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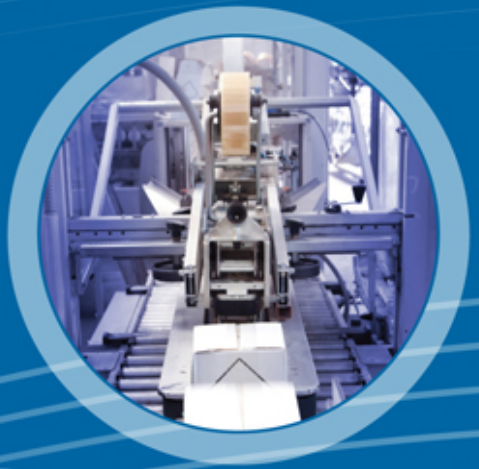
ICH Q7 Chapter 11:
Laboratory Control



PDA - PIC/S ICH Q7 Training

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- **Testing Intermediates & APIs** *(11.2)*
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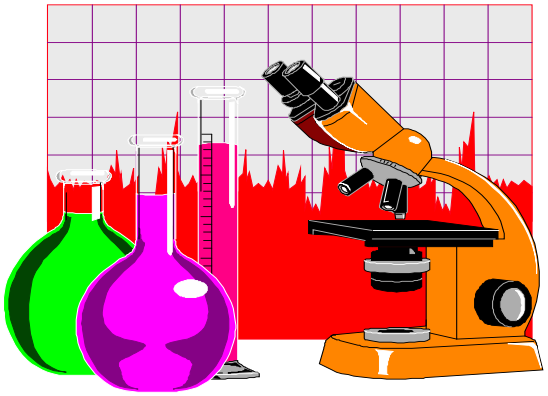
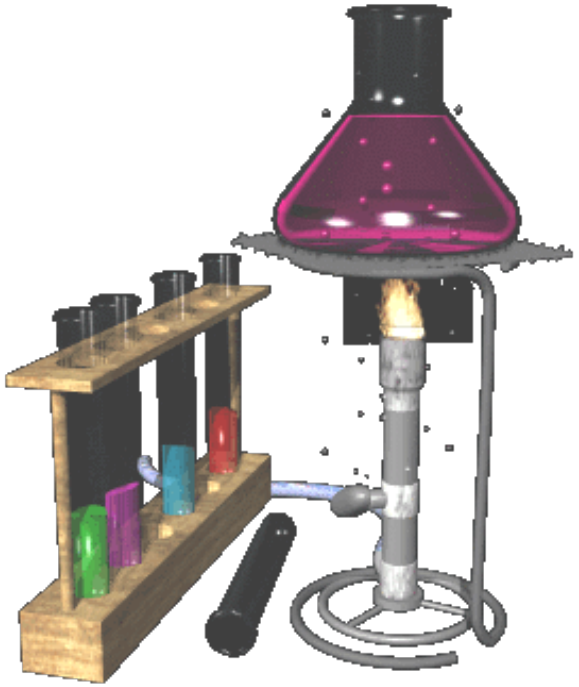
Laboratory Controls

Not appreciably different from expectations for laboratories that test medicinal products



11.1General Controls



- **Scope**
  - Raw materials
    - API starting materials
    - Reagents
    - Solvents
    - Process aids
  - Intermediates
  - APIs ◆ *(commercial supply, retained, stability samples)*
  - Packaging materials

11.1 General Controls

- **Documented procedures for** *(11.11)*
  - Sampling
  - Testing
  - Approval / Rejection
  - Recording Data
  - Storing Data
  - *Audit trail and data integrity must be given*
  - Out of Specification (OoS) results documented & justified

11.1 General Controls

- **Specifications, sampling plans, test procedures** *(11.12)*
  - Appropriate and scientifically sound
    - To ensure conformance to established standards
  - Prepared by appropriate unit
  - Reviewed and approved by Quality Unit(s)
  - Specifications and test procedures should be consistent with those in registration file
  - There can be specifications in addition to those in registration

