PIC/S Guide for GMP and Data Integrity relating to microbiological quality
Expectations for Microbiology Laboratories

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• Regulatory Requirements:
  – PIC/S PE009-13
  – Impact on Micro Labs

• Data Integrity
  – PIC/S PI041-1
  – DI in the laboratory
6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3. **Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross-contamination.** In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination.

| New Text: 6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3. **Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross-contamination.** In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination. | Comment | Review the movement of all equipment into, within and out of the microbiology laboratory |
Chapter 6 – Documentation

<table>
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<tr>
<td>6.7 iv. <strong>A procedure for the investigation of Out of Specification and Out Of Trend results;</strong> 6.9 Some kinds of data (e.g. tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. <strong>Any out of trend or out of specification data should be addressed and subject to investigation.</strong></td>
<td>Need specific procedures for microbiology OOS/OOT investigation</td>
</tr>
<tr>
<td>6.8 Any Quality Control documentation relating to a batch record should be retained following the principles given in chapter 4 on <strong>retention of batch documentation.</strong></td>
<td>QC record retention of expiry +1 year or 5 years, whichever is the longest</td>
</tr>
<tr>
<td>6.17 The tests performed should be recorded and the records should include at least the following data: <strong>ix. Reference to the equipment used.</strong></td>
<td>Updates QC records to capture all equipment used in analysis</td>
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### Chapter 6 – Trending of Data

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<td>6.16 The results obtained should be recorded. <strong>Results of parameters identified as critical quality attributes should be trended</strong> and checked to make sure that they are consistent with each other. Any calculations should be critically examined.</td>
<td>What data will be trended? Who is going to trend the data? Critical data trended as made available (Annex 15)</td>
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### Chapter 6 – Culture Media

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<td>6.23 Culture media should be prepared in accordance with the media manufacturer’s requirements unless scientifically justified. The performance of all culture media should be verified prior to use.</td>
<td>QC of media required, for each batch made/supplied, before use</td>
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<td>6.24 Used microbiological media and strains should be decontaminated according to a standard procedure and disposed of in a manner to prevent the cross-contamination and retention of residues. The in-use shelf life of microbiological media should be established, documented and scientifically justified.</td>
<td>Manage waste Need data for media shelf-life</td>
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Testing

6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the Marketing Authorisation or technical dossier should be carried out according to the approved methods.

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<td>Method transfer guidance in clauses 6.37 – 6.41 &amp; Annex 15</td>
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Chapter 7 - Outsourced activities

Outsourced activities:

• Training
• Waste management
• Outsourced engineering for facilities and equipment
• Contract hire services
• Suppliers of materials and components
• Regulatory affairs consultants
• Outsourced vendor auditing
• Expert consultation
• Certification
• Calibration
• Testing and analysis
• Contract manufacture
• cleaning
So.....what’s data integrity?

“The extent to which all data are complete, consistent and accurate throughout the data lifecycle”

from initial data generation and recording through processing (including transformation or migration), use, retention, archiving, retrieval and destruction.

(PIC/S Good Practice for Data Management and Integrity PI 041-1)
## General issues observed

### Manipulation of data
- No testing conducted
- Not counting all colonies
- OOL data not being investigated
- Resampling/retesting without justification

### Incomplete Testing
- Samples not taken or “lost” in transit
- No reconciliation of samples
- Incubation conditions incorrect
- Using unvalidated test methods

### Poor test records
- Not recording all key test data
- Worksheets ripped up and replaced
- No reconciliation of forms used
- Lack of proper computerised system security
- Colony morphology not matching identification results

### Contributing causes
- Competence/supervision
- Lack of effective controls
- Secondary Checks
- Computerised system configuration
- Organisational Culture / resources
Creating the right environment

- Data management controls embedded in PQS
  - System design to ensure good DI practices
  - QRM approach to data integrity
  - Ongoing risk review data criticality/risk
  - Self Inspection
- Clear understanding of importance of data integrity at all levels of the organisation
- Internal reporting is encouraged
- Mature, open management approach to data integrity
Designing Paper systems which reduce opportunities for falsification

- Attributable
- Legible / Permanent
- Contemporaneous
- Original
- Accurate

Signatures, Aliases; signature logs

No pencil, white-out, soluble ink, SOP for corrections and archiving

Workbooks, forms controlled, verified ‘true copy’ scans

System design: documents in right place at right time, clocks on wall, control of blank forms

Reflective of the observation; Data checking, raw data verification

SOP for corrections and archiving

No pencil, white-out, soluble ink, SOP for corrections and archiving

Workbooks, forms controlled, verified ‘true copy’ scans

System design: documents in right place at right time, clocks on wall, control of blank forms

Reflective of the observation; Data checking, raw data verification
Designing Electronic systems which reduce opportunities for falsification

- **Attributable**
  - User access control; e-signatures; metadata

- **Legible / Permanent**
  - Data security, audit trails; back-up; sys. validation

- **Contemporaneous**
  - Metadata which permits reconstruction
  - Auto-saving; step-wise recording; System clock synchronisation

- **Accurate**
  - Data capture; manual data entry; source data & audit trail review

- **Original**
  - System clock synchronisation
Risk management approach to Data Integrity

- **Data Criticality**
  - CQA Batch release data > cleaning records
  - Data relating to product quality/safety

- **Data Risk**
  - Vulnerability of data to alteration, deletion, recreation, loss or deliberate falsification

- **Outcome** - Effective control strategy to manage identified risks
DI controls – manual test methods

Sampling Procedures
- Sampling schedule/plans
- Training of technicians
- Sample forms
- Detailed collection methods
- Identity of sampler recorded

Test methods
- Test volumes/weights recorded
- Calibrated equipment used
- Reference to all reagents
- Reference to validated methods/dilution factors
- Samples processed under clean conditions, e.g. LAF
- Negative controls for processed samples
- Identity of tester/equipment recorded

Incubation
- Incubation records maintained
- Min/max incubation time defined and validated
- All transfers/sub-culturing recorded
- All incubated samples tagged and identified

Reading results
- Technicians trained in detection, enumeration and morphology – clear SOPs, photos
- Controlled environment for reading, light, magnification
- Counting device used for colonies
- Clear acceptance criteria/limits
- OOL & ID policy for manual recording
- All samples reconciled
- Results recorded
- Calculations applied correctly
- Second checks and verification in accordance with quality risk management
Encapsulated *B. anthracis*

*E. Coli* on blood agar

*S. Aureus* on MSA

*A. Fumigatus*

*B. cereus* on blood agar
Electronic systems

Validation
- Software validation
- Hardware qualification
- Configuration management
- Change management
- Periodic system review

Configuration
- Audit Trails
- OS security
- Data back-up/archiving
- Test method configuration

User Access
- SOPs for user access control
- Individual user access
- Defined user privileges
- System administrator

Data management
- Data review SOPs
- Raw data verification
- External calculation tools
- Audit trail review
- E-signatures
Summary

• Be aware of changes to PIC/S Guide to GMP
  – Check TGA website for change summaries
  – Implement changes into your pharmaceutical quality systems
• Check TGA position on Data Management and Integrity
  – Review the PIC/S guidance for DMDI
  – Incorporate DI checks into internal and external self-inspection programs
• Notify the TGA of any significant DI findings
Thank you for your attention