Microbiological Testing of CPM products and GMP Requirements for Microbiological Testing laboratory

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- Microbiological control of CPM products
- Understanding the compendial microbiological tests applicable for CPM products
- GMP requirements for Microbiological Laboratory (Micro Lab)
- Investigation of microbiological Out of Specification (OOS) and follow-up actions

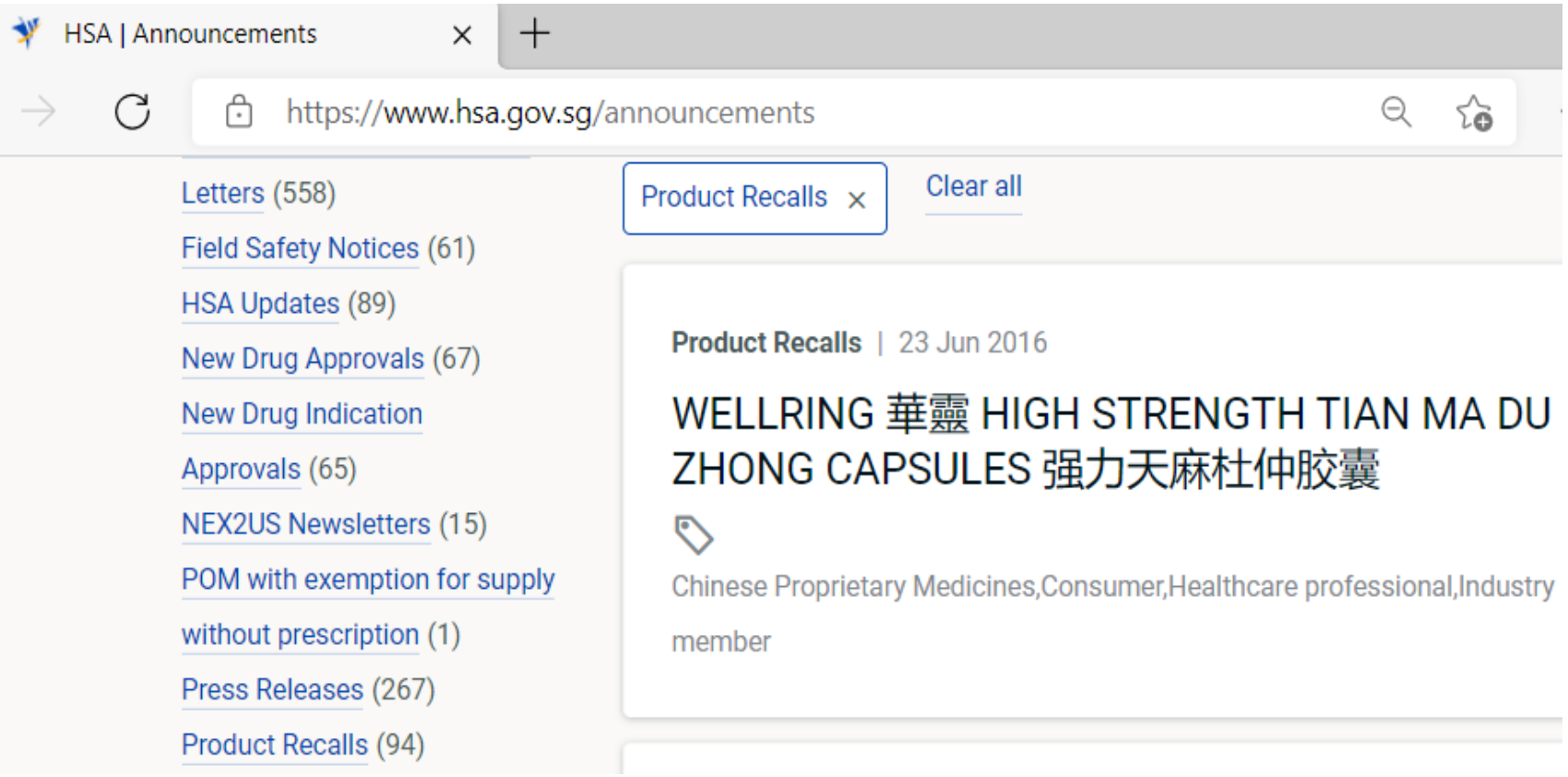
Introduction

- HSA has started regulatory control of CPM products under The Medicines Act since September 1999.
- Medicines (Prohibition of sale, supply and importation) order prescribes the microbiological and heavy metals limits for CPM products

Restriction on importation, sale and supply of Chinese proprietary medicine	
4.—(1) No person shall import, or sell or supply to any person, any Chinese proprietary medicine for **oral consumption** which contains — a) total aerobic microbial count of more than 10^5 per gram or millilitre; b) total yeast and mould count of more than 5×10^2 per gram or millilitre; c) any Escherichia coli in 1 gram or 1 millilitre; d) any Salmonella in 1 gram or 1 millilitre; or e) any Staphylococcus aureus in 1 gram or 1 millilitre, of the Chinese proprietary medicine.	(2) No person shall import, or sell or supply to any person, any Chinese proprietary medicine for **external application** which contains — a) total aerobic microbial count of more than 10^4 per gram or millilitre; b) total yeast and mould count of more than 5×10^2 per gram or millilitre; c) any Pseudomonas aeruginosa in 1 gram or 1 millilitre; d) any Staphylococcus aureus in 1 gram or 1 millilitre, of the Chinese proprietary medicine.

Recall of failed CPM products

15 Class 2 recalls in Nov 2016 to Jul 2021



- 27% of these recalls were due to microbiological limits exceeded legislated limits;
- Most commonly bacteria isolated were from the *Bacillus* species (commonly found in soil) and for fungi were from *Aspergillus* and *penicillium* species (found in external environment).

Concern for high microbiological counts

Consumer Health

- Patients seeking alternative treatment may have one or more of the existing medical condition(s):
  - ❑ Diabetes Mellitus;
  - ❑ High blood pressure (Hypertension);
  - ❑ High Cholesterol (Hyperlipidema).
- Patients may be taking more than one CPM product(s) or a combination of both western and traditional medicines.
- Patients may be immunocompromised (weaken immune system, reduced ability to fight infection or other diseases) due to health reasons or old age.