11.1 General Controls

- **API specifications** *(11.13)*
  - Include control of impurities
    - Organic, inorganic, residual solvents, ...
  - If API has specifications for microbiological purity, appropriate action limits established for
    - Total microbial count
    - Objectionable organisms
  - If API has specifications for endotoxins, appropriate action limits established

◆ *Consider Pharmacopieal monograph guidance depending on the nature of the drug product*

11.1 General Controls

- **Documented at time of performance** *(11.14)*
  - *Quality systems should be capable of monitoring occasions where records are not completed at the time activities are performed*

- **Departures from procedures documented and explained** *(11.14)*

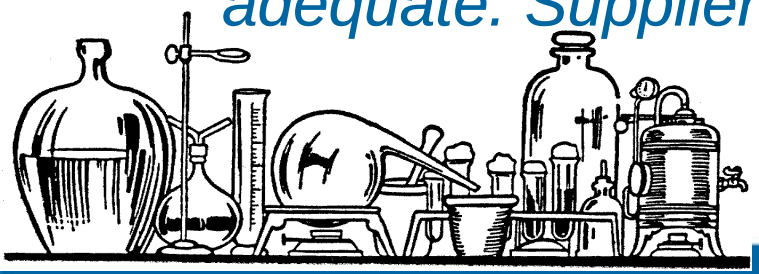
11.1 General Controls

- **Out of Specification (QoS) results** *(11.15)*
  - Procedure for investigation & documentation, including
    - Analysis of data
    - Assessment of significance of problem
    - Allocation of corrective action tasks
    - Conclusions
  - *The quality assurance should be involved in the assessment and review of the OoS before batch release*
  - Resampling / retesting performed according to procedure
  - *Re-sampling / Retesting plans and conclusions should based on a scientific justification*

11.1 General Controls

- **Reagents and standard solutions should be prepared and labeled following written procedures** *(11.16)*
- **“Use by” dates should be applied as appropriate** *(11.16)*

  - *It is **not** usual to have formal testing program to establish ‘use by’ date. Experience and scientific judgment is usually adequate. Supplier instructions should be followed at least.*



11.1 General Controls

- **Primary standard** *(11.17)*
  - Obtained from a recognized source
    - If official source: does not need to be tested
  - "In-house primary standard" *(11.18)*
    Prepared by independent synthesis or by further purification of existing production material or by use of a routine batch of adequate quality
    - This should be supported by an additional set of analytical tests, showing authentic material of established quality

◆ *It is best practice that this test typically should include an alternative test to quantify the purity*

11.1 General Controls

- **Secondary standard** *(11.19)*
  - A substance of established quality, as shown by comparison to a primary standard
  - Used as a reference standard for routine laboratory analysis (working standard)
  - Each batch of secondary standard compared to primary standard prior to first use
  - Periodically requalified according to written protocol
    - *To define the periodicity depends on e.g. stability, storage conditions*

11.2 Testing APIs & Intermediates

- **Each batch - appropriate tests conducted to determine conformance to specifications** *(11.20)*
  - Should be in compliance with registration

- *May be appropriate not to do complete testing after each step e.g. after blending, milling for parameters which had been demonstrated that they would not be affected*

11.2 Testing APIs & Intermediates

- **Impurity** *(see also ICH Q3/M7 series)*
  - An impurity is any component present in the intermediate or API that is not the desired entity
    - Residual Solvents *(ICH Q3C)*
    - Water
    - Metals *(ICH Q3D)*
    - Salts
    - Organics
    - Genotoxic *(ICH M7)*
    - Byproduct
    - Degradants
    - Reactants
    - Intermediates
    - Catalysts
    - Ligands
    - Process Aids

11.2 Testing APIs & Intermediates

- **Impurity profile (identified and unidentified) for API should be established** *(11.21)*
  - Identity (or some qualitative analytical designation)
  - Range observed
  - Classification (inorganic, organic, solvent, etc)
- **Impurity profile is for typical batch produced by specific controlled production process** *(11.21)*

