Australian Government
Department of Health
Therapeutic Goods Administration

Common inspection deficiencies

Microbiology Laboratories and Quality Assurance

Emmett Broderick
GMP Inspector, Manufacturing Quality Branch, TGA

TGA Health Safety Regulation

Overview

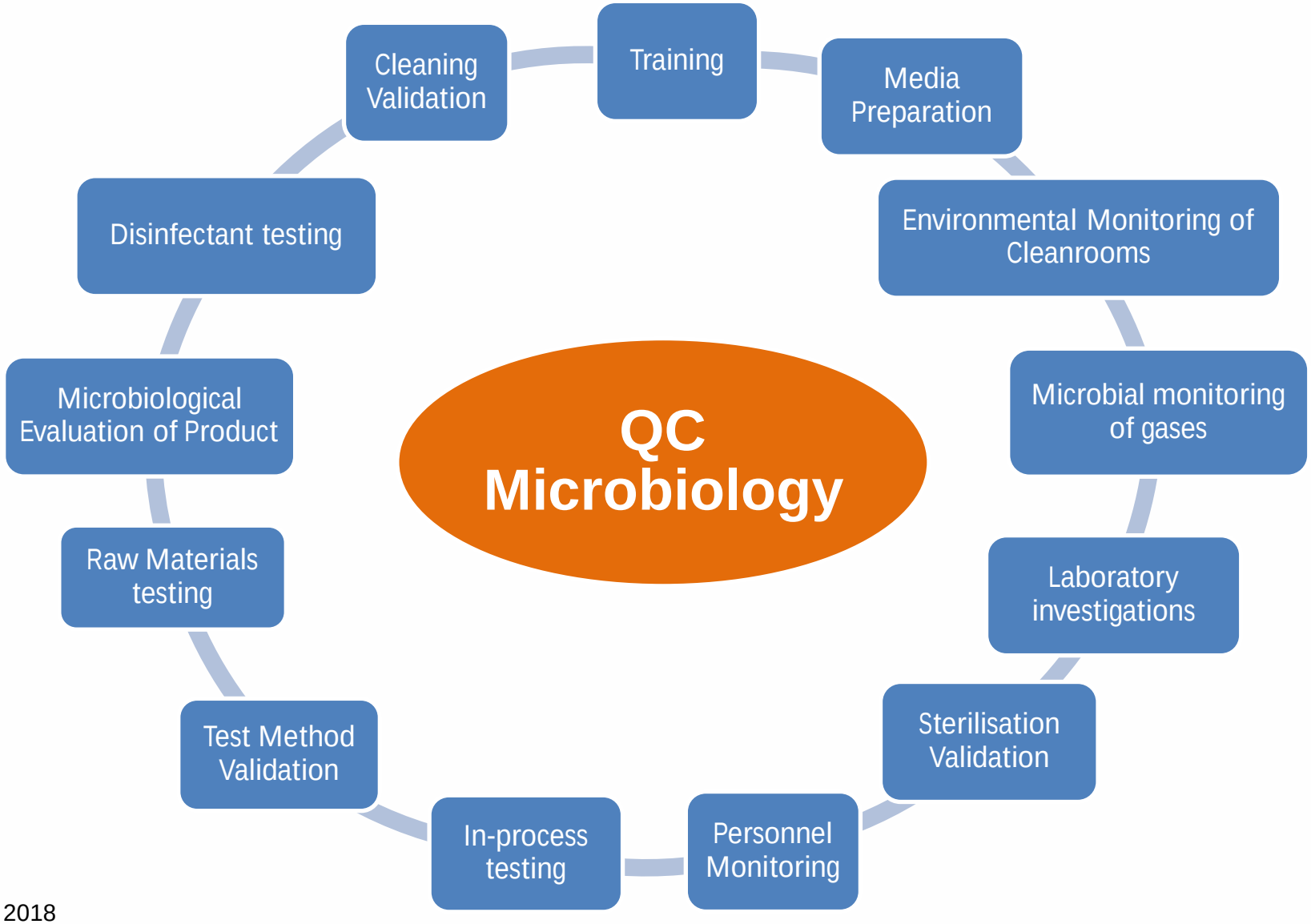
- Quality Control Microbiology in Medicine Manufacturing
- Compliance with GMP requirements
- Inspection Process
- Common inspection deficiencies
- Critical GMP deficiencies in QC Microbiology

