Hot topics

Overview about some developments in the European Pharmacopoeia in terms of physicochemical and pharmaceutical technical methods

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AGENDA

- Update on the harmonized chapter Uniformity of Dosage Units (UDU) (Ph.Eur. 2.9.40).
- Acceptance criteria for UDU based on large sample sizes
- Elemental Impurities (Heavy Metals chapter)
- Use of Reverse Osmosis (RO) for production of Water For Injection (WFI).

Update on the harmonized chapter Uniformity of Dosage Units (UDU) (Ph.Eur. 2.9.40).

Uniformity of Dosage Units

Can be demonstrated by either of 2 methods:

1. Content Uniformity (CU)
   - based on the assay of the individual contents of active substance(s) of a number of dosage units to determine whether the individual contents are within the limits set.
   - may be applied in all cases.
   - not required for multivitamin and trace-element preparations

Uniformity of Dosage Units

2. Mass Variation (MV)

- applicable for the following dosage forms:

(1) solutions enclosed in single-dose containers and in soft capsules;

(2) solids (including powders, granules and sterile solids) that are packaged in single-dose containers and contain no added active or inactive substances;

(3) solids (including sterile solids) that are packaged in single-dose containers, with or without added active or inactive substances, that have been prepared from true solutions and freeze-dried in the final containers and are labelled to indicate this method of preparation;

(4) hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of an active substance comprising 25 per cent or more, by mass, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other active substances present in lesser proportions is demonstrated by meeting content uniformity requirements.

Uniformity of Dosage Units

- Unless otherwise stated, the uniformity of dosage units specification is not intended to apply to suspensions, emulsions or gels in single-dose containers intended for cutaneous administration.

Uniformity of Dosage Units

Chapter 2.9.40

- Signed-off by PDG on 18 February 2004
- Implemented in Ph.Eur. 1st July 2005 (Supplement 5.2)

Uniformity of Dosage Units

Major changes compared to old approach in Europe:

- Test by variables instead of by attributes
- Increase of threshold from 2 mg/2% to 25 mg/25% of API in the dosage unit → increase of testing
- Expression in % label claim instead of average assay (JP: 1998 « Therapeutic effects of each unit are expected for the label claim »)

Uniformity of Dosage Units

EMA/QWP (current approach)

- UDU for products with MA granted after 1st July 2005, at release
- Old approach for already marketed products (2.9.5 and 2.9.6) and for shelf life testing (market surveillance)

Ph. Eur.

- Not for herbal drugs or herbal drug preparations present in the dosage form
- Unless otherwise stated, not for suspensions, emulsions or gels in single-dose containers intended for cutaneous admin.
- CU not for multivitamin and trace-element preparations

Uniformity of dosage units

2% RSD exemption (May 2010) :

- not acceptable for FDA
- accepted by JP for item (4) only
- accepted by Europe for all dosage forms subject to CU

Uniformity of Dosage Units

Future of the « old » methods 2.9.5 & 2.9.6 : phasing out?

- Enquiry in Pharmeuropa 20.1 (Jan. 2008)
- Assessment of results by Group 12 ➔ recommendation to Ph. Eur. Commission to keep status quo
- Recommendation from Ph Eur Commission to QWP: idem

Conclusion

- The deliberations on the future of the harmonized UDU test are not yet finalized at the level of ICH Q4B / PDG.
- The Joint CHMP/CVMP Quality Working Party is in favour of keeping the two methods as described in 2.9.40 and 2.9.5/2.9.6. in parallel, i.e. leaving the decision which method to apply to the user, should the three ICH regulators not agree on the 2% standard deviation exemption as foreseen in the harmonized UDU text signed-off by the three pharmacopoeias.
- The issue shall be clarified at the next ICH/PDG meeting in November.

Ph. Eur. PAT working party:

Relationship between sample size and acceptance criteria:
“Content uniformity test for large sample sizes”

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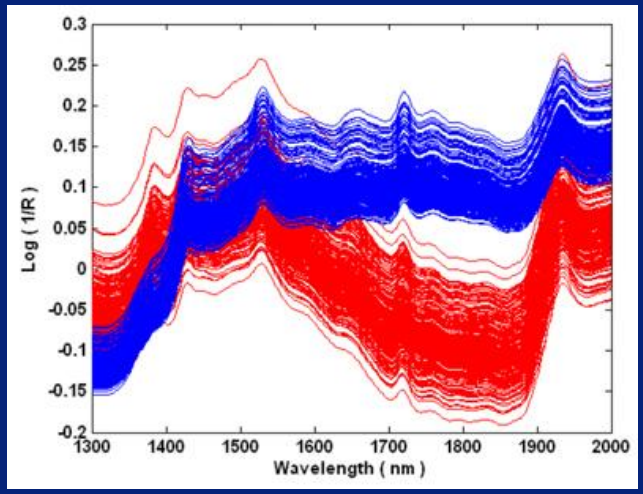

Ph.Eur. PAT Working Party

- Established on request of the EMA PAT team

- Composition:
  - licensing authorities and inspectorates
  - industry
  - academia
  - chair: Prof. G. Ragnarsson, Medical Products Agency, Sweden

Relationship between sample size and acceptance criteria: “Content uniformity test for large sample sizes”

Uniformity of dosage units:

To ensure consistency of active substance amount among dosage units, currently a test is performed on the basis of a random sample, where n = 30

Problem statement:

PAT tools enable to monitor larger sample sizes

e.g. by NIR at-line

with n between 100 and 10000.

