Implementation of ICH Q8, Q9, Q10

Breakout D
Pharmacopoeial Requirements and the New ICH Quality Paradigm – Time for a Change?
Introduction

• Structure of this session

  - Presentation of key principles of the European Pharmacopoeia – General Notices, General Chapters, General Monographs
  - Case study / discussion
  - Breakout report
General Notices
General Notices

Put at the very beginning of the Ph. Eur. (page 1), they address general issues and are aimed at providing the basic information to the user.

► Apply to **all** texts
► Rules to understand texts, conventional expressions

**Essential reading before starting to use monographs**
Quiz: what is repeated at least 3000 times in the Ph. Eur.?

- A: Test for heavy metals
- B: Reference to BSE/TSE
- C: Reference to General Notices
- D: « Unless otherwise justified and authorised »
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- A: Test for heavy metals
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- D: « Unless otherwise justified and authorised »
Typical questions that are answered in the General Notices

- Do specifications apply throughout shelf-life?
- Are alternative methods allowed?
- The monograph specifies 1.000 g to be weighed for the test, what is the tolerance?
- Is Solubility a mandatory requirement?
- Is the Second Identification compulsory?
Alternative methods

Ph. Eur. tests are reference methods, essential in cases of dispute. Compliance is required, but alternative methods may be used as long as they lead to the same pass/fail result. It is the responsibility of the user to demonstrate their suitability. Approval of the competent authority is necessary in many cases.
Quiz: The monograph specifies 1.000 g to be weighed for the test (test with a numerical limit)

- A: You must weigh between 0.9995 and 1.0005 g
- B: You may weigh a quantity between 0.9 and 1.1 g, but with a tolerance of +/- 0.5 mg
- C: You must weigh exactly 1.000 g
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Breakout D: Pharmacopoeial Requirements

Quiz: The monograph specifies 1.0 g to be weighed for a comparative test (sulphates, chlorides, etc...)

• A: You must weigh between 0.95 and 1.05g
• B: You may weigh a quantity between 0.9 and 1.1 g, but with a tolerance of +/- 0.05 g
• C: You must weigh exactly 1.0 g
Quiz: The monograph specifies 1.0 g to be weighed for a comparative test (sulphates, chlorides, etc…)

- A: You must weigh between 0.95 and 1.05g
- B: You may weigh a quantity between 0.9 and 1.1 g, but with a tolerance of +/- 0.05 g
- C: You must weigh exactly 1.0 g
Quiz: The monograph specifies 1.0 ml of a solution to used for a test

- A: You have to use between 0.95 ml and 1.05 ml
- B: You have to sample the solution with a pipette, a volumetric flask or a burette
- C: You have to use a balance for the determination
Breakout D: Pharmacopoeial Requirements

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Sample size

• Accuracy defined by the number of significant figures: $1.000\,\text{g} \Rightarrow \pm 0.5\,\text{mg}$

• For test/assay with calculated result, amount to be used is within 10% (absorbance, water, loss on drying etc.)

• For comparative tests (sulphates, chlorides, etc.) amount defined by number of significant figures: $1.0\,\text{g} \Rightarrow 0.95-1.04\,\text{g}$
Quiz: I have demonstrated that my process does not generate an impurity for which a test is prescribed in the monograph

- A: Compliance with Ph. Eur. necessitates the verification that the test is performed on each batch to verify that the level of the impurity is below the specific limit
- B: The test does not need to be carried out at all
Breakout D: Pharmacopoeial Requirements

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Quiz: The monograph prescribes a test for sterility

- A: A sterility test is to be used for compliance to Ph. Eur.
- B: I have demonstrated by appropriate equipment validation and in process controls that my process will consistently lead to a sterile product. With the agreement of the competent authority a sterility test can be omitted
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Waiving of tests

• In some cases some tests may be omitted based on validation data or other suitable justification

• Tests for process-specific impurities may be omitted if it is demonstrated that they will not occur with the particular process used
Waiving of tests

- «The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls. Parametric release in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.»
Legal status of monographs

- Monographs are “official standards”
- The Convention on the Elaboration of a European Pharmacopoeia makes the texts of the Ph. Eur. mandatory in all signatory parties
- Monographs may be accepted as suitable standards even when not obligatory
Quiz: Reference to regulatory documents

• A: When the Ph. Eur. refers to a regulatory document (e.g. EU note for guidance) it becomes mandatory.

