Connecting People, Science and Regulation

ICH Q7 Chapter 14: Rejection & Reuse of Materials

PDA - PIC/S
ICH Q7 Training 01/2014

Disclaimer

- **The slides set is based on the training sessions developed and performed by the members of the ICH Q7 Expert Working Group (EWG) on ICH Q7 2001/2002**
- **The slides have been updated 2012 and represents the views of the PDA / PIC/S committee for the purposes of a general training for regulators and industry.**

◆ ***We focused on elements in ICH Q7 where further explanation and/or clarification is useful.***

Content

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- **Reprocessing** *(14.2)*
- **Reworking** *(14.3)*
- **Recovery of materials and solvents** *(14.4)*
- **Returns** *(14.5)*

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14.1 Rejection

- **Intermediates and APIs failing to meet established specifications** *(14.10)*
  - Should be identified and quarantined
    - Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use. *(8.17)*
  - Can be reprocessed or reworked
- **Final disposition should be recorded** *(14.10)*

Reprocessing & Reworking in the Pharmaceutical Industry

Drug (medicinal) Product	API
• Often no clear distinction between reprocessing and reworking	• Clear distinction between reprocessing and reworking
• Reprocessing is atypical	• Reprocessing is typical
• Reprocessing rarely or not possibly improves drug quality	• Reprocessing generally improves API quality

Definition Reprocessing

- Introducing an intermediate or API, ***including one that does not conform to standards or specifications***, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the ***established manufacturing process***

Definition Reworking

- **Subjecting an intermediate or API *that does not conform to standards or specifications* to one or more processing steps that are *different from the established manufacturing process* to obtain acceptable quality material**
  - *e.g., recrystallizing with a different solvent or using charcoal that was not part of the established process*

Reprocessing versus Reworking

Reprocessing	Reworking
• **Intermediates and APIs**	• **Intermediates and APIs**
• **Conforming or non-conforming batches** (e.g. increase batch size, specific customer requirement, tailings if subjected to a manufacturing step)	• **Only non-conforming batches** (changes from original process e.g. increased filtration may be conducted to meet specific customer specifications)
• **Subject batch to one or more steps that are part of established manufacturing process**	• **Subject batch to one or more steps that are different from established manufacturing process**

14.2 Reprocessing

- **Reprocessing of intermediates and APIs is generally acceptable** *(14.20)*
- **If reprocessing is used for a majority of batches, it should be included as part of the standard manufacturing process** *(14.20)*
  - *It is not accepted to repeatedly reprocess until an acceptable material is obtained*
  - *It is an expectation that materials at the end of the expiry date are not routinely reprocessed; usually regulatory approval needed*

14.2 Reprocessing

- **Continuation of a process step after an in-process control test shows it is incomplete is considered part of the normal process, not reprocessing** *(14.21)*
  - *e.g. drying till an in process specification (e.g. moisture content)*
- **Introducing unreacted material back into a process and repeating a chemical reaction is considered reprocessing unless it is part of the *established* process** *(14.22)*

14.3 Reworking

- **Reason for non-conformance should be investigated before reworking batches** *(14.30)*
- **Reworked batches should be subjected to *appropriate evaluation*, testing, stability testing, if warranted, and documentation to show that the reworked batches are of equivalent quality to that produced by the original process** *(14.31)*
  - *Accelerated stability testing needs to be considered and the batch released after the results are available*

14.3 Reworking

- **Impurity profile of each reworked batch should be compared against batches manufactured by the established process** *(14.32)*
- **Additional analytical methods may be needed if routine methods are inadequate to characterize reworked batches** *(14.32)*