Concern for high microbiological counts

Product Quality and Efficacy

- Some microorganisms can alter the physiochemical characteristics of the products by metabolizing the active ingredients found in the product, leading to undesirable chemical changes.
- Other microorganisms may also produce metabolic by-products which alters the pH, causing differences observed in the smell, taste and even appearance.
- Changes to the pH may also cause the efficacy of the preservatives (if added) to decrease. Preservatives like Benzoic acid are pH dependent as they can be chemically ionisable.

Microbiological control of CPM products

Types of Contamination

Primary contamination: Refers to the natural microbiological flora found on the harvested herbs or plants.

Secondary contamination: Refers to the contamination of microorganism throughout the handling activities of the herbs or plant material (e.g. harvesting, equipment, transportation) during the manufacturing process.

Primary and secondary contamination should be controlled and minimized via the following:

- ❑ Prevention to reduce contamination from micro-organism
- ❑ Reduction via decontamination processes

Definition of Starting Materials & Finished Product

PIC/S GMP Guide Annex 7

The 'starting material' in the manufacture of an herbal medicinal product can be a medicinal plant (herbs), an herbal substance/material or an herbal preparation

WHO Annex 2: Guidelines on good manufacturing practices for the manufacture of herbal medicines

Herbs include crude plant materials such as leaves, flowers, fruits, seeds, stem wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials include, in addition to herbs: fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other plant materials.

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations 1 made of the same plant as well as herbal preparations from different plants. Products containing different plant materials are called "mixture herbal products").

Microbiological control of CPM products

Prevention of Microorganism Contamination

- **Herbal Plants or Substances**
  - ❑ Cultivation
    - ➢ Types of fertilizers – Organic, not of human origin
    - ➢ Pesticides – Fungicides for plants that are susceptible to fungus
    - ➢ Green House – Minimize exposure to airborne/ animal contamination
  - ❑ Harvesting – Reduce moisture during harvesting
  - ❑ Drying – Adequate drying temperature and duration
  - ❑ Washing – Control quality of water used for washing
  - ❑ Packaging – Packaging material should prevent microbial growth
  - ❑ Storage – Proper temperature and humidity settings to prevent condensation.

Microbiological control of CPM products

Prevention of Microorganism Contamination

- **Herbal Preparations**
  - ❑ The process steps and In-process controls should be well defined and ensure that secondary contamination are minimized
    - ➢ Extraction duration and time – Aqueous extraction of preparation of water, low alcohol concentration are at risk of microbial contamination
    - ➢ Distillation of essential oils – Low pressure steam distillation generally used, however important to determine the hold time and storage container used
    - ➢ Addition of preservatives – Is the usage of preservative justified
  - ❑ Secondary microbial contamination from extraction solvents, water, excipients as well as packaging material and storage conditions should also be controlled

Microbiological control of CPM Products

Prevention of Microorganism Contamination

- **Finished Products**
  - ❑ Storage area should be enclosed with cleaning in place
  - ❑ Storage conditions does not lead to microbiological contamination (e.g. warehouse for storage is temperature and humidity controlled)
  - ❑ The transportation conditions (e.g. vehicle used does not expose the product to direct sun light or rain, duration of the transportation) does not increase the microbiological contamination

Microbiological control of CPM Products

Reduction of Microorganism Contamination

- Microbiological contamination should first be prevented during the cultivation, harvesting, processing, transportation and storage phases.
- If the microbiological bioburden is still high after exhausting all preventive measures, decontamination process (to reduce the amount of microorganism present) should be considered.
- Most decontamination process may cause degradation or deterioration of the product and evaluated appropriately.
- Examples of decontamination processes:
  - ❑ Extraction process using High ethanol concentration (60-95%) have bactericidal & fungicidal effects or extraction using boiling water

Microbiological control of CPM Products

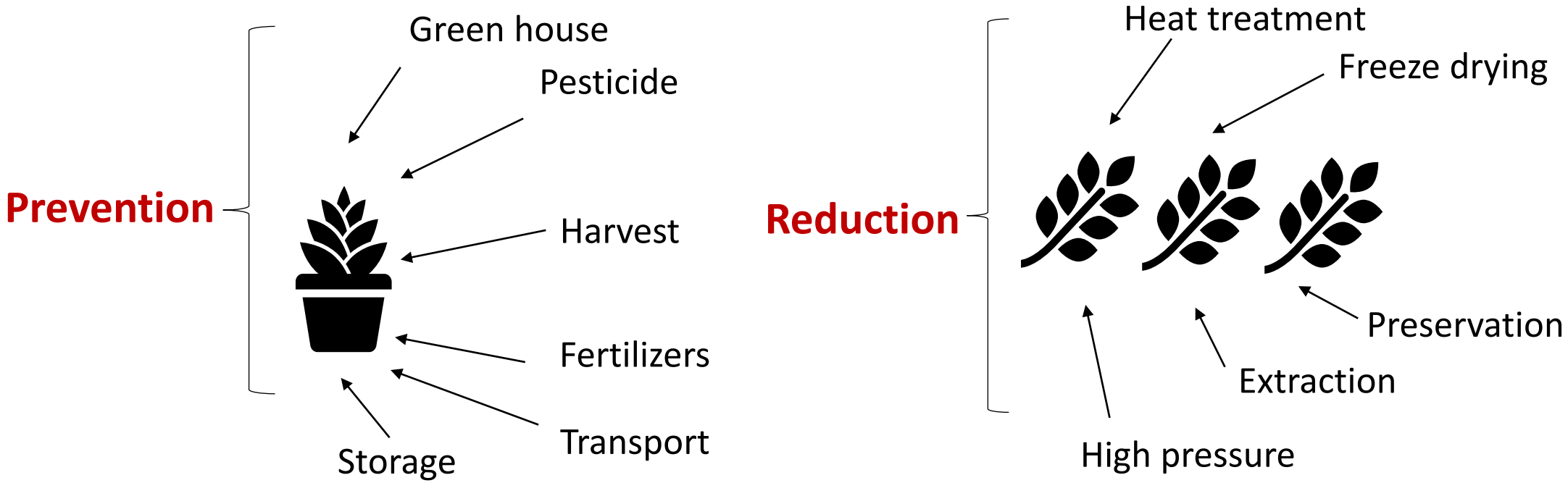
Reduction of Microorganism Contamination

