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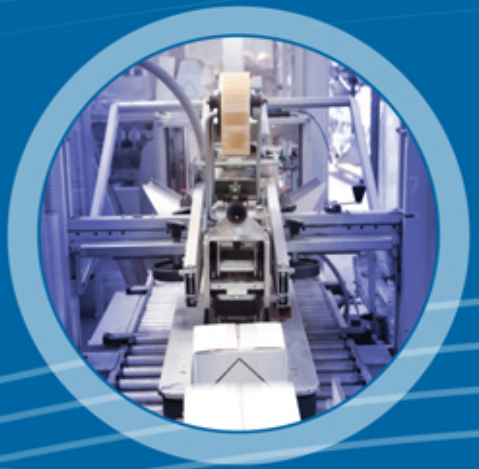
ICH Q7 Chapter 8: Production & In-Process Controls



PDA - PIC/S ICH Q7 Training

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- **Time Limits** *(8.2)*
- **In-process Sampling and Controls** *(8.3)*
- **Blending Batches of Intermediates or APIs** *(8.4)*
- **Contamination Control** *(8.5)*

8.1 Production Operations

- **Raw materials should be weighed or measured under appropriate conditions that do not affect suitability for use** *(8.10)*
  - *Goal: Avoid contamination and cross-contamination*

- **Weighing and measuring devices should be of suitable accuracy for intended use** *(8.10)*
  - *Depending on process requirements*

8.1 Production Operations

- **Materials subdivided for later use should be stored in suitable containers identified with** *(8.11)*
  - Material name and/or item code
  - Receiving or control number
  - Weight or measure of material in new container
  - Re-evaluation or retest date if appropriate

◆*Potential issues of mixing different materials, mislabeling, storage conditions*

8.1 Production Operations

- **Critical weighing, measuring, or subdividing operations should be *witnessed* or subjected to an equivalent control** *(8.12)*

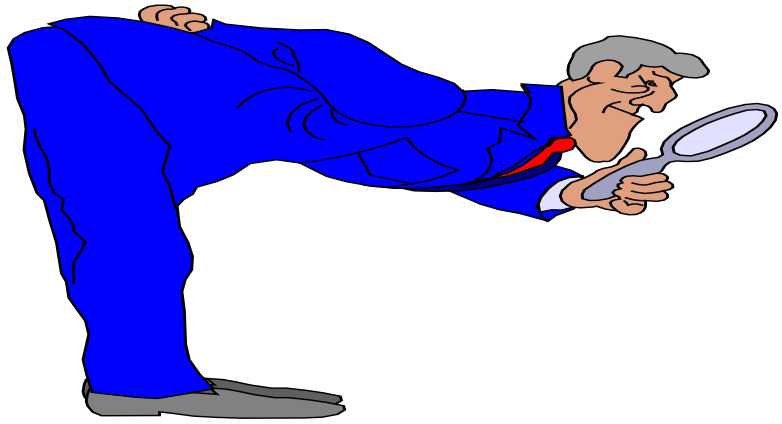
Witness: In law means to have been present and observed.

Within ICH: It is meant to be equivalent to supervision AND peers could also fulfil the role

- ***Two independent checks**: In case of a electronic print out you also need a check by an operator of the print out to be valid*

8.1 Production Operations

- **Other critical activities should be witnessed or subjected to an equivalent control** *(8.13)*
  - ***Equivalent control** means confirmation by a second independent means, e.g. printout from electronic or mechanical source.*
  - *Critical process parameters (CPP) have to be confirmed frequently. Documented evidence to demonstrate full control in line with the process requirements*

