apr 2001	
Manufacture of the finished dosage form	Draft concept paper Adopted guideline	EMA/CHMP/QWP/324350/2013	July 2013		End of consultation 31 December 2013
Annex: Start of Shelf-Life of the Finished Dosage Form	Adopted guideline	CPMP/QWP/072/96	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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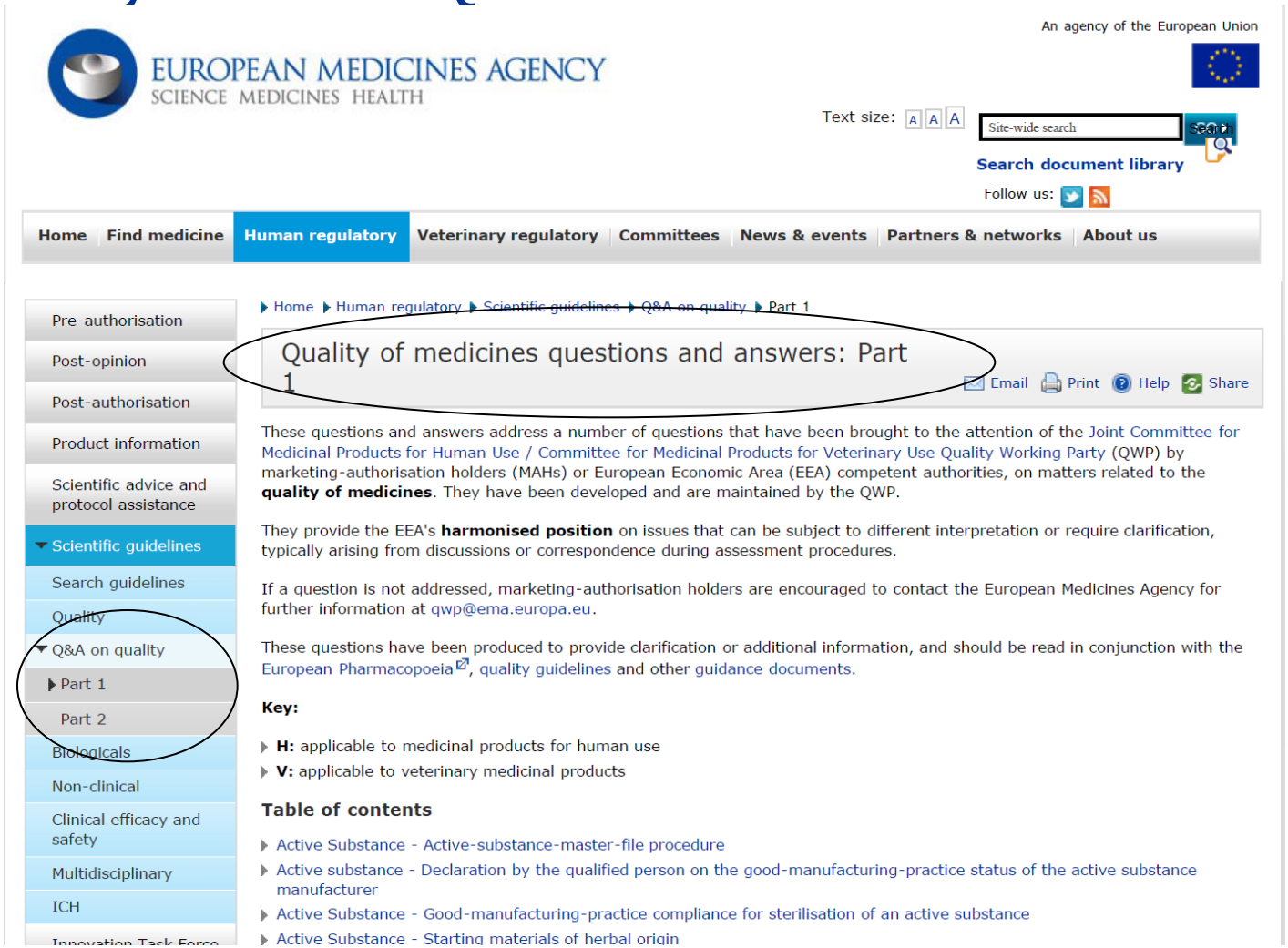
Topic	Documents	Reference number	Publication date	Effective date	Remarks
Real Time Release Testing	Overview of comments Adopted guideline Draft guideline Concept paper	EMA/CHMP/QWP/811210/2009	Apr 2012	Oct 2012	
ICH Topic Q8, Q9 and Q10 Quality Implementation Working Group Questions and Answers	Adopted guideline	CHMP/ICH/265145/09	Dec 2009	Dec 2009	
Q 4B Annex 11 Capillary Electrophoresis General Chapter	Draft guideline	CHMP/ICH/730028/09	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	EMEA/CHMP/CVMP/QWP/17760/2009 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	EMEA/CHMP/CVMP/QWP/17760/2009 Rev 1	Release for consultation Feb 2009		Deadline for comments 31 Aug 2009

← Adopted and will be published shortly

Quality – EU – Q&As



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.