Quality control microbiology

Good laboratory practices in a microbiology laboratory consist of activities that depend on several principles:

- Aseptic technique
- Control of media
- Control of test strains
- Operation and control of equipment
- Diligent recording and evaluation of data
- Training of the laboratory staff

USP <1117> Microbiological Best Laboratory Practices


QC Microbiology
Training
Media Preparation
Environmental Monitoring of Cleanrooms
Microbial monitoring of gases
Laboratory investigations
Sterilisation Validation
Personnel Monitoring
In-process testing
Test Method Validation
Raw Materials testing
Microbiological Evaluation of Product
Disinfectant testing
Cleaning Validation

GMP requirements

PIC/S cGMP - PE009-13

- Part I Chapter 1 Quality Control, Product Quality Review, QRM
- Part I Chapter 2 Training
- Part I Chapter 3 Premises & Equipment
- Part I Chapter 4 Documentation
- Part I Chapter 5 Production (Sampling & Contamination Control)
- Part I Chapter 6 Quality Control
- Part I Chapter 7 Outsourced Activities

- Part II Manufacturing of active pharmaceutical ingredients
- Annexes **1**, 2, 3, 7, 8, 9, **11**, **15**, 19

Therapeutic Goods Order No. 77

Requirements for Finished Products

- Sterile
- Multidose
- Non-sterile

Pharmacopoeia (Default Standard)

- British
- European
- United States

Objectionable Organisms

- Route of administration
- Formulation
- Method of application
- Intended recipient
- Use of immunosuppressive agents, corticosteroids
- Presence of disease, wounds, organ damage

Inspection process

- Inspection Plan
  - § Defines scope & used as inspection aide
- Review evidence of GMP compliance
  - § Record keeping and data integrity
  - § Equipment and method suitability
  - § Personnel qualification
  - § Handling of OOS

- Report deficiencies
  - § Rated based on product quality & compliance risk - Critical, Major and Other
  - § Supported by relevant clauses in cGMPs

Inspection scope

Sampling
- Technique
- Records
- Storage
- Hold Times

Media
- Preparation
- QC Program
- Storage
- Expiry

Equipment
- Calibration
- Logbooks
- Validation
- Maintenance

Personnel
- Training
- Deviations
- Resources
- Hygiene

Testing
- Raw Materials
- In-Process
- Finished Product
- Stability
- Reporting
- OOS
- Method Validation

Environmental Monitoring
- Sampling Plan
- Methods
- Excursions
- Trending
- Personnel Monitoring

Common inspection deficiencies in laboratory practice

- Training
  - Clause 2.10
  - Clause 2.11
- Test Method Validation
  - Clause 6.15
  - Annex 15 §22
- Culture media & lab reagents
  - Clause 6.21
  - Clause 6.23

- OOS Management
  - Clause 1.4 (xiv)
  - Clause 1.8 (vii)
  - Clause 1.9 (vi)
  - Clause 4.29
- Environmental Monitoring
  - Clause 1.9 (i)
  - Clause 4.29
  - Clause 6.7 (vi)
- Data Integrity
  - Clause 6.7

Training

The requirements of *Clause 2.10 and 2.11* were not fully met. For example:

a. The requirements for operator training in sterility testing were **not prescribed by procedure**.

b. The current training process for operators undertaking sterility testing **did not specifically address the techniques** or nuances associated with the testing of the **range of products** tested for sterility by the organisation.

c. The training documents reviewed in relation to endotoxin testing indicated that the initial test performed by the analyst on the 6/1/16 failed and a subsequent test on the 13/1/16 passed. The training record referred to the second (passed) result only, and there was **no comment or explanation of the reason regarding the initial failed test**.

d. The manufacturer had **not yet implemented a system** in the **QMS** for the ongoing **re-qualification for sterile gowning**, and the actions to be taken in the event that gowning qualification requirements are not met.