- Examples of decontamination processes (con't):
  - ❑ Heat treatment process like UHT- Ultra Heat Treatment or Pasteurisation, dry heat, (dry or moist)
  - ❑ Freeze drying – Reported to decrease microbial contamination but limited information is available
  - ❑ High pressure processing – Kill microorganisms while retaining the freshness of the product
  - ❑ Others like fumigation, irradiation, treatment with alkaline or acidic substances and adding of preservation
  - ❑ If extraction increases the microorganism count, expectation is to lower with other suitable process

Microbiological control of CPM Products

Summary

Prevention and reduction of microbiological contamination should be considered throughout all stages of the manufacturing process as far as possible



Compendial Microbiological Tests

Introduction to Compendial Microbiological Test Methods

- In-house microbiological testing laboratory should be adequately resourced with microbiologists who are knowledgeable of the standard tests for the CPM products manufactured at their site
- Most the CPM products manufacturers in Singapore outsourced the microbiological testing to external laboratories. It is the responsibility of the manufacturer (contract giver) to:
  - ❑ Assess if the external laboratory is suitable, competent in performing the outsourced tests and compliant to applicable GMP guidelines, and
  - ❑ Provide relevant information on the product to be tested to the external laboratory and ensure that appropriate handling of the samples, testing method is applied for their products.

Compendial Microbiological Tests

- Compendial test methods are found in the US, European and Chinese Pharmacopeias.
- Methods are standardized between the pharmacopeias and while minor differences are observed, there is no impact.
- General test can be found in USP<61> and selective test in <62>

Description	US Pharmacopeia (USP)	European Pharmacopeia (EP)	Chinese Pharmacopeia (CP)
General Test method	<61> Microbiological Examination of Nonsterile Product: Microbial Enumeration Tests	2.6.12 Microbiological Examination of Nonsterile Product: Microbial Enumeration Tests	(1105) Microbial limit test for non-sterile products: microbial count method
Selective Test method	<62> Microbiological Examination of Nonsterile Product: Tests for specific Microorganisms	2.6.13 Microbiological Examination of Nonsterile Product: Tests for specific Microorganisms	(1106) Microbial limit test for non-sterile products: control bacteria test method

Compendial Microbiological Tests

- Microbiological regulatory limits:
  - ❑ USP <61> General test methods Total Aerobic Microbial count & Yeast and mould count;
  - ❑ USP <62 > Test methods for selective microorganisms.

Test for	Method	Oral CPM	Topical CPM
Total aerobic microbial count	**USP<61>,** EP2.6.12, CP<1105>	Not more than 10^5 per gram or millilitre	Not more than 10^4 per gram or millilitre
Yeast and mould count	**USP<61>,** EP2.6.12, CP<1105>	Not more than 5 x 10^2 per gram or millilitre	Not more than 5 x 10^2 per gram or millilitre
Selective microorganisms	**USP<62>,** EP2.6.13, CP<1106>	Absence of Escherichia coli, Salmonella and Staphylococcus aureus in 1 gram or 1 millilitre,	Absence of Pseudomonas aeruginosa and Staphylococcus aureus in 1 gram or 1 millilitre,

Compendial Microbiological Tests

General Test methods: USP <61> Microbiological Examination of Non-Sterile Product: Microbial Enumeration Tests - Quantitative enumeration of mesophilic bacteria & fungi under aerobic conditions*

- Product type
  - Water soluble or insoluble depending on the excipient used (e.g. Sucrose or Cane sugar 蔗糖/白糖/砂糖), starch (AMYLUM 淀粉)
  - Non-fatty or Fatty products?
  - Aerosols?
  - Transdermal patches?
  - Neutralization due to the presence of preservatives used (e.g. sodium benzoate, benzoic acid)
  - Removal of antimicrobial activity naturally found in some active ingredients (e.g. Cortex phellodendri 黄柏, Radix et Rhizoma Rhei 大黄)

*Alternative methods can be pursued if equivalence to pharmacopeial method is demonstrated.