Biotech APIs are covered in ICH Q6B

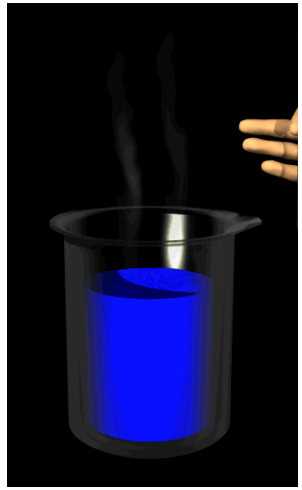
API manufacturing which do not include chemical synthesis (e.g. from herbal or animal tissue source) this is not always relevant

11.2 Testing APIs & Intermediates

- **Impurity profile for API** *(11.22)*
  - Compared at appropriate intervals versus profile in regulatory submission or historical data
    - *e.g. by online trending or the product quality review*
  - To detect changes resulting from modifications in raw materials, equipment operating parameters, production process
- **Appropriate microbiological tests on intermediates and APIs *where defined microbial quality is specified*** *(11.23)*

12.8 Validation of Analytical Methods

- **Methods should be validated** *(12.81)*
- **Suitability of all methods should be verified under actual conditions of use and documented** *(12.80)*
  - … where a Pharmacopeial method is used



12.8 Validation of Analytical Methods

- **Degree of validation should reflect purpose of analysis and stage of API production process** *(12.81)*

Typically 'Fit for purpose' methods
(demonstrating realistic results)

- Raw materials
- Solvents
- Packaging materials
- In process controls (IPC)

Typically requires analytical method validation
(according ICH Q2 A/B, Q6A/B)

- API Starting material
- Intermediates (exceptions for some non isolated intermediates)
- API

12.8 Validation of Analytical Methods

- **Validation should include consideration of characteristics included in ICH guidelines** *(12.81)* *(ICH Q2A & Q2B)*
- **Analytical equipment appropriately qualified before methods validation** *(12.82)*
- **Records maintained for modifications of validated methods, including** *(12.83)*
  - Reason for modification
  - Appropriate data to verify results are as accurate and reliable as established method ◆ follow the change control procedure and consider the need for revalidation

11.4 Certificates of Analysis (CoA)

- **Information on CoA & Label** *(11.41)*
  - **Name**
  - **Grade (where appropriate)**
  - **Batch No.**
  - **Release Date**
    - *The date of manufacturing is typically expected*
    - *Expiry date on the CoA & label*
    - *Retest date on the CoA and/or label*

11.4 Certificates of Analysis (CoA)

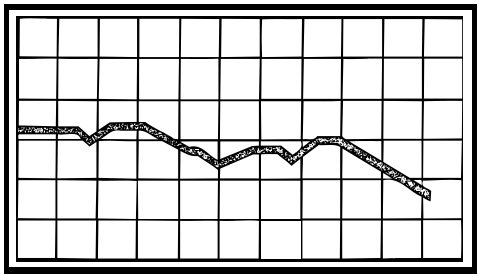
- **Information on CoA (original manufacturer)** *(11.43)*
  - Each test with acceptance limits & numerical results
    - *...rather than 'conform with specification' (exception e.g. IR)*
    - *The results reports should be inline with analytical method validation reporting e.g. 'less than limit of detection'*
  - Dated & signed by authorized quality personnel
  - Name, address, phone of original manufacturer
    - *Note the actual manufacturing site address not company only*

11.4 Certificates of Analysis (CoA)

- **Information on CoA (repacker/reprocessor)** *(11.44)*
  - Name, address, phone of repacker / reprocessor
  - Reference to original manufacturer
  - Original CoA attached
    - *Transcriptions should be clearly identified as such but not replacing the original*

