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Residual Solvents Testing:

Supplier Qualification, Audits, & Acceptance by CoA

A Risk-based Approach to Assessing ICH Q3C Requirements

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Topics

- Scope of the Guideline
- Translating the Contents
- Possible Approaches to Compliance
- Remaining Questions
- References

Scope of the Guideline



Residual solvents in drug substances, excipients, and drug products are within the scope of this guidance.

Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. **It is only considered necessary to test for solvents that are used or produced in the manufacture or purification** of drug substances, excipients, or drug products. Although manufacturers may choose to test the drug product, **a cumulative method may be used to calculate the residual solvent levels in the drug product** from the levels in the ingredients used to produce the drug product. **If the calculation results in a level equal to or below that recommended in this guidance, no testing of the drug product for residual solvents need be considered.** If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. **Drug product should also be tested if a solvent is used during its manufacture.**

Translating the Contents



Solvent Classes per Guideline



Class 1 – Solvents to be avoided

- Known human carcinogens, strongly suspected human carcinogens, and environmental hazards



Class 2 – Solvents to be limited

- Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity



Class 3 – Solvents with low toxic potential

- Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs (permitted daily exposure) of 50 mg or more per day

Class 1 Solvents Recap

- API/Excipient Manufacturers can:
 - Use them as starting materials with justification
 - Maximum acceptable limits are according to Guideline
 - Benzene, 2 ppm
 - Carbon tetrachloride, 4 ppm
 - 1, 2-Dichloroethane, 5 ppm
 - 1, 1-Dichloroethane, 8 ppm,
 - 1, 1, 1-Trichloroethane, 1500 ppm
 - Must be routinely controlled in either:
 - an intermediate
 - final active substance.

Class 2 Solvents Recap

- Class 2 solvents used as starting material should be routinely controlled in an intermediate or in the final active substance and its limits should be set according to the relevant guideline.^{1, 2}
- Class 2 solvents used prior to the last step in the synthesis may be exempted from routine testing if it has been demonstrated that their content is not more than 10% of the acceptable limit.^{1, 2}
- Two Options for accepting results:
 - Option 1: Determine concentration of solvent(s) per item; each solvent < PDE limit
 - Option 2: Add concentration of solvent present in components; total for each solvent < PDE limit

¹CPMP/ICH/283/95 Impurities: Guideline for Residual Solvent

²CVMP/VICH/502/99 Guideline on Impurities: Residual Solvents

Class 3 Solvents Recap

- Regarded as less toxic and of low risk to humans
- Acceptable limits requiring no justification
 - ≤ 50 mg / day (corresponding to 5000 ppm or 0.5%)

ICH Supplier Requirements

- Class 1: Identify and quantify solvents
- Class 2: Name solvent(s) & indicate below limit
- Class 3: Not required to name & loss on drying $\leq 0.5\%$
- Class 2 or 3 above limits: Name solvent and quantify

Note: Drug manufacturer can use Option 2 (see slide 8) if limits are not met



Risk-based Strategies for Compliance



Surveying Supplier

- Develop supplier survey
- Survey APIs Suppliers for Residual Solvent Usage
- Determine Need for Surveying Excipient Suppliers
 - Prepare criteria for surveying (GRAS concepts?)
 - Survey only Suppliers of Specialty Items (ink, dyes)
 - Do not survey Suppliers of Common Items (NaCl, gases)
- Establish Criteria and Prioritize Suppliers to be Surveyed
 - Type of product (tablet, injection, inhalant vs. topical)
 - Formulation of product
 - Use of product (chronic vs. one-time)
- Evaluate Supplier Responses/Relationship
 - Develop risk strategy

Strategy 1 – No Solvents Used

- Survey Data Indicates:
 - Synthesis process does not use solvents
- Risk Assessment
 - Accept supplier statement “no solvents present”
 - Do not test
 - Consider periodically confirming supplier statement

Strategy 2 – Class 1 Solvents Used

- Survey Data Indicates:
 - Synthesis process uses Class 1 solvents
- Risk Assessment:
 - Develop/validate test method(s) for solvent(s)
 - Test on incoming until supplier history is established
 - Accept on CoA
 - Consider periodically confirming supplier results