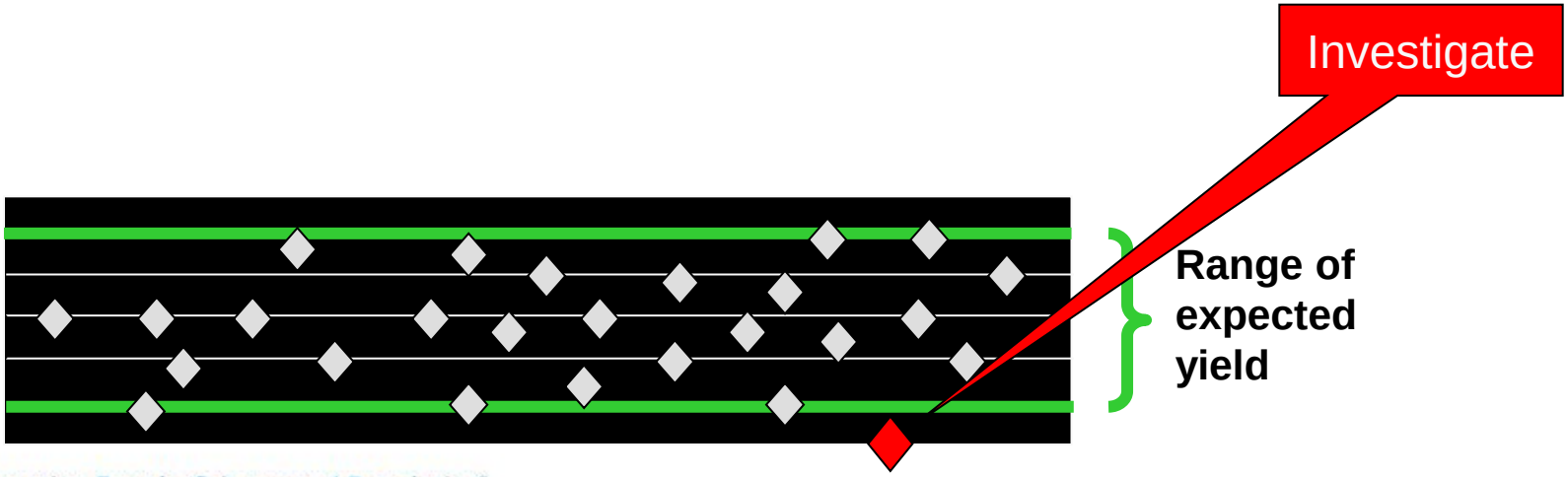


8.1 Production Operations

- **Actual versus expected yields**
- **Expected yields should take into account**
  - Heels added or removed, carryover
  - Chemistry
  - Campaign length
- **Deviations from expected ranges should be investigated for critical steps** *(8.14)*
  - *It is expected that manufactures have an understanding of the process capabilities / requirements and of the process critical steps and ranges*

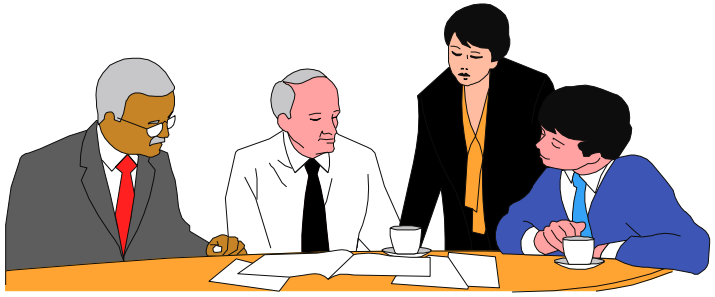
Example: Yield Deviations

- **Deviations in yields *associated with critical process steps* should be investigated to determine impact or potential impact on quality of affected batches** *(8.14)*