Test method validation

The requirements of *Clause 6.15 and Annex 15§22* that test methods should be validated were not met.

- The current procedure for the validation of the sterility test stated that the validation was deemed successful if visible growth was detected with each organism. There was **no instruction** to ensure that the growth in the test-articles under validation was **comparable to the growth in the positive control**.
- The first attempt at the sterility validation for XXXXX **failed to recover *A. brasiliensis***, and the test was repeated without modification and passed. There was **no detail within the report** regarding the investigation of the initial failure and no evidence of any modification of the test prior to repeating the validation.
- The **method** for the microbiological testing of filtered ethanol used in the aseptic sterility testing areas of the facility **was not validated**.

Test method validation - continued

- For PET testing of XXXXX, the initial test for the neutralisation validation for ***A. brasiliensis*** **failed due to inadequate recovery** of the organism and the test was repeated without modification and passed. There was **no out-of-specification report, investigation or details of any modification** of the test following the initial failure.

- The validation instructions for bile-tolerant Gram negative bacteria test validation did not ensure that results were read at the **shortest permissible incubation times** (*Also refer to* ***BP***)

- There were **no records** relating to the **maximum valid dilution** determination for XXXXX kit testing.

- The method for the microbiological assay of antibiotics for XXXXX from XXXXX required a primary solvent extraction prior to testing. The **method used for the extraction** for antibiotic testing had **not been validated**.

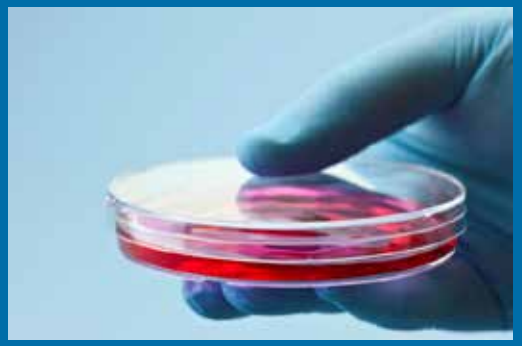
Microbiological media

The requirements of *Clause 6.19* that special attention should be given to the quality of laboratory reagents and culture media was not fully met as evidenced by the following examples:

a. There was **no QC testing** (growth promotion) performed on media received for the microbiological environmental monitoring of the facility.
b. The QC of R2A agar used in the lab **did not include a batch-batch comparison** of microbial recoveries.
c. Media used for environmental monitoring (HBA) was **not sterilised** (irradiated) prior to use in the grade **A/B areas**. In addition, there was no record of the pre-incubation of the HBA plates used in production as required by internal procedures.
d. There was **no routine QC testing** performed on semi-solid media that had been **melted by microwave**. In addition, the microwave melting process was **not clearly defined by procedure**.
e. The methods for the QC growth promotion testing of media were **not in accordance with or equivalent to those specified by the British Pharmacopoeia**:
    - The initial QC testing for all agars (both non-selective and selective) was stated to be performed by the **ecometric** method. However, the method was not appropriate for the QC testing of agars used for **enumerative** tests due to the fact that the **inoculum was not <100cfu**.

OOS management

- The procedure for microbial "out of specification" results permitted a single retest which if passed, would allow acceptance of the product. The company had not established a statistically valid re-sampling plan for retesting activities.
- The company did not have a formal procedure in place to review and assess their products for the presence of objectionable organisms.
- Water produced in the unqualified purified water system located at the XXXXX site was inappropriately approved for use at the XXXXX site. There was no investigation to determine the potential risk of microbial contamination on therapeutic products.



OOS investigation

- Non-conformance report XXXX relating to a TNTC microbiological result for process water did not adequately investigate the contamination source. No microbial identification was performed on the TNTC sample

Retesting

- The XXXX Powder in OOS-XXXX was not appropriately handled. The retest result was accepted from a second contract laboratory but no root cause had been documented to invalidate the initial OOS results from the first contract laboratory.