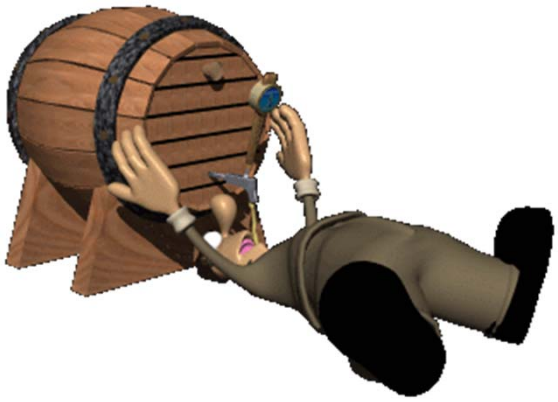
14.3 Reworking

- **Concurrent validation is often appropriate** *(14.31)*
  - *The effectiveness of rework should be proven. By definition reworking is not a routine activity and not to be validated but verified. However if it gets routine it's a change in the manufacturing process.*
- **Protocol should define** *(14.31)*
  - Rework procedure
  - How performed
  - Expected results
- **Report on conclusion** *(14.31)*

14.4 Recovery of Materials / Solvents

- **Recovery of solvents, reactants, intermediates or the API from *mother liquor* or filtrate is acceptable provided** *(14.40)*
  - Approved procedures exist for recovery
  - Recovered materials meet specifications and are suitable for their intended use
  - *The use of the mother liquor should be part of the registration*

EWG's initial definition of mother liquor



14.4 Recovery of Materials / Solvents

- **Definition Mother Liquor:**
  The residual liquid that remains after crystallization or isolation processes
- **May contain**
  - Unreacted materials
  - Intermediates
  - Levels of the API and/or impurities

14.4 Recovery of Materials / Solvents

- **Solvents can be recovered and reused in the same processes or different processes provided recovery procedures are *controlled and monitored* *(14.41)***
- **Ensure solvents meet *appropriate* standards before reuse or co-mingling *(14.41)***

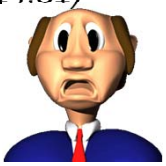
◆ ***Appropriate Standards?***
Recovered solvents may need different specifications from virgin solvents such as absence of process related impurities

14.4 Recovery of Materials / Solvents

- **Fresh and recovered solvents can be combined if adequate testing shows suitability for use in manufacturing** *(14.42)*
  - ◆ *Related to solvent recovery confidence of effectiveness is expected*
- **Use should be adequately documented** *(14.43)*
  - ◆ *It is important to keep the traceability of the batches of the solvents*

14.5 Returns

- **Returned intermediates and APIs should be identified and quarantined** *(14.50)*
  - *It needs to be understood what really happened outside of the companies control*
  - *Consider if the original seal is still there*
- **Any *doubt* regarding quality due to conditions of storage, shipping or handling** *(14.51)*
  - Reprocess
  - Rework
  - Destroy



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14.5 Returns

- **Records of Returns should include** *(14.52)*
  - Name and address of consignee
  - Intermediate or API
  - Batch number
  - Quantity returned
  - Reason for return
  - Final decision regarding use, recovery or disposal of returned material
  - *Consider to make a full testing of a returned batch*

Key Messages

- **Reprocessing**
  - Generally an acceptable way
  - If used routinely it should be part of the established process
  - Normally covered by the existing registration
- **Reworking**
  - Alternative way of treating material which may not initially have met the specification
  - Only be used after an extensive evaluation
  - May need additional approval by the authorities
- **Recovery**
  - Limited to specific and predetermined situations (e.g. solvents or second crops of crystals)
  - For the API itself approval of the authorities is required

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Acknowledgement

- **This version represents an update of the 2001/2002 version by ICH Q7 EWG members organised in a joint initiative between PDA and PIC/S developed in 2012**
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  - Mikael Le Bihan (co-chair)
  - Karl-Heinz Bender
  - Rosimeire Pereira Alves da Cruz
  - Graeme McKilligan
  - Jacques Morenas
  - Edwin Rivera
  - Georg Roessling
  - Lionel Viornery

  with input form members of the PIC/S Q7 expert cycle and other PDA volunteers


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