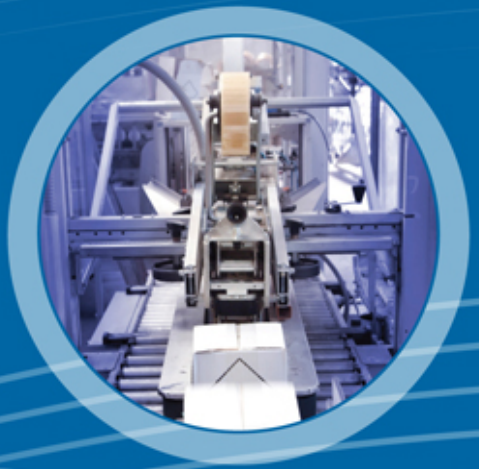
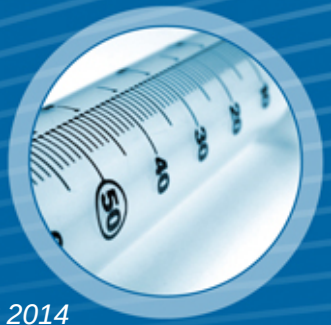
Connecting People, Science and Regulation®

ICH Q7 Chapter 6: Documentation, Records, Data Integrity





PDA - PIC/S ICH Q7 Training

Content

- **Documentation System and Specifications** *(6.1)*
- **Equipment Cleaning and Use Record** *(6.2)*
- **Records of Raw Materials, Intermediates, API Labeling and Packaging Materials** *(6.3)*
- **Master Production Instructions** *(6.4)*
- **Batch Production Records** *(6.5)*
- **Laboratory Control Records** *(6.6)*
- **Batch Record Review** *(6.7)*