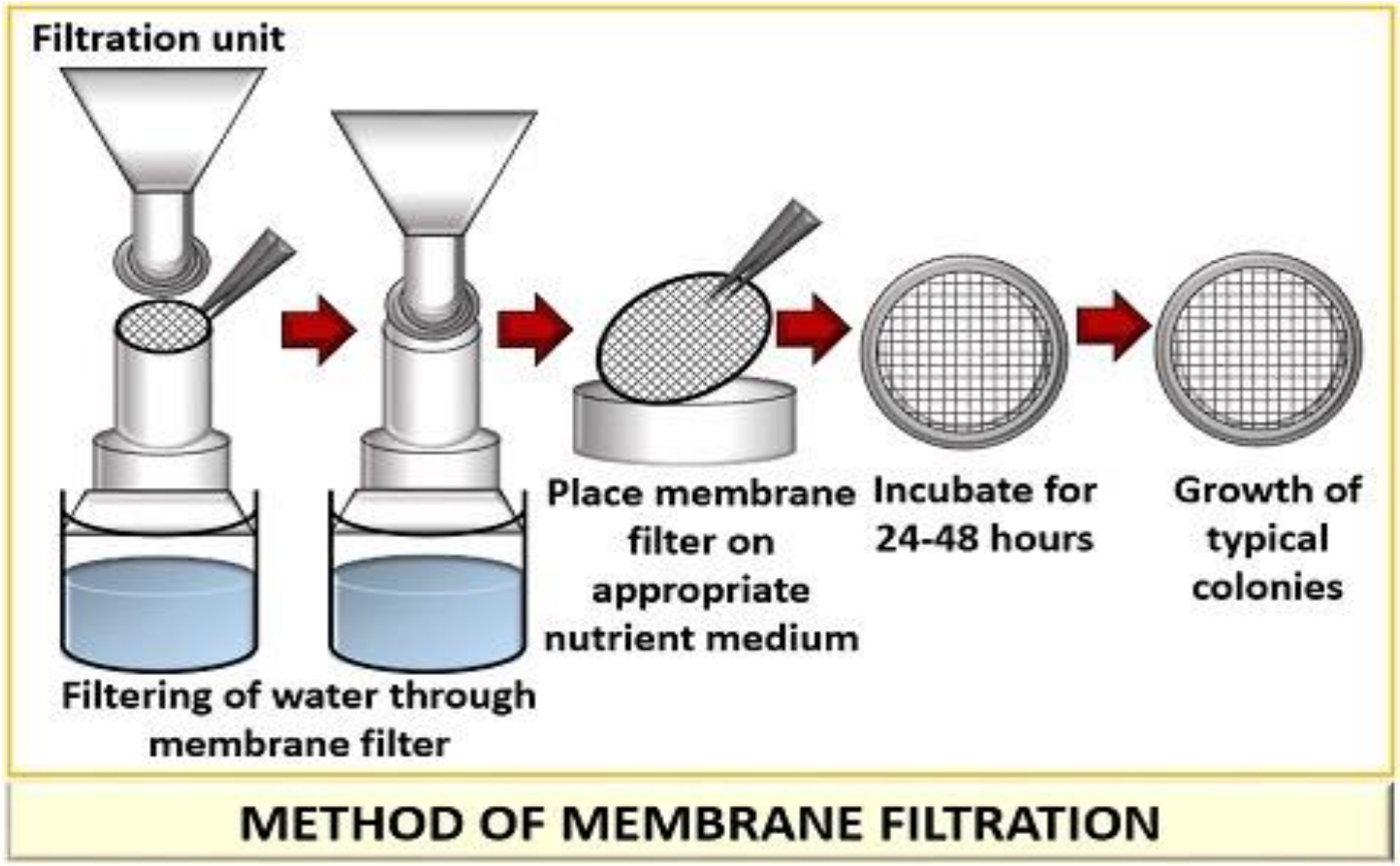
Compendial Microbiological Tests

General Test methods: USP <61> Microbiological Examination of Non-Sterile Product: Microbial Enumeration Tests (con't)

- Preparation of products for testing
  - Dissolve
  - 1/10 dilution
  - Addition of inactivators
- Suitability of media
  - Growth Promotion Test - Recovery of microorganisms
  - Types of ATCC (American Type Culture Collection) micro-organisms used

Compendial Microbiological Tests

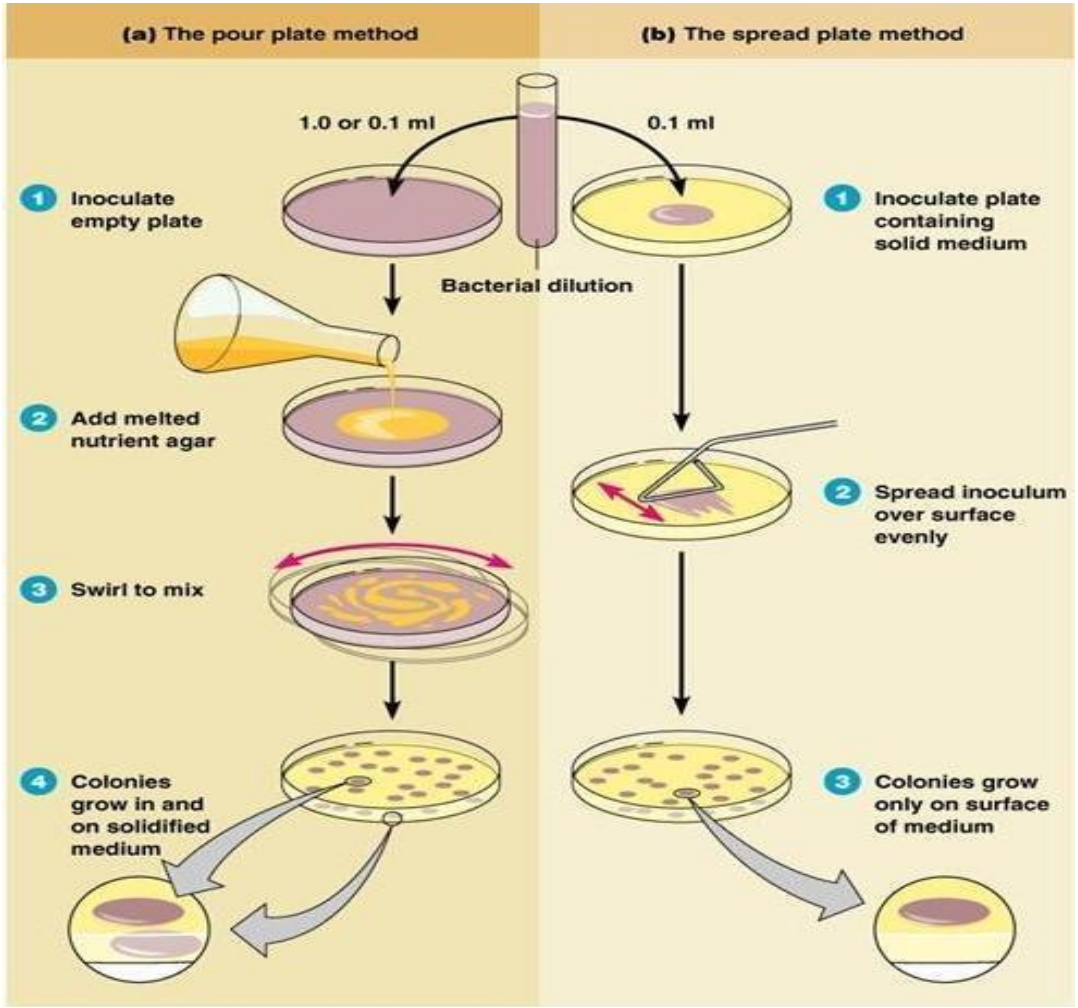
General Test methods: USP <61> Microbiological Examination of Non-Sterile Product: Microbial Enumeration Tests (con't)