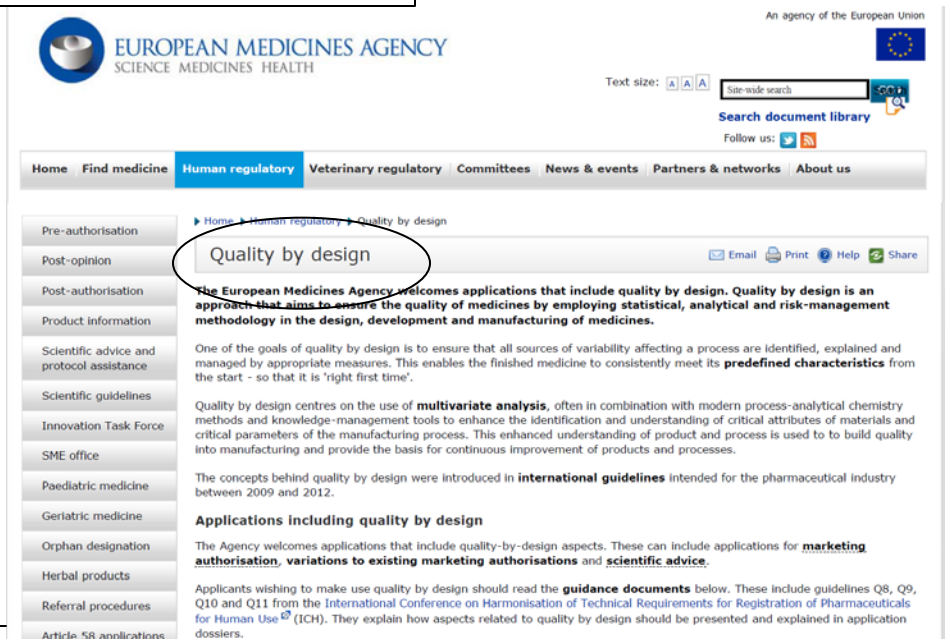
With the agreement of the applicants, experts from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) participate as observers in the programme.

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.