Environmental monitoring

Sampling

- Room 1 was the only room/area included in the routine environmental monitoring program.
- The environmental monitoring program was conducted annually and thus such monitoring was considered too infrequent without any scientific justification

Method

- The incubation conditions stated by the procedure for EM plates were at a single temperature for 3 days; however, an incubation period of 5 days was actually performed by the external lab. The appropriateness of the single temperature incubation had not been validated.

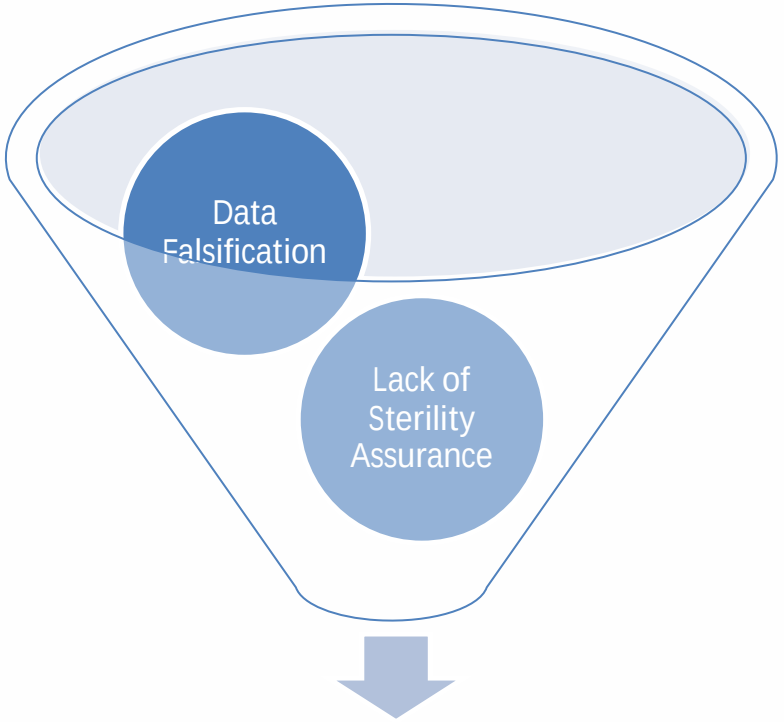
Limits

- The specification applied to environmental monitoring i.e. <5000cfu/swab was not scientifically justified.
- Environmental action limit breaches in 2016 had no microbial identifications performed.
- There was no heightened level of monitoring required in the event of an action limit breach in the purified water or environmental monitoring programs to verify the state of control.

Data integrity

The requirements of *Clause 4.9* that data handled by electronic means should be subject to detailed procedures and the accuracy of electronically produced records should be checked was not met for example, from the laboratory report (ref #XXXX) held by the company; displayed an environmental monitoring result recorded as **<100cfu.** However, the **original report** (report ref #XXXX) obtained from XXXX Laboratory recorded **220cfu** for the same sample. Telephone communications confirmed that the 220cfu report results were the original results and had not been changed by XXXX Laboratory.

Critical deficiencies in QC microbiology



Significant Risk to Patient Safety

The requirements of *Annex 1§8 & 18* that clean rooms and clean air devices be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during classification, and that where aseptic operations are performed, monitoring should be frequent using appropriate methods were not fully met.

The data summary spreadsheet indicated that the environment was under control; however, there was limited data available to support and substantiate the EM data summary for January YYYY. A number of raw data reports from the external laboratory were missing. Forty (40) samples were recorded as being taken and reported; however, only seven (7) raw data reports were available. The manufacturer has subsequently confirmed that the data was mis-represented.

The sample record indicated that sampling was performed on the 11/1/YY; however, the lab results presented indicated that samples were received on the 2, 4 & 19/1/YY.