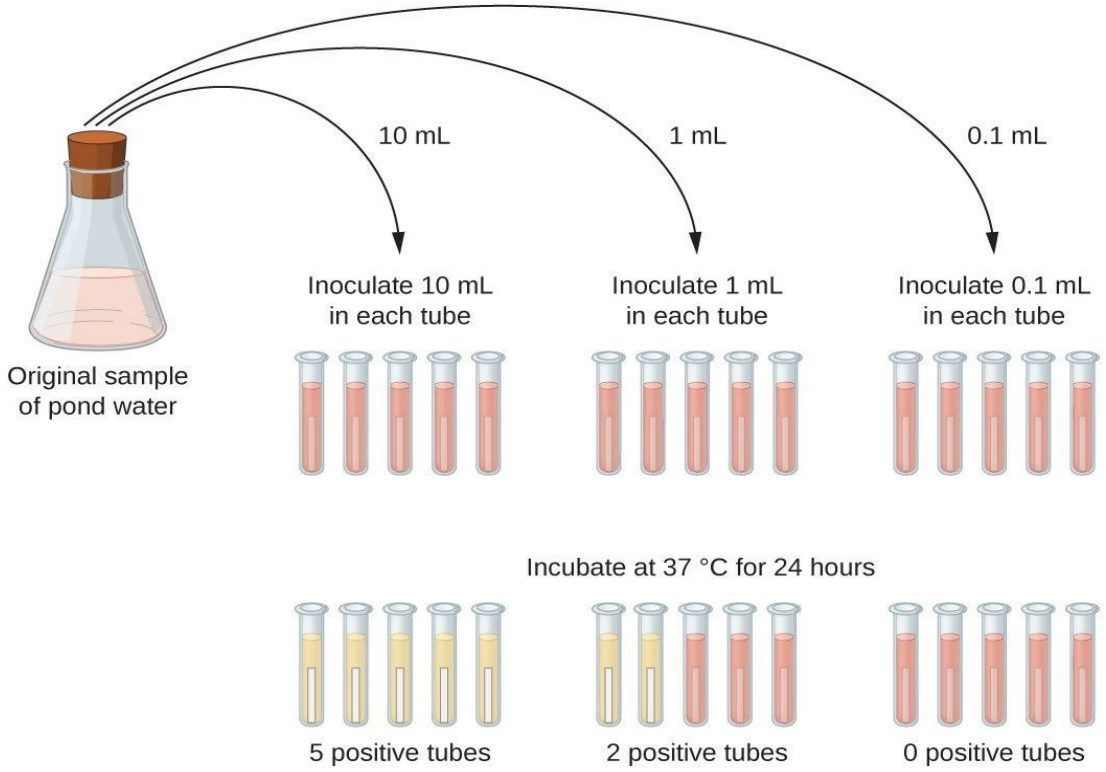
- Suitability of method
  - Membrane filtration (Using Vacuum pump)

Compendial Microbiological Tests

- Plate-count (Pour plate or spread plate method)



- Most-Probable-Number (MPN)



Compendial Microbiological Tests

Selective Test methods: <62> Microbiological Examination of Non-Sterile Product: Tests for specific Microorganisms - The detection of specific microorganisms under certain conditions*

Table 1. Growth Promoting, Inhibitory, and Indicative Properties of Media

Test/Medium	Property	Test Strains
Test for bile-tolerant Gram-negative bacteria		
Enterobacteria Enrichment Broth Mossel	Growth promoting	*E. coli*
		P. aeruginosa
	Inhibitory	*S. aureus*
Violet Red Bile Glucose Agar	Growth promoting + Indicative	*E. coli*
		P. aeruginosa

- Type of growth promoting media
- Inhibitory properties of the media
- Suitability of the media

*Alternative methods can be pursued if equivalence to pharmacopeial method is demonstrated.

Compendial Microbiological Tests

Selective Test methods: <62> Microbiological Examination of Non-Sterile Product: Tests for specific Microorganisms

- Negative controls
  - Usage of diluent, any failed Negative control requires an investigation
- Suitability of the test used for selection
  - Aerobes (presence of Oxygen, O_2), facultative anaerobes (presence or absence of O_2), anaerobes (absence of O_2)
  - Antimicrobial activity consideration? Modify test method if required
  - If it cannot be neutralized, then it is to be assumed that the inhibited microorganism will not be present in the product.

Compendial Microbiological Tests

Selective Test methods: <62> Microbiological Examination of Non-Sterile Product: Tests for specific Microorganisms

- Methods

Salmonella

SAMPLE PREPARATION AND PRE-INCUBATION

Prepare the product to be examined as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* 〈61〉, and use the quantity corresponding to not less than 10 g or 10 mL to inoculate a suitable amount (determined as described under *Suitability of the Test Method*) of *Soybean–Casein Digest Broth,* mix, and incubate at 30° to 35° for 18 to 24 hours.

SELECTION AND SUBCULTURE

Transfer 0.1 mL of *Soybean–Casein Digest Broth* to 10 mL of *Rappaport Vassiliadis Salmonella Enrichment Broth,* and incubate at 30° to 35° for 18 to 24 hours. Subculture on plates of *Xylose Lysine Deoxycholate Agar*. Incubate at 30° to 35° for 18 to 48 hours.

INTERPRETATION

The possible presence of *Salmonella* is indicated by the growth of well-developed, red colonies, with or without black centers. This is confirmed by identification tests.

The product complies with the test if colonies of the types described are not present or if the confirmatory identification tests are negative.

Compendial Microbiological Tests

Summary

- Compendial test methods prescribed in the pharmacopeia are used to test the microbiological regulatory limits set for CPM products
- Product knowledge is required to consider the appropriate method required for testing:
  - ❑ Starting materials (e.g. Cortex phellodendri 黄柏), Radix et Rhizoma Rhei 大黄);
  - ❑ Excipients (e.g. Sucrose (Cane sugar 蔗糖(白糖/砂糖), starch (AMYLUM 淀粉);
  - ❑ Preservatives (e.g. sodium benzoate, benzoic acid);
  - ❑ Manufacturing process (e.g. extractions, mixing & boiling).
- If testing is outsourced, the manufacturer should assess suitability, competency of the lab and ensure right handling of samples and appropriate testing method for their products is applied

GMP Requirements for Micro Lab

PIC/S GUIDE TO GMP PART I

Chapter 1 – Pharmaceutical Quality System

- Principle
- Pharmaceutical Quality System
- GMP for medicinal Products
- Quality Control
- Product Quality Review
- Quality Risk Management

Chapter 6 – Quality Control

- Principle
- General
- Good Quality Control Laboratory Practice
  - Documentation
  - Sampling
  - Testing
  - On-going Stability Programme
  - Technical Transfer of testing methods

Chapter 7 – Outsourced activities

- **Principles**
- **General**
- **The Contract Giver**
- **The Contract Acceptor**
- **The Contract**

- If the testing is outsourced to external lab, the manufacturer should assess if the proposed contract laboratory is fit for purpose (suitable, competent and GMP compliant)?
- Is written contract or quality agreement with contract laboratory in place?