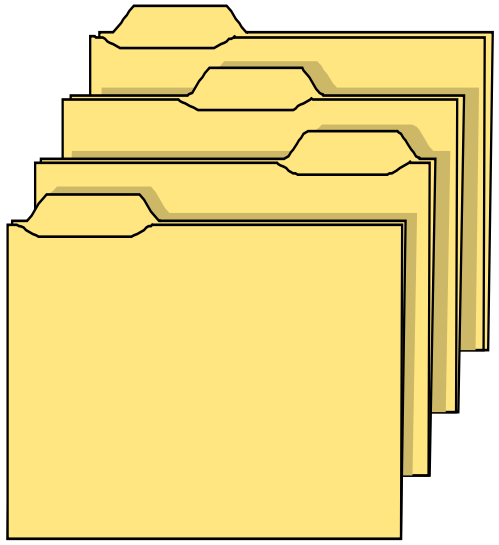
6.1 Doc System & Specifications

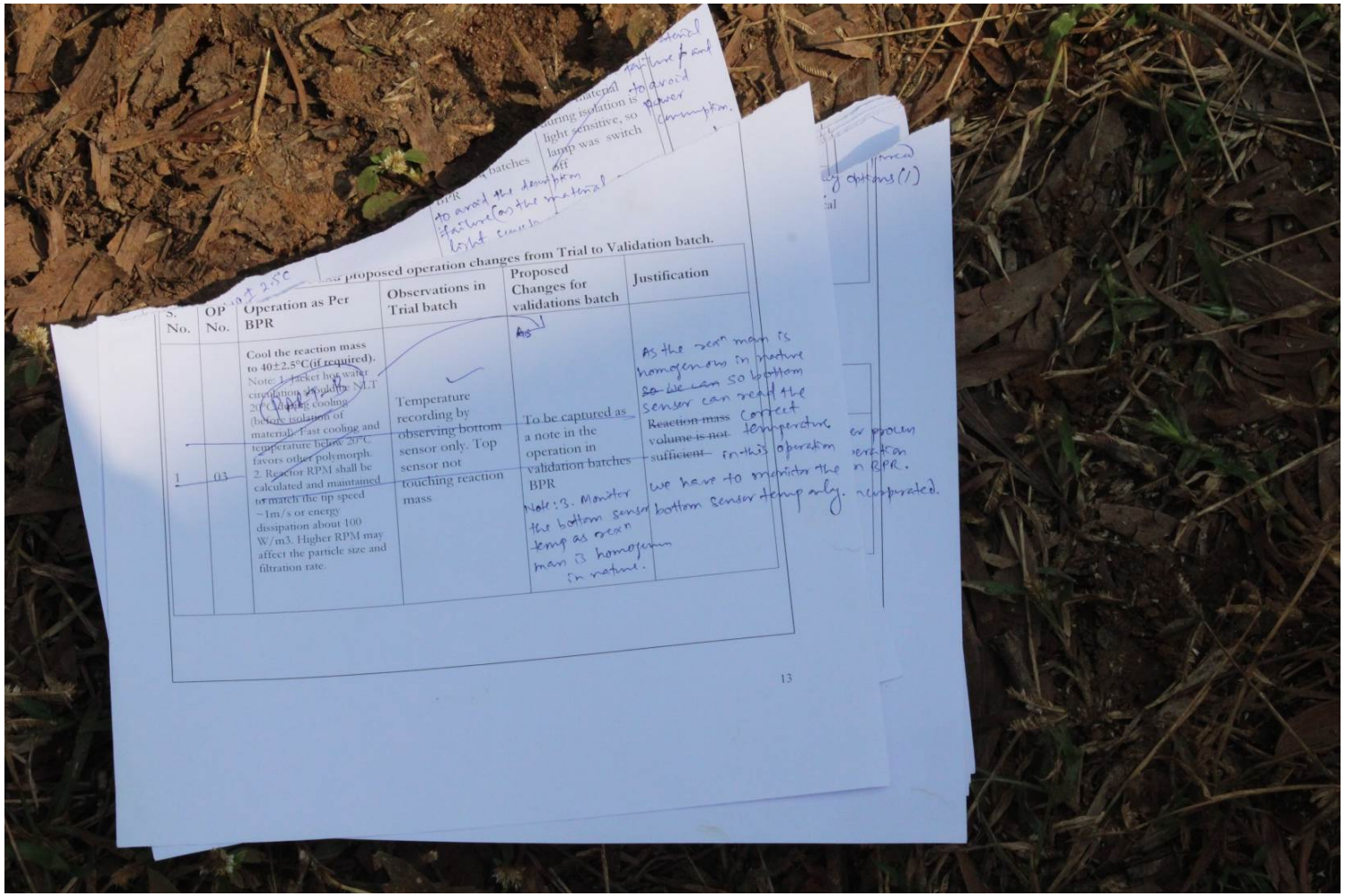
- **Record retention** *(6.13, 6.15)*
  - **What?**
    - Production records, Control records, Distribution records
  - **How long?**
    - At least 1 year after expiry date
    - At least 3 years after complete distribution of the batch for APIs with retest date