Lab reports were not reviewed in a timely manner, e.g. report XXXXX generated on the 10/1/YY was reviewed on the 23/3/YY.

The monthly EM (monthly) data summary for February 20YY had been falsely generated: There was limited data available to demonstrate that the monitoring had been performed as prescribed. A number of raw data reports from the external laboratory were missing

USFDA warning letter

Letter 320-18-38: Quali-Controle & Quali-Controle (France)

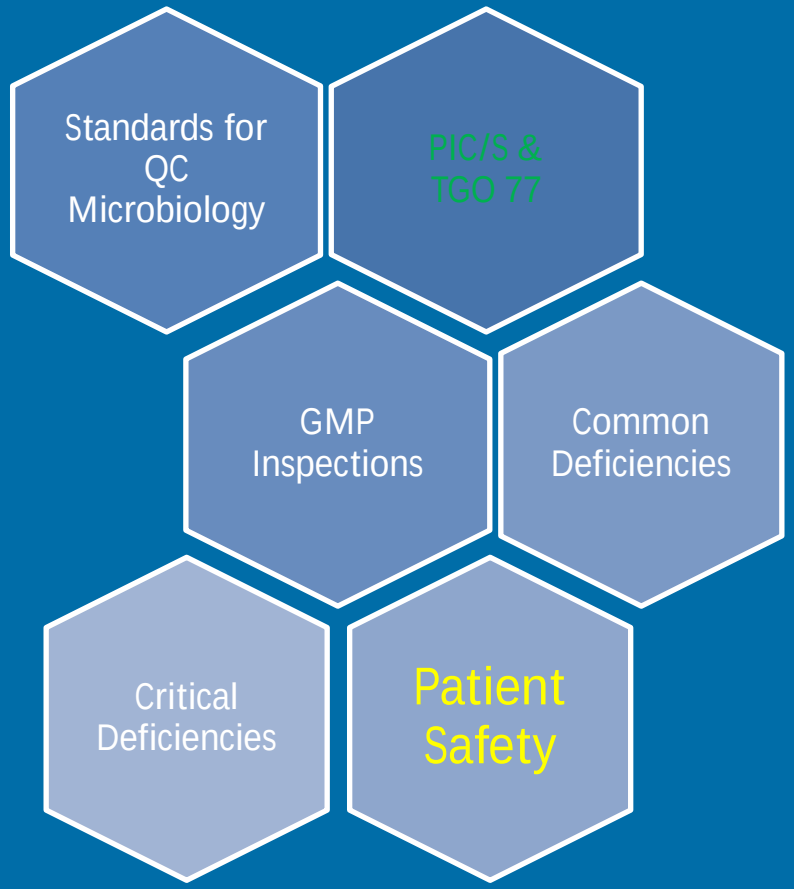
- Issued March 2018
- Contract testing laboratory
- Firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods (21 CFR 211.165e)
- Correction - procedure to assure that all future non-compendial methods used in your facility are properly validated or transferred, and all compendial methods are verified prior to use.

2018 USFDA safety alerts for human medical products

§ ~20% relating to Microbiology Risk (Similar trend reported on System for Australian Recall Actions)

- Compounded Drug Products from Cantrell Drug Company: FDA Warning - Serious Deficiencies in Quality and Sterility Assurance
- Compounded Sterile Products by PharMEDium Services: Recall - Lack of Sterility Assurance
- Gericare Eye Wash by Kareway Products: Recall - Potential Product Contamination
- Kratom-containing Powder Products by PDX Aromatics: Recall - Potential for Contamination with Salmonella
- Pasta De Lassar Andromaco Skin Protectant 25 Percent Zinc Oxide by MarcasUSA: Recall - Potential Contamination
- X-Jow and Acne Shave Products by Shadow Holdings: Voluntary Recall - Due to Possible Bacterial Contamination

Summary


Standards for QC Microbiology
PIC/S & TGO 77
GMP Inspections
Common Deficiencies
Critical Deficiencies
Patient Safety

Questions

Australian Government

Department of Health

Therapeutic Goods Administration