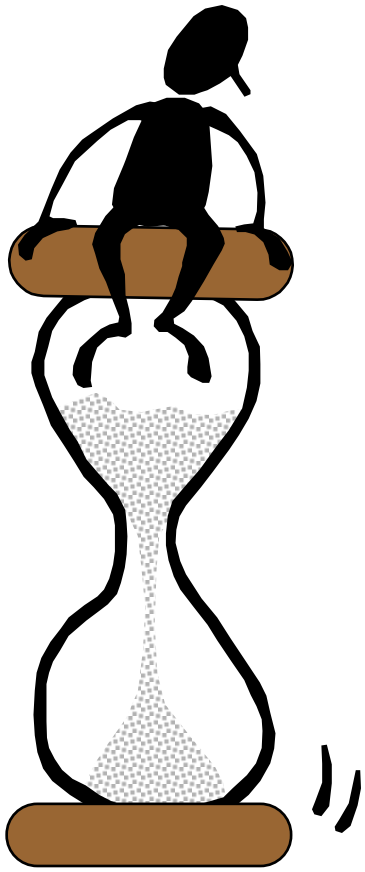
8.1 Production Operations

- **Deviations**
  - Any deviation documented and explained *(8.15)*
  - **Critical** deviations investigated and documented *(8.15)*
  - *The level of effort and formality commensurate with the level of risk (ICH Q9)*
- **Status of major equipment should be indicated on equipment itself or by** *(8.16)*
  - Appropriate documentation
  - Computer control systems, or
  - Alternative means
  - *The benefit is to avoid misunderstanding or misuse of the equipment*



8.2 Time Limits

- **Should be met if specified in the master production instruction** *(8.20)*
- **Deviations from time limits should be documented and evaluated** *(8.20)*



- *Time limits might not be always necessary when a process is controlled via target value*
- *However it's important to consider the typical time needed and the cause of deviation from typical times*

8.2 Time Limits

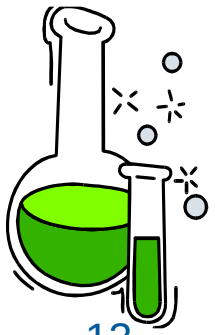
- **Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use** *(8.21)*

- *Supported by appropriate analytical data and/or justification*

8.3 In-Process Sampling & Controls

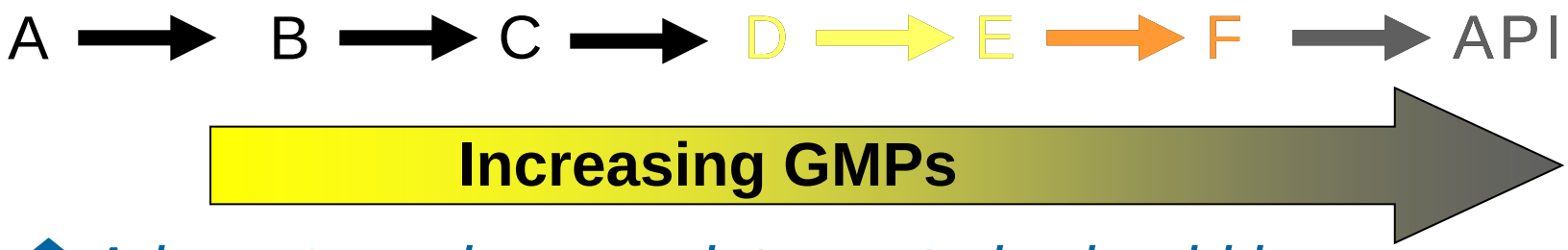
- **In-process controls and acceptance criteria should be defined based on information gained during developmental stage or from historical data** *(8.30)*

  - *For old processes development data may not be available*
  - *Historical data must be reviewed based on a statistically significant data set*



8.3 In-Process Sampling & Controls

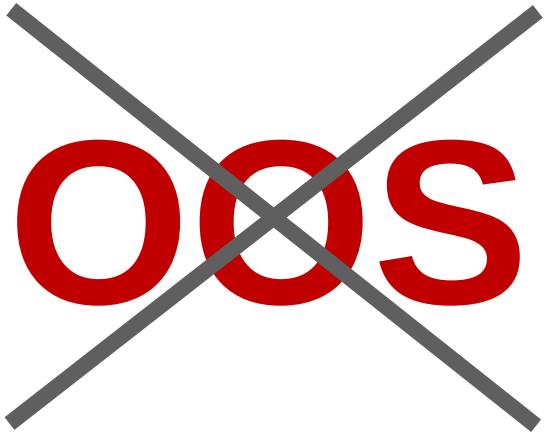
- **Less stringent in-process controls may be appropriate in early processing steps** *(8.31)*
- **Tighter controls may be appropriate for later processing steps (e.g., isolation and purification)** *(8.31)*