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

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

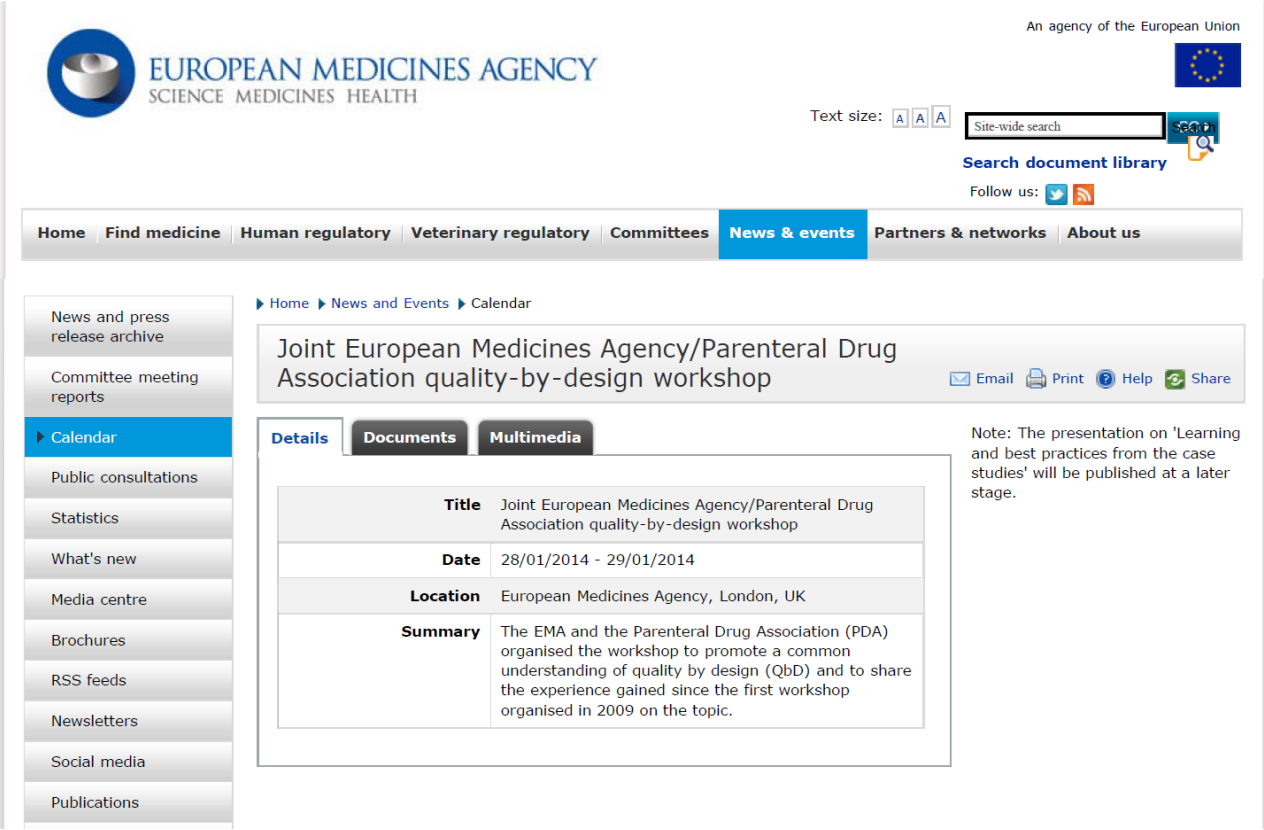
Identify bottlenecks/obstacles to QbD

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)



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

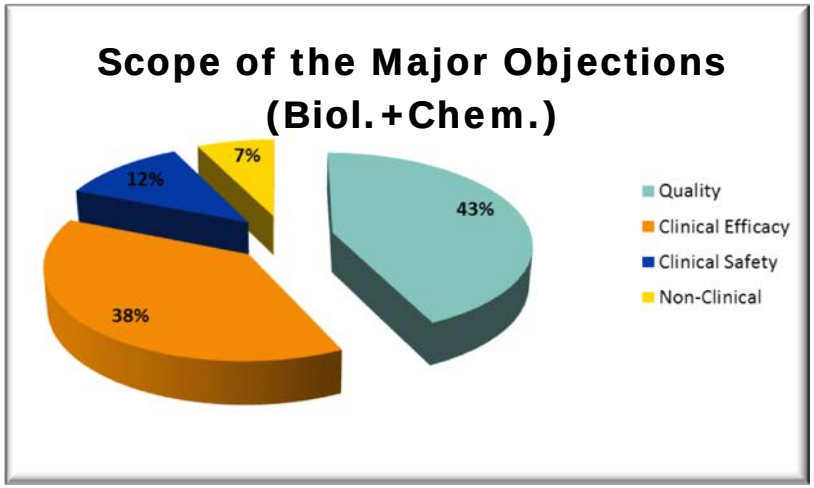
- amending/updating something
- providing additional supporting information/justification (may require additional studies to be carried out)

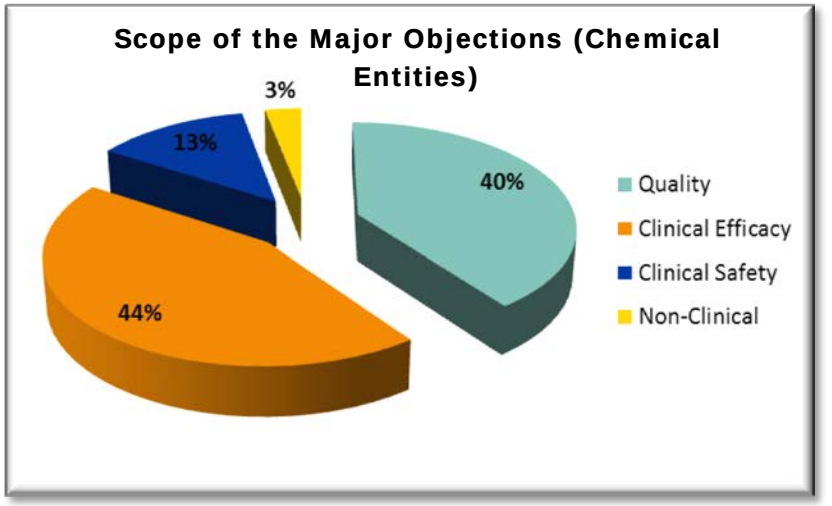
General Overview of MA Applications by SMEs

2011, 2012 and 2013

AVERAGE Number of Major Objections:

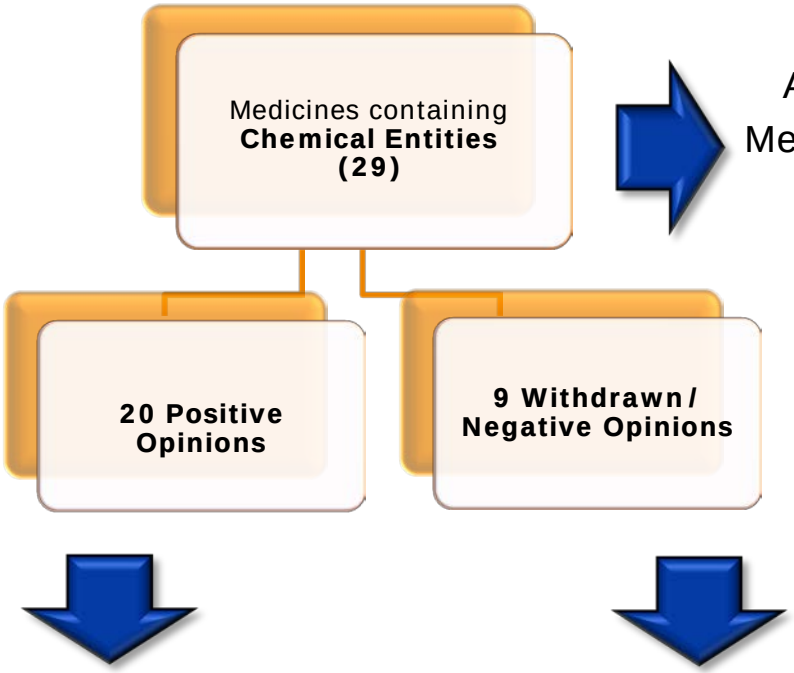
- **7** for Positive MAAs
- **13** for Negative/Withdrawn MAAs
- **6** for MAAs of Medicines containing Chemical Entities (positive and negative)
- **18** for MAAs of Medicines containing Biological Entities (positive and negative)





Major Objections for SME dossiers containing Chemical Entities

2011, 2012 and 2013



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

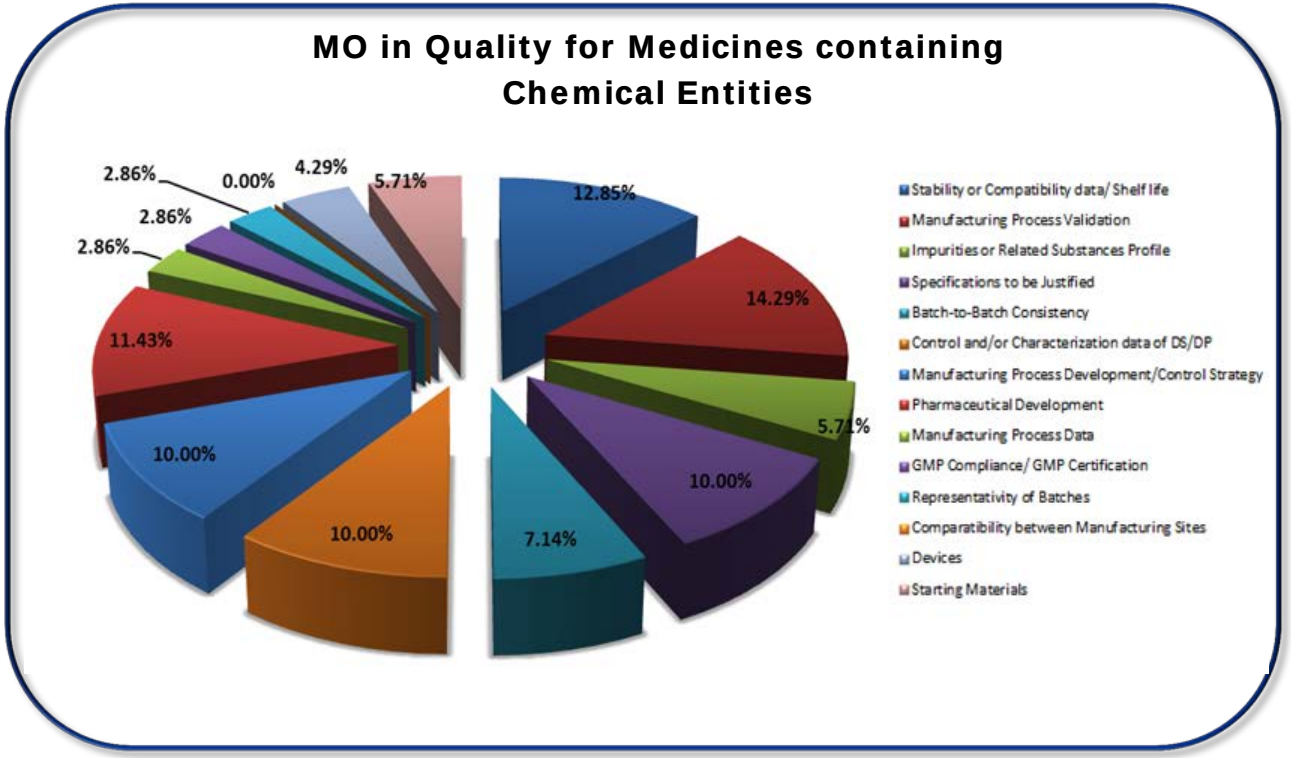
Major Objections in Quality Aspects for SME dossiers containing Chemical Entities

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!