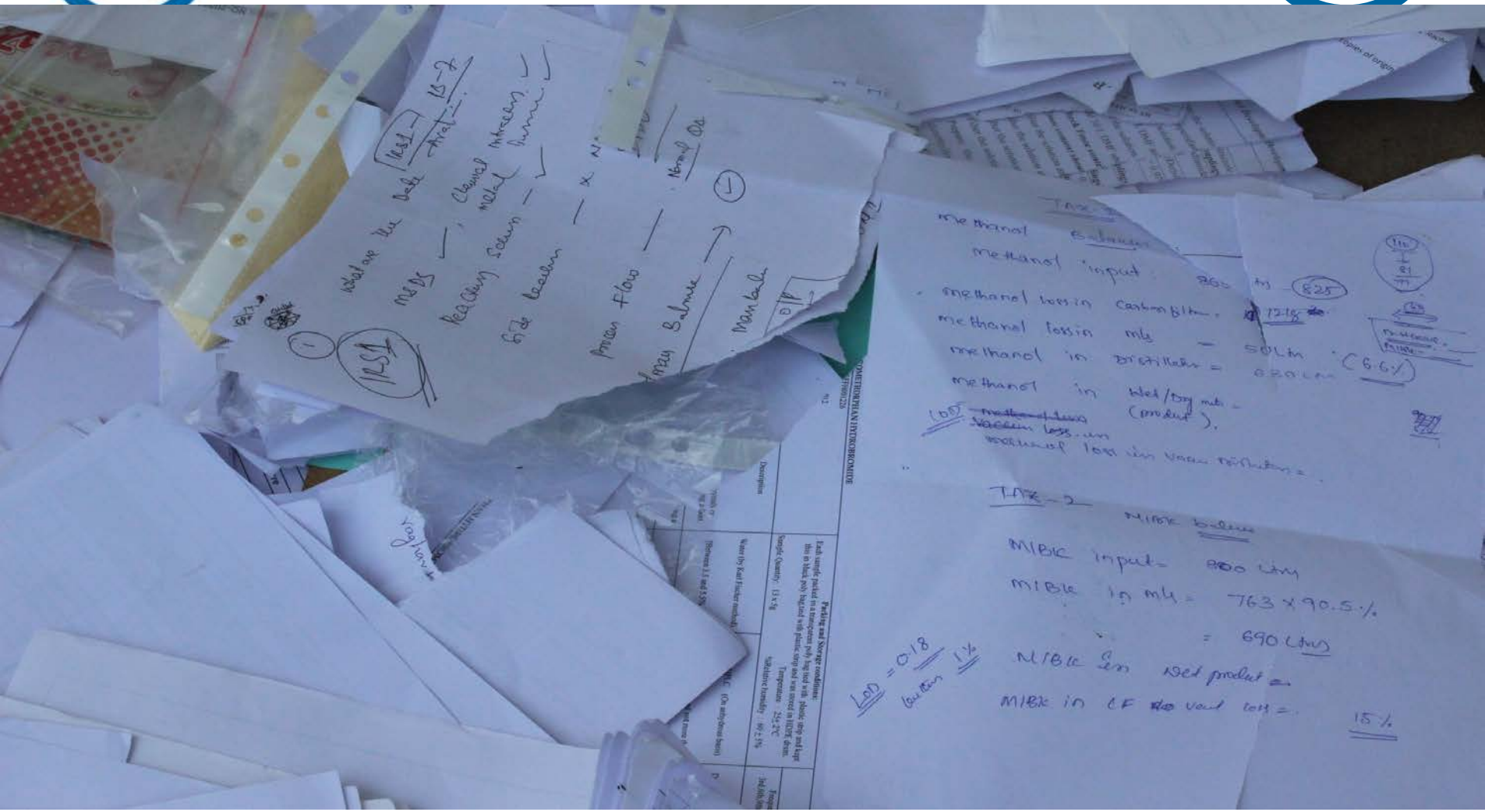
◆ *Legal provisions and/or costumer requirements may require a longer retention period to ensure availability of API records along the life of the drug product*

6.1 Doc System & Specifications

- **Should have procedures to describe**
  - Issuance, review, approval and distribution of documents *(6.10 / 6.11)*
  - Revision history *(6.12)*
  - Record retention
    - Documents can be in paper or electronic form




proposed operation changes from Trial to Validation batch.
S. No.
OP No.
Operation as Per BPR
Observations in Trial batch
Proposed Changes for validations batch
Justification
Cool the reaction mass to 40±2.5°C(if required).
Temperature recording by observing bottom sensor only. Top sensor not touching reaction mass
To be captured as a note in the operation in validation batches BPR
1
03
13

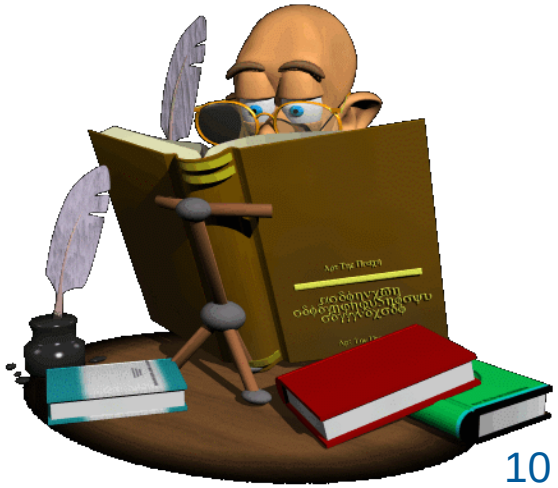

methanol
methanol input
methanol loss in
methanol loss in
methanol in
methanol in
MIBK input
MIBK in
MIBK in
MIBK in