GMP Requirements for Micro Lab

PIC/S GUIDE TO GMP PART I Chapter 6 – Quality Control

- General
  - ❑ Independent QC, not part of production (in-house lab)
  - ❑ Adequate manpower to perform QC role e.g. independent reviewer (applicable for both in-house & external lab)
  - ❑ Separate lab from production to prevent cross contamination (in-house lab)
- Documentation
  - ❑ Specification of products, intermediates, In process control, starting materials
  - ❑ Procedures for sampling, testing, records (including recording & verifying)
  - ❑ Equipment calibration and maintenance procedures and records
  - ❑ Out-Of-Specification & Out-of-Trend investigation procedures
  - ❑ Test reports and Certificate of Analysis
  - ❑ Environmental monitoring data

GMP Requirements for Micro Lab

PIC/S GUIDE TO GMP PART I Chapter 6 – Quality Control

- Sampling

  - ❑ The method and equipment used
  - ❑ Amount of sample taken and Sub-division of samples (if required)
  - ❑ Type and condition of sample container
  - ❑ Identification of containers sampled (i.e. labelling with product name and batch number, etc.)
  - ❑ Special precautions (e.g. storage conditions) with regards to samples
  - ❑ Instructions for cleaning and storage of sampling equipment

GMP Requirements for Micro Lab

PIC/S GUIDE TO GMP PART I Chapter 6 – Quality Control

- Testing
  - ❑ Test method validation or method suitability for compendia methods
  - ❑ Recording, trending of results identified as critical quality attributes
  - ❑ Testing records should include information on:
    - ➢ Identification of material, product, its dosage form
    - ➢ Batch number, and manufacturer/supplier where necessary
    - ➢ References to testing procedures, specification, equipment used
    - ➢ Test results and relevant observation, calculation and referenced COA
    - ➢ Identify the date, time and analyst that performed the test as well as verifier
    - ➢ Test disposition whether approved or reject and its subsequent actions
  - ❑ Approved methods for In-process control testing should be used
  - ❑ Culture media, ATCC cultures & consumables preparation
  - ❑ Decontamination of waste (Used ATCC cultures, growth plates)

GMP Requirements for Micro Lab

PIC/S GUIDE TO GMP PART I Chapter 7 – Outsourced activities

Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver (manufacturer) is also responsible for ensuring by means of the contract that the principles and guidelines of GMP are followed.