• B: Reference to a regulatory document does not change its original status.
Quiz: Reference to regulatory documents

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• B: Reference to a regulatory document does not change its original status
Reference to regulatory documents

- « These references are provided for information for users for the Pharmacopoeia. Inclusion of such a reference does not modify the status of the documents referred to, which may be mandatory or for guidance. »

General Notices, 7th edition
Quiz: Do Ph. Eur. specifications apply throughout shelf-life?

• A: Yes, specifications apply until time of use for raw materials and throughout period of validity for preparations
• B: No, Ph. Eur. requirements are for release only.
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What does compliance mean?

- Compliance with a **monograph**
- All **mandatory** parts of a monograph
- Compliance **until time of use** for raw materials, ingredients
- Compliance **throughout period of validity** for preparations
- In-use compliance decided by licensing authority for each preparation
What must comply?

- Mandatory for all substances for pharmaceutical use
- Ingredients (incl. excipients) of final formulation
- Components of solvents, buffers etc in or used to make up final formulation
- Solvents used for purification? If a monograph exists, then compliance will usually be required
- Reagents? Not usually needed for upstream use
What is mandatory?

• Mandatory unless otherwise indicated:
  - Characters, Storage, Functionality-related Characteristics sections
• “Should” ⇒ informative or advisory (i.e. not mandatory)
• “This chapter/section is published for information and guidance”
Quiz: Validation of Pharmacopoeial methods

- **A**: All methods of the Ph. Eur. need to be revalidated in order to check robustness
- **B**: Methods of the Ph. Eur. have been validated. Validation by the analyst is not required.
Quiz: Validation of Pharmacopoeial methods

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Validation of Pharmacopoeial methods

- « The test methods given in monographs and general chapters have been validated in accordance with accepted scientific practice and current recommendations on analytical validation. Unless otherwise stated in the monograph or general chapter, validation of the test methods by the analyst is not required. »

General Notices, 7th edition
Human and veterinary use

• Unless otherwise stated, monographs cover human and veterinary use.
• Where a substance is used in both human and veterinary products, the same quality specification is applied.
• When the monograph title bears “for veterinary use” the substance is intended only for veterinary products.
General Chapters
Why general chapters?

• Analytical methods:
  - Editorial convenience: avoid repeating standard methods in each monograph
  - Provide standard methods that can be used where there is no monograph
  - Give general requirements for equipment, equipment verification
General chapters

- Not mandatory “per se”
- When referred to in a monograph, they become part of the standard
- Can be used for substances not covered by monographs, may need validation
- Some general chapters are not referred to in any monograph (Raman spectrometry): useful guidance, can be referred to in applications
General chapters (2)

- Many have validity or equipment-verification requirements
- These requirements become part of monograph
Chromatographic separation techniques

2.2.46

- LC, SEC, GC, TLC and SFC
- System suitability:
  - Peak symmetry
  - Repeatability (for assays)
  - Limit of quantification
- Adjustment of operating conditions
- Requirements apply wherever methods are prescribed in monographs
General chapters in section 5

not analytical methods

5.1 Preparation of sterile products / Microbiology
5.2 Production and QC of vaccines
5.3 Statistical Analysis
5.4 Residual solvents
...
5.9 Polymorphism
5.10 Control of impurities (5.10)
Microbiological quality

• Microbiological examination of non-sterile products: total viable aerobic count (2.6.12)
• Microbiological examination of non-sterile products: test for specified micro-organisms (2.6.13)
• Microbiological quality of pharmaceutical preparations (5.1.4)
General Monographs
Why general monographs?