6.1 Doc System & Specifications

- **Record retention** *(6.13-6.16)*
  - Records may be retained as originals or true copies (accurate reproductions)
  - Originals or copies should be available at the establishment where the activity occurred
  - Prompt retrieval from another location by electronic or other means is acceptable
  - If reduction techniques (microfilm) or electronic records are used, suitable retrieval equipment and means to produce hard copy should be readily available
- *Maintain the capability to read the records (e.g. IT)*

6.1 Doc System & Specifications

- **Entries in records should** *(6.14)*
  - Be indelible
    (incapable of being removed, erased or washed away)
  - Made in spaces provided
  - Made directly after performing the activity (2.15)
- *Back dated data question the reliability of all data*
  - Identify the person making the entry
- *It is a good practice a second person checking the raw data and the completed record*



6.1 Doc System & Specifications

- **Corrections** *(6.14)*
  - Leave the original entry readable
  - Dated
  - Signed

◆ *Anything more than obvious corrections there should be an explanation of the why.*

6.1 Doc System & Specifications

- **Signature can be** *(6.14)*
  - Full handwritten signature
  - Authenticated and secure electronic signature
  - Initials

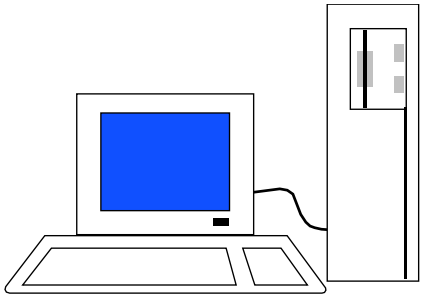
◆ *Initials are preferably unique to individuals*

◆ *A correlation list is needed to retrieve the full name*

6.1 Doc System & Specifications

- **Electronic signatures (if used) should be** *(6.18)*
  - Authenticated
  - Secure

◆ *An electronic signature should be equivalent security to a pen signature (e.g. unique to the individual)*



6.2 Equip Cleaning & Use Record

- **Records of major equipment** *(6.20)*
  - Use
  - Cleaning
  - Sanitization and / or sterilization (if performed)
  - Maintenance

- *Unique records per major equipment has shown to be helpful*
- *Traceability should also be available to auxiliary equipment*

6.2 Equip Cleaning & Use Record

- **These records should include** *(6.20)*
  - Date
  - Time (if appropriate)
  - Product
    - *including the manufacturing step*
  - Batch number
  - Person performing cleaning and maintenance

    - *Note: Making sure that the premises and equipment are maintained and records kept (2.3-7)*

6.2 Equip Cleaning & Use Record

- **Dedicated equipment** *(6.21)*
  - Individual equipment records not necessary if batches follow in traceable sequence
  - Records of cleaning, maintenance and use can be part of batch record or maintained separately

◆ *Attention should be given to auxiliary equipment*

6.3 Records of Materials

- **For raw materials, intermediates, API packaging and labelling** *(6.30)*
  - Name of manufacturer
  - Identity and quantity of each shipment of each batch
  - Name of supplier
  - Supplier’s control number or identity number
  - Number allocated on receipt
  - Date of receipt

6.3 Records of Materials

- **For raw materials, intermediates, API packaging and labelling** *(6.30) (cont.)*
  - Results of any test or examination and conclusion
  - Records tracing use
  - *Attention should be given on dispensing activities and with tailings*
  - Final decision regarding rejected materials
  - Master (approved) labels should be maintained for comparison to issued labels *(6.31)*

Clarification of terms

- **Master Production Instruction**
  - Master recipe or SOP
- **Batch Production Record**
  - Record of actual batch produced