- *Adequate and appropriate controls should be implemented based on a clear understanding on the process e.g. where an impurity is created*

8.3 In-Process Sampling & Controls

- **Out-of-specification (OOS) investigations are not normally needed for in-process tests performed for the purpose of monitoring and/or adjusting the process** *(8.36)*
  - *There is the need to understand each result and question any atypical result. However if there is an OoS expected (e.g. 'Dry until 1.3% water content') a formal investigation is not needed*



8.4 Blending of Intermediates/APIs

- **Blending defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API** *(8.40)*
- **Activities not considered blending include** *(8.40)*
  - Routine In process mixing of fractions from single batches - final combination must meet specification
  - Combining fractions from several batches for further processing

8.4 Blending of Intermediates/APIs

- **Acceptable blending operations include but are not limited to** *(8.42)*
  - Blending of small batches to increase batch size
  - Blending of tailings from batches of the same intermediate or API to form a single batch

- *These should be on a routine planned and documented process*
- *There is no restriction on number of batches to be used*

8.4 Blending of Intermediates/APIs

- **Each batch introduced into a blend should be**
  - Manufactured by established process
  - Individually tested and found to meet appropriate specifications
- **The blend should**
  - Be tested for conformance to specifications *(8.43)*
  - Allow traceability back to individual batches *(8.44)*
  - Have an expiry or retest date based on the oldest *(8.47)*
- **No blending of OOS batches**
  - *Consider cases where specifications are met but the impurity profile is not the same*

8.4 Blending of Intermediates/APIs

- **Where physical attributes of the API are critical, blending operations should be validated to show homogeneity of the combined batch** *(8.45)*
- **Should include testing of critical attributes that may be affected by the blending process, such as** *(8.45)*
  - Particle size distribution
  - Bulk density and tap density

8.4 Blending of Intermediates/APIs

- **If blending could adversely affect stability, blended batches should be placed on stability program** *(8.46)*

  - *Consider stability studies using blended batches as representative of materials supplied to the customers*
  - *How to know that blending does not effects stability without conduction a stability program (more likely physical properties effected e.g. particle size)?*

8.4 Blending of Intermediates/APIs

- **Expiry or retest date of blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend** *(8.47)*

  - *Also this is a very clear statement it is often misunderstood*

8.5 Contamination Control

- **Residual materials can be carried over into successive batches of the same intermediate or API if** *(8.50)*
  - There is adequate control and carryover does not adversely alter the established API impurity profile
- **Examples of acceptable carryover include** *(8.50)*
  - Residue adhering to wall of micronizer
  - Residual layer of damp crystals remaining in a centrifuge bowl after discharge
  - Incomplete discharge of fluids or crystals from a processing vessel upon transfer of material to next step in process
- *The frequency of cleaning between batch of the same product should be established based on process knowledge to ensure the control of quality is maintained*
- *The level of carry over should be understand to take into consideration when assessing the impact of any kinds of deviations*

8.5 Contamination Control

- **Production operations should be conducted in a manner that prevents contamination of intermediates or APIs** *(8.51)*

  - *This relates to no process materials from other sources e.g. adequate containment needed and/or separation form other materials*

8.5 Contamination Control

- **Precautions to avoid contamination should be taken when APIs are handled after purification** *(8.52)*
  - *In general contamination should be prevented at all stages of manufacturing*
  - *There is no more processing to remove contamination*

Key Messages

- **All controls should be based on clear understanding of process capability and process requirements**
- **There should be a strong scientific bases for all decisions and controls**
- **Adequate sampling plans and procedures**
- **No blending of batches having an OoS**
- **Understand and manage risks to minimize contamination and cross-contamination**

ICH Q7 QaA *Clarification of Uncertainties*

1. Can yield ranges defined for the first batch differ from latter batches within a campaign?
2. What is meant by ‘appropriate specifications (of each batch) prior to blending’ [ICH Q7, 8.41]?

ICH Q7 Q&A, 2015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