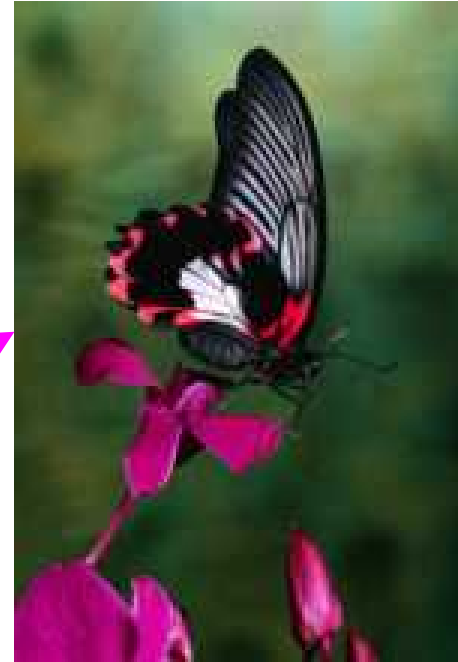
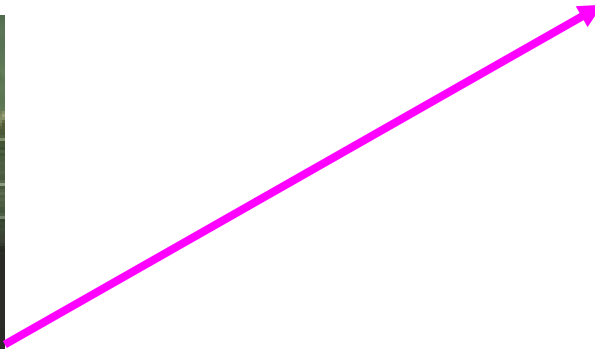
Strategy 3 – Class 2/3 Solvents Used & Removed

- Survey Data Indicates:
 - Class 2/3 solvents used but removed downstream
 - Validated method used by supplier
- Risk Assessment
 - Accept supplier material on CoA
 - Consider periodically confirming supplier results

Strategy 4 – Class 2/3 Solvents Present

- Survey Data Indicates:
 - Class 2/3 solvents are present
 - Supplier states levels are below ICH threshold
- Risk Assessment
 - Assume the ingredient is all solvent
 - Determine amount of solvent in final product (calculation)
 - Option 2 requirements met – do not test

Transitioning from OVI to ICH



Transition Scenario 1

USP OVI Requirement*

- Supplier indicates:
 - No solvents present

- Risk Assessment:
 - No testing required
 - Eliminate testing requirements

* Monograph and/or registration filing require OVI

Transition Scenario 2

USP OVI Requirement*

- Supplier indicates:
 - Solvent(s) other than OVI are used
- Risk Assessment:
 - Validate/verify method
 - Establish specification
 - Register methods, specifications and testing results
 - Establish supplier history
 - Accept supplier CoA
 - Consider periodically confirming supplier's result

* Monograph and/or registration filing require OVI

Remaining Questions



- Are limit tests acceptable for excipients and APIs since ICH limits are for Dosage Form?
 - Patients will never be exposed to the raw material
- What can be exempted from the requirement?
 - Topicals, Gases, other
- Should there be different criteria for the same item depending on its use?
 - Item can be used as API, Excipient, Diluent
- Can data from other industries be used to establish the safety of an item?
 - Sugar, Salt, Citric Acid, Vitamins, used more prevalently by Food Industry

- How should the Agency be informed of changes?
 - PAS, CBE-30, CBE-0, Annual Report, Design Space
- How should it be reflected in the regulatory filing?
 - Meets ICH, Solvent and Limit, Other
- Other Questions?

References

- ICH Q3C
- Federal Register December 24, 1997
- FDA Guidance: Q3C Impurities, Residual Solvents
- EP General Chapter 5.4, Residual Solvents
- USP General Test Chapter <467>
- CPMP/ICH/283/95
 - Annex 1: Specifications for Class 1 and Class 2

Thank You