No single preferred or correct system

- *Some companies include the blanks to be completed in the Master Instruction so that instructions and results are one document*
- *Some companies have instruction as one document and then a separate very short document for recording results*

Pay attention in case of updates of individual documents and other affected documents including registration filing

6.4 Master Production Instructions

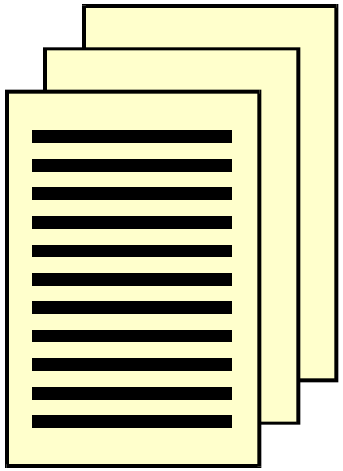
- **A Master Production Instruction should include** *(6.41)*
  - Name of intermediate or API being manufactured
  - Identifying document reference code
  - Complete list of raw materials and intermediates
  - Accurate statement of the quantity or ratio of each material to be used (including unit of measure)
  - Major production equipment to be used
  - Special notations or precautions ◆ *(e.g. safety instructions)*
  - Instructions for storage of intermediate or API where appropriate

6.4 Master Production Instructions

- **A Master Production Instruction should include**
  - Detailed production instructions
    - Sequences to be followed
    - Ranges of process parameters
    - Sampling instructions
    - In-process controls with acceptance criteria
    - Time limits
    - Expected Yield
  - *The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing*
  - *Separate Master Production Instructions (Master Batch Record) are needed for rework / reprocessing*

6.5 Batch Production Records

- **Should be prepared for each intermediate and API** *(6.50)*
- **Should include complete information relating to production and control of the batch** *(6.50)*



6.5 Batch Production Records

- **Prior to issuing for use** *(6.51)*
  - Checked that it is the correct version and a legible accurate reproduction of the master
  - Numbered with a unique batch or identification number, dated and signed

- *In case of an update of the Master Production Instructions ensure the unused copies of the older version are destroyed*

6.5 Batch Production Records

- **Documentation of completion of each significant step should include** *(6.52)*
  - Dates
  - Times, when appropriate
  - Identity of major equipment
  - Specific information for each material used
    - Weights or amount
    - Batch or identification number

◆ *In continuous production, the product code, date and time can serve as the unique identifier until final number is allocated*

6.5 Batch Production Records

- **Documentation of completion of each significant step should include** *(6.52)*
  - Actual results for critical process parameters
    - *Highlight critical parameters in the batch record in an appropriate manner*
  - Sampling
  - Signatures of persons
    - Performing each critical step in the operation
    - Directly supervising or checking critical step
  - In-process or lab test results
  - Actual yield

6.5 Batch Production Records

- **Documentation of completion of each significant step should include** *(6.52)*
  - Description of packaging and label
  - Representative label
  - Results of release testing
  - Any deviation noted
  - Investigation (if appropriate)
    - *Critical deviations should be investigated*
    - *Initiate investigations in a timely manner*
    - *Investigation should extend to other batches that may be associated*

6.6 Laboratory Control Records

- **Complete data from all tests conducted** ***(6.60)***
- **Description of sample** ***(6.60)***
  - Material name or source
  - Batch number or other distinctive code
  - Date taken
  - Quantity and date received for testing (where appropriate)
- **Reference to test method used** *(6.60)*
- **Weight or measure of sample used** *(6.60)*

6.6 Laboratory Control Records

- **Data on preparation and testing of** *(6.60)*
  - Reference standards, Reagents, Standard solutions
- **Complete record of raw data generated in addition to graphs, charts, and spectra** *(6.60)*
  - *Manage the transcription of data into an electronic system (e.g. LIMS) by appropriate controls*
  - *Traceability to the reference standard / spectrum used*
  - *There must be a clear and permanently recorded audit trail of any ammentments to raw electronic data*
- **Record of calculations including** *(6.60)*
  - Units of measure, Conversion factors, Equivalency factors

