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RESIDUAL SOLVENTS CONTROLS EUROPEAN PHARMACOPOEIA PERSPECTIVE

18th Jan 2007

PDA /USP Joint Meeting

North Bethesda Marriott Hotel &
Conference Center

North Bethesda, Maryland

Development of a common European Standards for medicines

- 1964- need for common standards agreed between Six EEC states, CH and UK.
- Agreed to work on a new European Project
- European Pharmacopoeia Convention 1964 under the Council Of Europe (1948)
- One year before first EC Directive 65/65/EC
- 2004 Ph. Eur celebrated 40th Anniversary coinciding with revision in legislation



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European Pharmacopoeia Goals

- Harmonise the quality of medicines for human and veterinary use in Europe
- Contribute to the protection of Public health
- Promote free movement of medicines in Europe

Activities based on an international convention of the Council of Europe



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The Council of Europe



- 46 member states; 850million people



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The Convention

- Progressively elaborate a Pharmacopoeia which shall become **common** to the countries concerned...
- Take the necessary measures to ensure that the monographs...shall become the **official standard** applicable within the respective countries



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Partnership CoE/EU

- CoE Potential for work sharing among 46 European countries

Partial agreement offers flexibility of adherence

EU- Whole entity incorporated in Ph. Eur.
Convention

Ph. Eur. Has special mandatory status in
Directives 2001/83/EC, 2003/63/EC, and
2001/82/EC as amended



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MEMBERSHIP of Ph.Eur

- 35 member countries + the European Union
- Ph.Eur. is recognised as the only official Pharmacopoeia in Europe and has to be used for international trade.
- 16 observer countries + World Health Organisation
- Working languages: English and French



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5th Edition

- 5th Edition (June 2004 → 2007) :
updated 3 times per year
- Book, CD-ROM and on-line versions
- 2 initial volume 5.0 + a collection of 8 non cumulative supplements
- About 1800 Specific monographs including 120 on vaccines, 54 radio-pharmaceutical preparations, 180 herbal preparations and 11 homeopathic products.
- 15 general monographs, 28 pharmaceutical forms, 268 general methods
- 2210 reagents.



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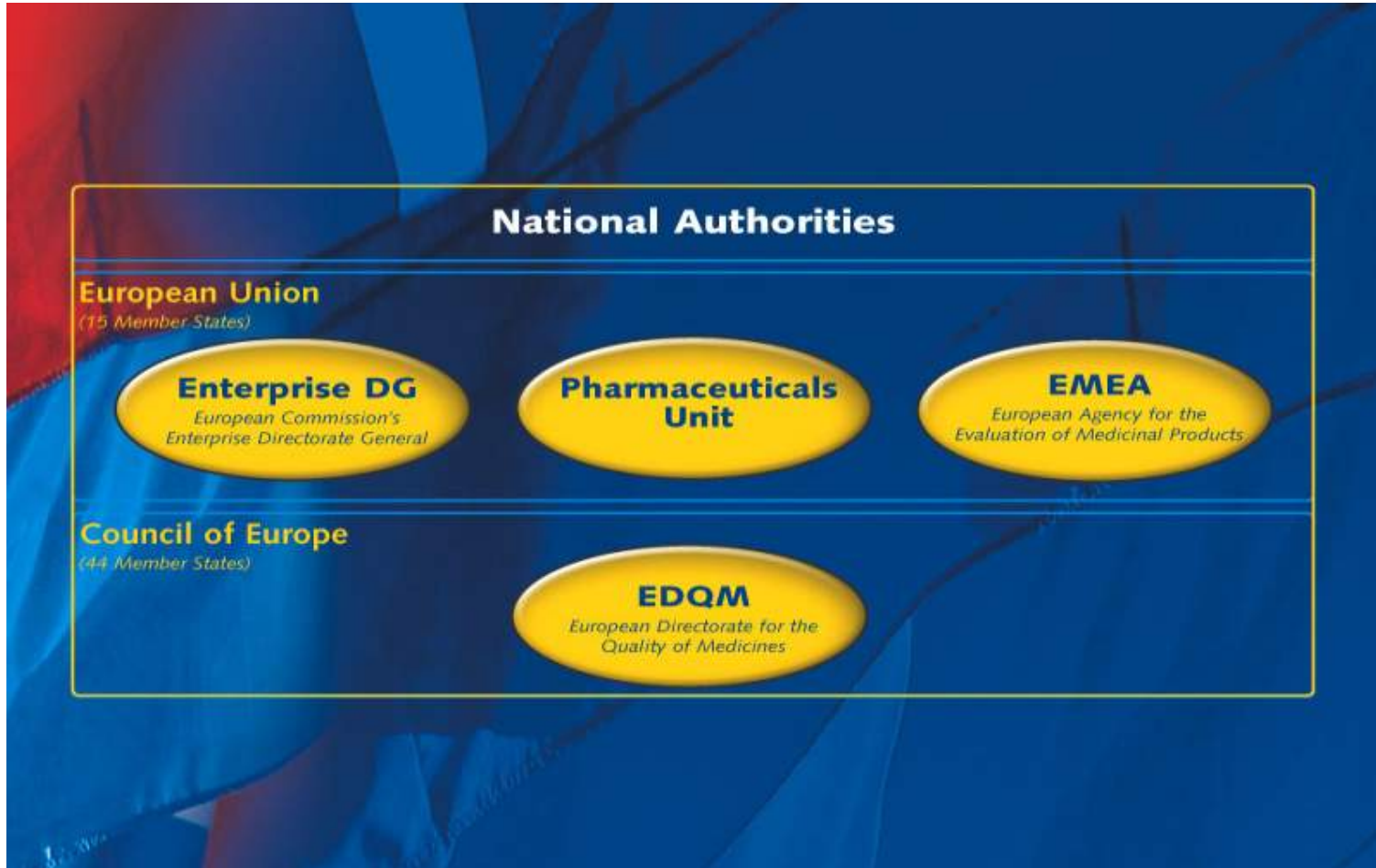
SIXTH EDITION

