Residual Solvents: A PhRMA Perspective

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A PhRMA Perspective

- History
- USP adoption
- The way forward
- Discussion points

Timeline

History

Timeline

1997 ICH guideline Q3C adopted by FDA, EMEA, MHLW for new products

1998 EMEA announced adoption of Q3C for existing products, effective July 2000

2000 Ph.Eur. chapters 5.4 and 2.4.24 take effect

2002 ICH revised limits for 2 solvents based on tox data

2005 USP proposed replacing Organic Volatile Impurities with Residual Solvents

→ Industry raised issues over differences from Q3C

2006 Revised USP proposal resolving many issues

2007 USP requirement to be effective in July; revisions take effect this December

Adoption for new products

- ICH guideline Q3C provides a consistent means of evaluating drug products to ensure patient safety
- Initially applied only to new products
- Submission in registrations → approval by regulatory agencies

Adoption for existing products

- Implemented by EMEA / PhEur for products marketed in Europe in July 2000
- Implementation pending by USP July 2007
- Regulatory submission may not be required, depending on registration; much of the documentation is internal
- Application to all products requires significant effort to implement

Global implementation steps

- Form global core team of experts
- Assign site implementers
- Obtain and review supplier data
- Obtain and review manufacturing data
- Perform qualification testing to confirm data, as needed
- Add tests and acceptance criteria, as needed
- Change suppliers, as needed
- Compile document packet
- Update registrations, as needed
- Establish maintenance strategy

Lessons learned

From EMEA/Ph.Eur. implementation, we learned:

- Products met Q3C without manufacturing changes
- Some changes:
  - New suppliers
  - Additional tests and limits
  - Registration updates
- *Q3C is a workable way of demonstrating control and ensuring patient safety*

What about OVIs?

What about OVIs?

- 5 vs. 60 solvents
- Different philosophical approaches
  - OVI is a traditional compendial requirement – a prescribed method and limit for each ingredient
  - ICH Q3C considers patient exposure to solvent in the drug product, cumulative approach allowed
- OVI conflicts with Q3C
  - A material might be acceptable by Q3C, but fail by OVI
- *Pharmaceutical manufacturers supported using ICH guideline Q3C in place of OVIs*

USP adoption

Proposal in PF 31(5), Sep-Oct 2005

- Chapter <467> changed to Residual Solvents
- Industry noted significant differences from ICH guideline Q3C:
  - Alteration of text →subtle changes in meaning
  - References to <467> added to individual monographs
  - Methods and limits to be submitted to USP to be added to monographs
  - Instructions for reporting levels (COAs) omitted
  - USP solvent reference standards required for testing

Industry positions on 2005 proposal

- ICH text should be preserved
- Monographs are not the right place for most solvent information; depends on manufacturer
- Methodology should be left to manufacturer
- ICH flexibility should be maintained
- *Revised proposal in PF 32(5), Sep-Oct 2006*

USP adoption

Proposal in PF 32(5), Sep-Oct 2006

- Many industry concerns addressed
- In some cases, method and limit must still be submitted for possible inclusion in monograph
  - If solvent limit above Q3C
  - Class 3 solvent above 0.5%, with specific method
  - If solvent not listed in Q3C
- Class 3 solvents must be tested by a specific method if LOD is not in monograph
- *Philosophical difference remains: USP sees a significant role for monographs in controlling solvents, while ICH controls through process*

Industry observations on methodology

- 3 methods are suitable for screening only
- Methods not validated for particular materials
  - Known issues with some solvents / matrices
- <467> allows other validated methods, but:
  - "…only the results obtained by the procedures given in this general chapter are conclusive."
  - Use of a different validated method would require method comparison
- *A manufacturer's solvent method, validated for a material, should not require comparison data to the methods in <467>*

The way forward

What pharmaceutical manufacturers have done…

The way forward

What pharmaceutical manufacturers have done…

- Complied with ICH guideline Q3C for hundreds of products
  - New products approved since 1998
  - All products marketed in Europe since 2000
- Identified methodology and established routine testing as needed
- Established processes to meet Q3C for new products and maintenance of existing products

The way forward

… and what we want to do.

- Continue to use the documentation, testing, and processes already created to comply with ICH guideline Q3C, apply to meet USP
- Conversely, we do not want to revisit established documentation, testing, and processes to comply with USP standards different from Q3C
- Implement Q3C for additional existing products in the United States to ensure patient safety
- *Build upon what has already been done*
- *Focus on patient safety*

Discussion Points

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- How can we minimize work which does not improve patient safety?
  - Revisions to existing documentation
  - Comparison studies to <467> methods
- Does the typical USP model for methods and limits work for ICH guidelines?
  - Q3C written to guide registration
  - Q3C states the goal, but allows flexibility to achieve the goal
  - “Official” methods vs. other validated method

Thank you!