- Two types:
  - General monographs on classes of substances
  - General monographs on dosage forms
General monographs

• “Classes” defined by different criteria: production method, origin, risk factors
• Aspects that cannot be treated in each individual monograph
  - Residual solvents
  - TSE/BSE
  - Pesticides in herbals
  - etc.
General monographs (2)

- Apply to all products

- No cross-reference in individual monographs

CHECK WHICH GENERAL MONOGRAPH APPLIES!
Quiz: From general monographs and individual monographs which are the ones which have priority?

- A: General monographs overrule individual monographs
- B: Individual monographs overrule general monographs
- C: There is no such priority
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Complementarity of General & individual monographs

- « General monographs and individual monographs are complementary. If the provisions of a general monograph do not apply to a particular product, this is expressly stated in the individual monograph. »

General notices, 7th edition
General monographs on dosage forms

- Contain requirements common to all dosage forms of the type defined (tablets, capsules, parenteral preparations etc)
- Classified by pharmaceutical form/route of administration
- Applied during licensing
- Framework specification: acceptance criteria and extra tests are proposed by manufacturer and approved by competent authority
Case Study
Blending Process Control Options
Decision on conventional vs. RTR testing

Control strategy 1: Control items
- Blending time
- Blending speed
- Equipment
- Scale
- Drug substance particle size

Control strategy 2: Control items
- Control of blending end point by NIR
- Drug substance particle size

Figure 2.3.P.2.3-7  Control Strategy for Blending Process

Note) In the case of employment of control strategy 1, it is possible that drug substance particle size as an input variable is combined with process parameters of blending time and blending speed to construct and present a three dimensional design space.

Key message: Both approaches to assure blend uniformity are valid in combination with other GMP requirements
Process Control Option 2

Blend uniformity monitored using a process analyser

- Control Strategy to assure homogeneity of the blend
  - Control of blending end-point by NIR and feedback control of blender
  - API particle size

In this case study, the company chooses to use online NIR to monitor blend uniformity to provide efficiency and more flexibility.
Process Control Option 2: Blend uniformity monitored using a process analyser (ctd)

- On-line NIR spectrometer used to confirm scale up of blending
- Blending operation complete when mean spectral std. dev. reaches plateau region
  - Plateau may be detected using statistical test or rules
- Feedback control to turn off blender
- Company verifies blend does not segregate downstream
  - Assays tablets to confirm uniformity
  - Conducts studies to try to segregate API

Data analysis model will be provided
Plan for updating of model available

Acknowledgement: Adapted from Paul Stott (AZ) - ISPE PQLI Team
Conventional automated control of Tablet Weight using feedback loop:
Sample weights fed into weight control equipment which sends signal to filling mechanism on tablet machine to adjust fill volume and therefore tablet weight.

**Control strategy:** Assay assured by control of weight of tablets made from a uniform powder blend that has acceptable API content by HPLC
RTRT of Assay and Content Uniformity

- Finished Product Specification – use for stability, regulatory testing, site change, whenever RTR testing is not possible
  - Assay acceptance criteria: 95-105% of nominal amount (30mg)
  - Uniformity of Dosage Unit acceptance criteria
  - Test method: HPLC

- Real Time Release Testing Controls
  - Blend uniformity assured in blending step (online NIR spectrometer for blending end-point)
  - API assay is analyzed in blend by HPLC
  - Tablet weight control in compression step

- No end product testing for Assay and Content Uniformity (CU)
  - Would pass finished product specification for Assay and Uniformity of Dosage Units if tested because assay assured by combination of blend uniformity assurance, API assay in blend and tablet weight control (if blend is homogeneous then tablet weight will determine content of API)
Breakout D: Pharmacopoeial Requirements

Topics to discuss

• Would RTR/on-line testing be in line with regulatory and pharmacopoeial requirements?
• Does RTR have an impact on the sampling plan?
• Which acceptance criteria would you apply?
• Is there a need for changes in the pharmacopoeia?
  Is the current structure of monographs adequate?