- Published July 2007
- Effective January 2008
- Continue tradition and new style
- 8 supplements 3 per annum
- Monographs modernised and harmonised where possible with other compendia



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EUROPEAN REGULATORY FRAMEWORK



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STRUCTURE OF THE Ph.Eur

- General notices
- General chapters
- General monographs
- General monographs on dosage forms
- Monographs on active substances and excipients
- Vaccines
- Immunoserum
- Radiopharmaceutical preparations
- Sutures
- Homoeopathic preparations
- Index



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RESIDUAL SOLVENTS AND THE PHARMACOPOEIA

- General Chapter 5.4 reproduces the ICH guidance verbatim
- Updated automatically as the guideline changes in line with the maintenance procedure
- General analytical method provided in G.C. 2.4.24 “Identification and control of residual solvents”



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RESIDUAL SOLVENTS AND THE PHARMACOPOEIA (2)

- General Chapters are not of themselves mandatory but reference in General Monograph (2034) “Substances for pharmaceutical use” makes the requirements mandatory.
- This GM (2034) covers any substance (organic or inorganic) used as active substances or excipients in medicinal products for human or animal use.
- Any solvents used in the preparation of such substances must be of suitable quality, including water
- Residual solvents are limited in accordance with the principles of GC 5.4 [ie ICH].



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RESIDUAL SOLVENTS AND THE PHARMACOPOEIA (3)

- GM 2034 applies to all substances which are covered by a specific monograph in Ph. Eur.
- Under consideration to remove this restriction i.e apply to all substances.
- However in practice competent authorities can, and generally do, apply exactly the same principles to non-pharmacopoeial substances.
- Implementation of GM 2034 in the 5th edition (2005) takes away the need to mention residual solvents in specific monographs, with occasional exceptions (see below).
- Freedom from solvents guaranteed by compliance with GM 2034



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RESIDUAL SOLVENTS AND THE PHARMACOPOEIA (4)

- General Chapter 2.4.24 provides the analytical methodology for RS control although 2034 allows the use of “other suitable (ie validated) methods”.
- (I) Provides a method for ID and control of Class 1 or Class 2 solvents in substances or products when solvent unknown
 - (II) Provides a limit test for Class 1 and Class 2 solvents
 - (III) Provides quantitative assay of Class 2 solvents when levels $> 0.1\%$ and for Class 3 solvents when required
- Uses head space injection GC using two chromatographic systems, A or B. A is the preference.



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RESIDUAL SOLVENTS AND THE PHARMACOPOEIA (5)

- Class 1 Solvents not usually mentioned in specific monograph unless it is known that certain sources are unavoidably prepared using a Class 1 solvent.
- Based on information from actual sources of substances, known to have been approved for marketing
- Information confirmed by the competent (regulatory) authorities
- Examples – certain of the older cytotoxic drugs where switch to alternative solvents has been unsuccessful
- Benzene limited in carbomer (2ppm – ICH limit)



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RESIDUAL SOLVENTS AND THE PHARMACOPOEIA (6)

- Class 2 solvents not mentioned in specific monographs because they are controlled by the general monograph in accordance with ICH limits
- Where levels higher than the ICH limits had been accepted by the CA's it was on a case by case basis for specific products in accordance with Option 2
- For these exceptions they would be granted based on specific product formulations (Policy decision 2005).
- Exception 1,4 dioxan specifically retained in monographs on ethoxylated substances (e.g polysorbate) since it is a specific quality marker.

Typical limit for dioxan 10ppm (ICH nmt 380ppm).



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RESIDUAL SOLVENTS AND THE PHARMACOPOEIA (7)

- Class 3 solvents would be mentioned in the monograph only where they occur at levels $> 0.5\%$ (ICH).
- This could be for feasibility and GMP reasons and would have been accepted case by case by a competent authority, on grounds of little safety concerns
- A new process could result in batches with lower amounts in practice resulting in the need for the CA to consider imposing a lower acceptance criterion.
- Special cases arise due to solvation effects during crystallisation resulting in high levels of Class 3 solvents being unavoidable in practice
 - examples
 - ethylacetate nmt 2.5%
in sultamicillin
 - acetone nmt 3.5%
in paroxetine



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RESIDUAL SOLVENTS SUMMARY

ICH guideline Q3C lays down levels of residual solvents acceptable in new active substances and their products

Guidance developed on the basis of chemical and toxicological evaluation for products

Logical to extend to established substances and products – EMEA QWP decision

Incorporated in Ph. Eur to form mandatory requirement in Europe

Independent validated methods available



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Questions?

Thank you for your attention.



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