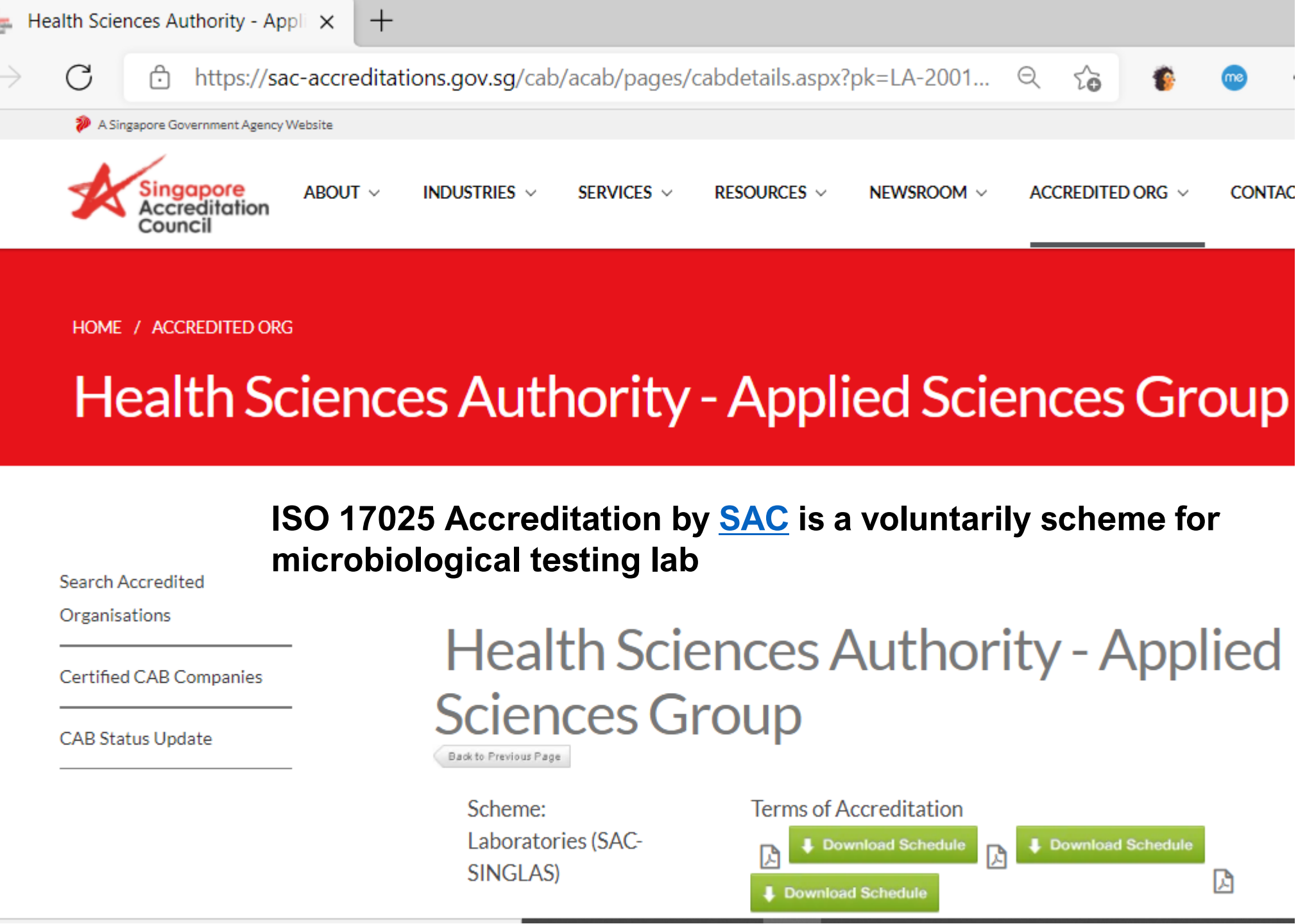
Check

- ☑ Does the lab has an appropriate quality management system in place for the testing operations?
- ☑ Who are the personnel responsible for handling microbiological testing and quality control or approval of the test?
- ☑ What is the lab sample management (timeline for collection, transportation and storage)?

GMP Requirements for Micro Lab

Check

- ☑ Discuss with the lab if they have the knowledge to select the suitable method for your product and have the equipment or facilities to perform test within the acceptable requirements
- ☑ How are the test recorded and would these data be provided when necessary
- ☑ Discuss what information should be provided in the test report, timeline
- ☑ Discuss how would both parties manage in the event of Out of Specification (OOS) (e.g. lab investigation, identification of microbes, criteria for retest, return plates to perform confirmatory test with another lab)
- ☑ Does the outsourced testing lab agree and accept that the outsourced analytical activities may be subject to inspection by the regulatory authority.
- ☑ Does the lab agree to be named in the Manufacturer's Licence
- ☑ Ensure that a written contract or Quality Agreement which describes the GMP responsibilities of each party, and also refers to the scope of testing and type of tests covered by the agreement is put in place.



HSA Health Sciences Authority

Check the schedule for

- ✓ Product tested
- ✓ Test
- ✓ Standard methods

GMP Requirements for Micro Lab

Is ISO 17025 accreditation alone sufficient to demonstrate that the contract lab is fit for your purpose and compliance to relevant GMP requirements?

- ISO17025 standard consists of similar quality system requirements for laboratory operations as described in the PIC/S Guide for GMP
- Complementary Management Requirements
  - ❑ Control of nonconforming testing and/or calibration – Responsibilities and actions required, evaluation of the Non-Conformity, corrections implemented
  - ❑ Subcontracting of test and calibrations – Responsibility of the lab to inform and obtain appropriate approval from customer, registry of subcontractors
- Complementary Technical Requirements
  - ❑ Selection of appropriate methods pertaining to the needs of the customer
  - ❑ Measurement traceability – Established program, procedure for calibration of equipment

GMP Requirements for Micro Lab

- ISO 17025 Accreditation by SAC is a voluntarily scheme for testing lab.
- ISO 17025 accreditation could be a useful evidence that the laboratory has suitable quality system for testing laboratory and fulfilled the technical requirements for performing the specific test for the type of product
- However, ISO 17025 accreditation alone does not automatically and always confirm that the contract lab is fit for the manufacturer's purpose or capable of performing the test required and able to fulfil the applicable GMP requirements
- Manufacturer is still responsible for assessing the suitability of the contract test lab for its purpose and ensure that the technical details pertaining to the test, records and any quality requirements are formally agreed between both parties.

GMP Non-compliance for Outsourced Testing

Examples of GMP deficiencies

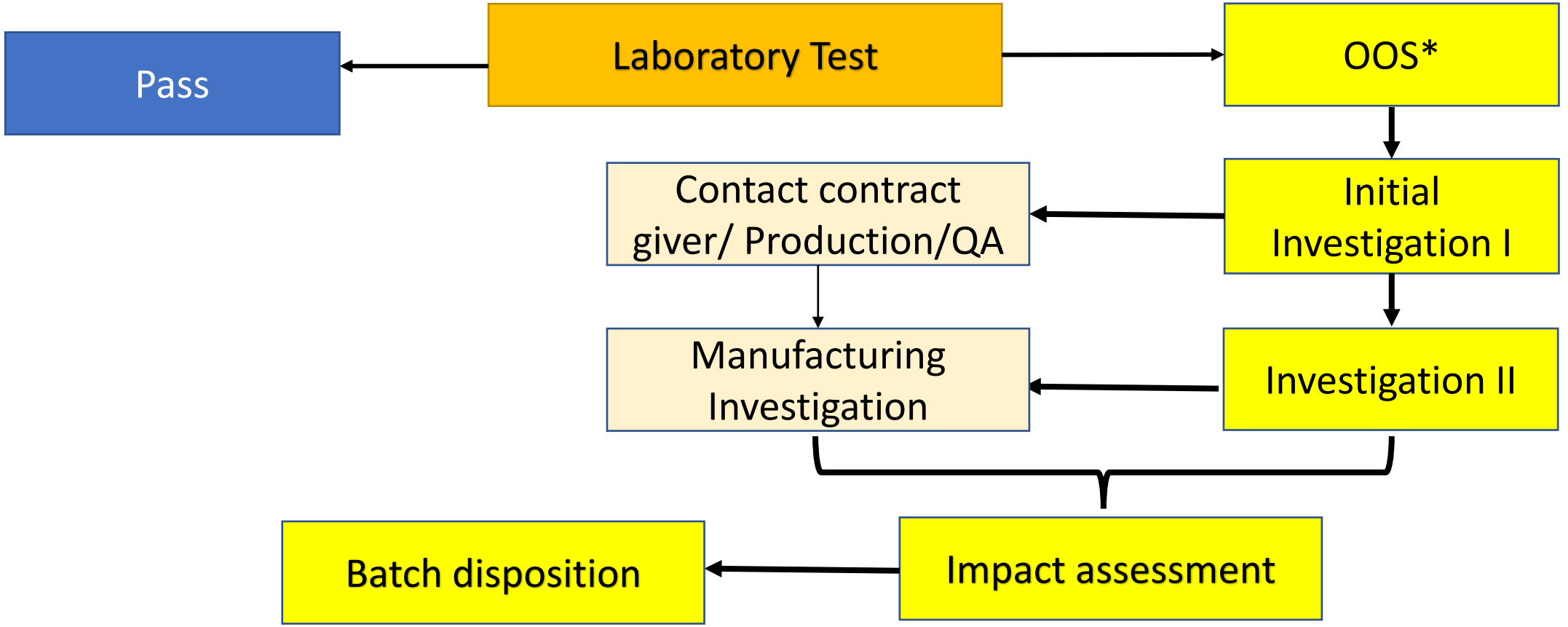
- There was no quality or technical agreement with contract testing lab engaged for testing of CPM products. No information was available on the test method and the suitability of the method used by the contract testing lab for performing this assay
- The quality agreement with contract testing lab for microbiological testing of products did not fulfil GMP requirement in that:
  - ❑ There was no explanation on what was meant by ‘two levels of actions’ taken by the contract acceptor without notifying the contract giver;
  - ❑ The agreement implied that the contract acceptor is allowed to perform retest and invalid the first test result without notifying the contract giver;
  - ❑ The timeline for the contract acceptor to report OOS result was not stipulated; and
  - ❑ The expectation for the contractor acceptor to provide investigation report for OOS result was not stated.