11.5 Stability Monitoring of APIs

- **Documented on-going program** *(11.50)*
  - *Be compliant with the registration*
- **Monitoring to confirm** *(11.50)*
  - Appropriate storage conditions
  - Retest / expiry dates



- **Validated stability indicating test procedures** *(11.51)*
  - *Pharmacopeia test are not necessarily indicating stability*
- **Samples in simulated market container (material composition)** *(11.52)*

11.5 Stability Monitoring of APIs

- **First 3 commercial batches (normally)** *(11.53)*
  - If stable for 2 years, fewer may be used
- **Thereafter: 1 batch / year (if produced)** *(11.54)*
  - *For routine stability studies (monitoring) there is an expectation for studies to be conducted at long term conditions and not accelerated storage*
- **Tested annually (at least)** *(11.54)*
- **API with short shelf-life, more frequent testing** *(11.55)*
- **Consistent with ICH guidelines on stability storage conditions (as appropriate)** *(11.56)*
  - *Traditional validation, reprocessed / reworked (14.31), blending (8.46), repacked (17.50) batches are usually expected to put in stability*
  - *Overall: According to QRM (ICHQ9) specified and/or acceptable levels could depend on many parameters and should be decided on a case-by-case basis*

11.6 Expiry & Retest Dating

- **Based on data from stability studies** *(11.61)*
- **Preliminary dates may be based on pilot scale batches if** *(11.62)*
  - Manufacture simulates commercial scale
  - Quality represents commercial scale material

11.6 Expiry & Retest Dating

- ***Retest Date*** *- date when material should be re-examined to ensure still suitable for use under defined storage conditions*
- ***Expiry Date*** *- date designating time during which material expected to remain within specs if stored under defined conditions, and after which it should not be used*
- *ICH Q7 does not include guidance regarding user re-assigning retest date*
  - *Retest prior to use is commonly applied usually within 90 days after retesting*

11.6 Expiry & Retest Dating

- **Intermediates**
  - If with an expiry/retest date assigned and
  - If intended to be transferred outside manufacturer's material management system
  - Supporting stability information should be available

- *This does not require a stability monitoring program*
- *Could use initially published data. However retesting on actual product manufactured would typically be good practice*

11.7 Reserve / Retention Samples

For potential future evaluation of quality if necessary - not for stability testing purposes *(11.70)*

- **API with expiry date - keep longer of 1 year after expiry or 3 years after distribution** *(11.71)*
- **API with retest date - keep 3 years after distribution** *(11.71)*
  - *The availability of the API retain sample has to be considered between API and (typically) the drug product manufacturer*

11.7 Reserve / Retention Samples

For potential future evaluation of quality if necessary - not for stability testing purposes (cont'd) *(11.72)*

- **Stored in same, equivalent or more protective packaging material than marketed package**
- **Sufficient sample for at least 2 full compendial / specification analyses**
  - *The samples are stored in an at least monitored environment*

Key Messages

- **Expectation not appreciably different from expectations for laboratories that test medicinal products (e.g. Standards, OoS)**
- **Management of reference standards**
- **Clarity and integrity of raw data**
- **Methods validated or fit for purpose**
- **Expiry & Retest Dating based on data from real time stability studies**

ICH Q7 QaA *Clarification of Uncertainties*

1. What is expected in terms of impurities for APIs extracted from herbal or animal tissue origin [ICH Q7, 11.2]?
2. In cases where an API test method is changed, which method should be used for stability studies already in progress?
3. When is it acceptable for an API manufacturer to extend an API retest date [ICH Q7, 11.6]?
4. What is meant by ‘completely distributed’ in [ICH Q7, 11.71], which indicates reserve/retention samples should be retained for 3 years after the batch is completely distributed by the manufacturer?
5. Why does ICH Q7 permit the use of a packaging system for reserve/retention samples that is ‘more protective than the marketed packaging system’ [ICH Q7, 11.72]?

ICH Q7 Q&A, 2015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