6.6 Laboratory Control Records

- **Statement of test results and comparison with acceptance criteria** *(6.60)*
- **Signature of person who performed each test** *(6.60)*
- **Date the test was performed** *(6.60)*
- **Date and signature of person reviewing for** *(6.60)*
  - Accuracy
  - Completeness
  - Compliance with established standards

6.6 Laboratory Control Records

- **Any modification to an analytical method** *(6.61)*
  - *Handle under change control*
- **Calibration of lab instruments** *(6.61)*
  - *Consider difference on 'calibration' versus 'verification' in a daily operations*
  - *Contractors should follow the companies procedures*
- **Stability testing on APIs** *(6.61)*
- **Out of specification (OoS) investigations** *(6.61)*

6.7 Batch Records Review

- **Review of batch production record and lab control records before batch is released or distributed** *(6.70)*
  - According to written procedure
  - Any deviations, investigations or OoS should be included in this review
    - *... and conclude before release*
- **Review by quality unit for critical process steps** *(6.71)*
- **Non-critical process steps may be** *(6.71)*
  - Reviewed by qualified production personnel
  - Following procedures approved by quality unit
    - *Independency of the review must be given*

6.7 Batch Records Review

- **Quality unit is responsible for releasing or rejecting all APIs** *(Section 2.22-1)*

- **Quality unit can delegate to production the authority for release of intermediates** *(6.73)*
  - Except intermediates that are sold ("*shipped outside the control of the manufacturing company*")