In this case

Traditional acceptance criteria for n = 20 (based on the acceptable number of outliers 85-115 % resp. 75-125 % range) are no longer applicable and appropriate,

too strict for higher sample size

Discussion started based on scientific papers

"Development of a content uniformity test suitable for large sample sizes"

- Limberg et al., Pharmeuropa Scientific Notes 2 (2006) 45ff
- Sandell, Vukovinsky et al. Drug Information Journal 40 (2006) 337ff
- Andersen et al., Drug Information journal 43 (2009) 287ff

→ A counting test for UDU giving the same assurance as the current harmonised pharmacopoeial test was proposed.

Current draft no. 1:

- Count the number of samples outside

T±L1 (=c1) e.g. corresp. to 85 -115 %

T±L2 (=c2) e.g. corresp. to 75-125 %

Acceptable number of dosage units outside these ranges

(extract of the complete table)

n =	80	100	200	500	1000	2000	5000	10000
c1	3	4	8	23	47	95	239	479
c2	0	0	0	1	2	6	16	34

Current draft no. 2

- Applicable typically for sample sizes >240
- Based on capability indices Cpk
- Compares output of in control process data to the alert or rejection limits
- Linked to a predefined sampling plan
- Concept already used in other industries

➢ Both drafts have been presented in a public hearing for interested parties on 29 Sept. 2010

Elemental Impurities (Heavy Metals chapter)

Mrs C. Vielle, September 2010

Elemental impurities

- Decision in 2008 to appoint a working party to deal with Heavy Metals as contaminants or catalysts (= HM Working party)
- Experts nominated in 2009

Terms of reference _

Metal catalysts or metal reagents:

- Drafting of a general chapter to implement the future ICH Q3D guideline on the specification limits for residues of metal catalysts or metal reagents (which shall be based on the CHMP guideline).
- In this context, identification of technical issues which need to be addressed by ICP working party such as sample preparation and instrumental determination by *atomic emission spectrometry*, *inductively coupled plasma - atomic emission spectrometry* and *inductively coupled plasma - mass spectrometry* and which would require an update of the respective general methods.

Terms of reference _
Metals as contaminants:

- See above: drafting of a general chapter to implement the future ICH Q3D guideline on the specification limits for metal as contaminants such as As, Hg, Pb and Cd or quality aspects (e.g. iron).
- Assess the capability of the current 2.4.8 chapter to appropriately limit the above mentioned priority metals
- and consider the introduction of instrumental screening methods, but allowing also other means of assuring compliance, where possible and justified.

Where do we stand?

- To define adequate and appropriate methods of analysis, the working party needs to know the limits which will be proposed by ICH Q3D.
- HM Working party has therefore started to draft a general chapter (using the 5.4 Residual Solvent as a model)

Use of Reverse Osmosis (RO) for production of Water For Injection (WFI).

Main monographs on water

- Purified Water (Ph. Eur. N°0008)
- Water for injections (Ph. Eur. N°0169)
- Water highly purified (Ph. Eur. N°1927)
- *These 3 monographs are listed in the Note for guidance on quality of water for pharmaceutical use.*

History (1/2)

1969

Ph. Eur. 1st edition:

Purified water

Prepared by distillation, ion exchange or suitable method

Ph. Eur. 1st edition 1973 supplement: Water for injection

1st publication – Distillation only

1983 - Ph. Eur. 2nd edition 5th Addendum: Water for injection, Revised monograph

Distillation only, but first discussions about RO – RO discarded not enough experience and concerns with biological quality of water

1999 – Preparation of Ph. Eur 4th Edition: Water for injection, Revised monograph under discussion.

Distillation only, but renewed discussions about RO – International seminar organized

History (2/2)

Jan 2002 - Ph. Eur. 4th edition: Highly purified water is introduced

Production by RO coupled with UF and deionisation is allowed

March1999

International seminar

Conclusion: Need for data and guidance

May 2002 – Adoption by CPMP/CVMP of Note for guidance on quality of water for pharmaceutical use

Where are we now? (1/2)

- Three monographs *[Purified Water (Ph. Eur. N°0008), Water for injection (Ph. Eur. N°0169), Water Highly purified (Ph. Eur. N°1927)]* , clear guidance for the use of the different water grades.
- In 2008-2009: Discussions were re-opened mainly requested by GMDP Inspectors Working Group
- Concerns from regulators are essentially similar since the 80s and linked to the microbiological safety of the water produced (see EMEA/CHMP/CVMP/QWP/28271/2008) .
- Has the main concern changed? Question was referred to Ph. Eur. for further investigations

Where are we now? (2/2)

- 1st objective: Gather data DONE!
  - How?: A survey is currently ongoing (deadline 30/05/10)
  - Key element: Participation from a maximum number of companies
  - What kind of data are expected?

- 2nd objective: Assess the data, compile them
  - Determine if these data are sufficient to initiate a revision process of the monographs ON GOING

Possible outcomes

- No interest or data are still insufficient
  - ➢ Situation will remain identical
- Appropriate data are provided
  - ➢ All options are open for revision of the different monographs