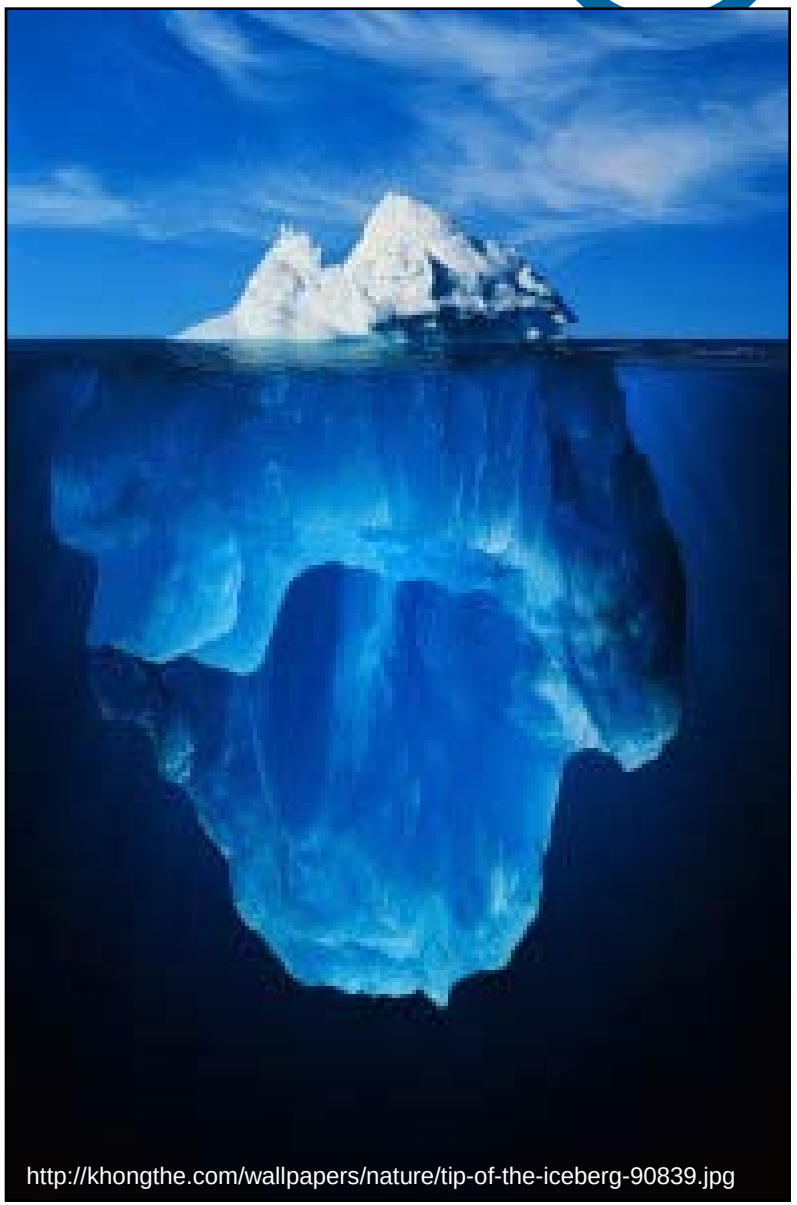
Data Integrity

CGMP – minimum requirements

Data integrity underpins CGMP

Lapses obscure other problems

Tip of iceberg



http://khongthe.com/wallpapers/nature/tip-of-the-iceberg-90839.jpg

What is Data Integrity?

***Data integrity* – requirements for complete, consistent, and accurate data.**

The concept of data integrity underpins CGMPs.

Applies to CGMP and Good Clinical Practice (ICH E6).

ALCOA
Attributable
Legible
Contemporaneous
Original or true copy
Accurate

Data Integrity Failure Examples

Common problems:

- Lack of controlled access to computer systems
- "Trial" HPLC injections
  - Trial injections in stand alone equipment, outside a quality structure
- Deleted data
- Not recording activities contemporaneously
- Backdating
- Fabricating data
- Copying existing data as new data
- Re-running samples

Why is data integrity important?

- **FDA depends on reliability of information to ensure drug quality**
- **A data integrity breach (records, electronic) breaks confidence**
- **FDA relies on firms to do the right thing when we are not there.**
- **FDA GMP surveillance inspections are usually focused to determine adherence to CGMPs, not to verify all data. Changing due to recent events.**

Data Integrity (e.g.)

- **Manufacturing**
  - Torn Batch Production Records found in a trash can. Upon further followup, we found that batches had failed blend uniformity testing
  - Records (e.g., batch, training) fabricated during the inspection.
  - Shadow/Show factories; equipment and records removed during inspection.

Examples of BDI

- **Quality Control Data**
  - Destruction of raw data not meeting specification
  - Missing raw data
  - Re-writing laboratory notebooks
  - Unjustified invalidation of data and re-testing without a laboratory investigation

Examples of BDI

- **Microbiological testing**
  - Growth on microbiological plates was observed and recorded as no growth
  - The plates were double checked by a second employee
  - This happened at three unrelated firms manufacturing sterile finished dosage forms

Examples of BDI

- **Making up records during an FDA inspection**
  - Batch records
  - Training records
  - Removing records and equipment before the inspection

Key Messages

- **Documents need to be managed: issued, distributed, when and where used, reviewed, archived etc.**
- **Documentation system needs to be described and maintained appropriately**
  - Equipment, Cleaning & Use Record
  - Records of Materials
  - Master production instructions, batch record and batch record review
  - Laboratory Control Records

Acknowledgement

The following training material was initially developed by the ICH Q7 EWG in 2001/2001. It has been jointly reviewed and updated by PIC/S and PDA in 2012 and 2014.

Special thanks to ICH and the ICH Q7 EWG as well as to all those who contributed to the update, in particular:

PIC/S:

- Carmelo Rosa, US FDA, Chairman of PIC/S Expert Circle on API
- Florence Benoit-Guyod, EDQM
- Rosimeire da Cruz, ANVISA / Brazil
- Mikael Le Bihan, ANSM / France
- Graeme McKilligan, MHRA / UK
- Jacques Morénas, ANSM / France
- Larry A. Ouderkirk, US FDA
- Rebecca Parrilla, US FDA
- Daniel Roque, ANSM / France
- Karen Takahashi, US FDA
- Lionel Viornery, ANSM / France
- Jeffrey Hodgson, PIC/S Secretariat

PDA:

- Stephan Rönninger, Amgen
- Georg Roessling, PDA
- Melanie Decker, PDA
- Karl-Heinz Bender, consultant
- Betsy Fritschel, Johnson & Johnson
- Edwin Rivera, Sanofi


PDA
SM
Parenteral Drug Association


PIC/S