GMP Non-compliance for Outsourced Testing

Examples of GMP deficiencies

- The procedure on *OOS Investigation* did not include the investigation and follow-up actions to be taken if microbiological OOS is detected;
  - ❑ The Contract Agreement with *XXX* was incomplete as it was only signed by the contract acceptor.
  - ❑ The scope of tests, including the type of materials and products as well as the test methods, performed by the contract testing lab was not specified in the agreement.
  - ❑ The third party testing lab subcontracted by *contract acceptor* was not discussed and agreed in the contract. There was also no information on the third party testing lab in the test reports.
  - ❑ The minimal period for the contract testing lab to notify the contract giver in the event of any suspected OOS was not stated in the agreement.
  - ❑ The responsibility of the contract testing lab to conduct of investigation for OOS, including tests that were sub-contracted to the third party lab, was not stipulated in the agreement.
  - ❑ The agreement did not include the requirement and timeline for the contract testing lab to provide investigation report for OOS detected.
  - ❑ There was no provision to ensure that all records and procedure related to the outsourced testing would be made available to the contract giver in the event of complaints or suspected defect or investigation.

Investigation of Microbiological OOS and follow-up actions



*OOS – Out of specification test results that did not meet the set acceptance criteria

Investigation of Microbiological OOS and follow-up actions

Initial Investigation (Part IA)

- Performed by QC analyst
- Obvious error → invalidate results → No further investigations required (e.g.):
  - ❑ Power failure → Outage affecting the Biosafety Cabinet/Laminar Air Flow hood while performing Microbiological testing
  - ❑ Equipment failure → Vacuum pump unable to function after a few samples tested
  - ❑ Sample handling → Tested samples dropped prior to incubation
- After incubation completion and reading of results
- Proceed to Initial investigation (Part IB) if the error is not obvious
- Expected to trend

Investigation of Microbiological OOS and follow-up actions

Initial Investigation (Part IB)

- Performed by QC analyst and supervisor
- Lab investigation checklist:
  - ❑ Correct test methodology
  - ❑ Proper sampling and handling
- Restricted to equipment/ data/ analysis review only
- Assignable cause → Invalidate data → repeat analysis → record results → CAPA:
  - ❑ Test plate dried up after 7 days incubation → incubator temperature monitoring probe and alarm disabled wrongly during maintenance of other incubator
- No assignable cause → Contact contract giver → Proceed to Investigation II:
  - ❑ Important to include considerations in the contract agreement in the event of Out-of-Specification as previously presented

Investigation of Microbiological OOS and follow-up actions

Investigation (Part II)

- Investigational protocol:
  - ❑ Identify areas that may have contributed to the OOS
  - ❑ Test hypothesis to confirm
- Outcome:
  - ❑ Confirmed as OOS → No further retest
  - ❑ Assignable cause → Report retest results / invalidate original → Impact assessment & batch disposition / CAPA
  - ❑ No assignable cause → report all results → batch disposition
- Manufacturing Investigation :
  - ❑ Similar principles where the investigation revolves around the manufacturing activity and its related premises, equipment, documentation

Investigation of Microbiological OOS and follow-up actions

Considerations for Microbiological OOS

- Investigate/ evaluate both lab and manufacturing information in depth
- Likely to have 1 to 2 weeks delay because of the incubation period
- Investigation should consider:
  - ❑ Microorganism (Identity and source of the microorganism);
  - ❑ Test Media used (Inhouse preparation or purchased commercially);
  - ❑ Test Equipment (Calibration, maintenance, cleaning validation and hold time);
  - ❑ Test Method (method validated, compendia, non-compendia).
- Trending of previous samples performed (starting material, intermediate, finished products)
- Environment of test area, support areas – Biosafety Cabinets, incubators, water systems

Investigation of Microbiological OOS and follow-up actions

Considerations for Microbiological OOS

- Materials – COAs, raw material test results, atypical event
- Process – Batch records review, equipment logs, operators involved (looking for atypical events like spillage, addition of new personnel, equipment not cleaned, line clearance not performed adequately)
- Personnel – Training related to process, sampling and cleaning activities
- Environment – Cleaning log, preparation of cleaning equipment and cleaning solution used. Environmental monitoring results (temperature/humidity of rooms)
- Equipment – Process equipment usage and cleaning log, Water system monitoring trend and results
- Pass trends observed related to the product

Investigation of Microbiological OOS and follow-up actions

Impact Assessment & Batch Disposition

- No assignable root cause but retest pass -> all data should be reported and considered during batch disposition
- Impact to other products
- Impact to future products
- CAPA:
  - ❑ Correction- Action to eliminate a detected nonconformity
  - ❑ Corrective action- Action to eliminate the cause of a nonconformity and to prevent recurrence
  - ❑ Preventive action- Action to eliminate the cause of a potential nonconformity or other potential undesirable situation
- Batch Disposition
  - ❑ Reject if not released or distributed yet or
  - ❑ Recall from market

Investigation of Microbiological OOS and follow-up actions

Problem statement

- *B. cepacia* detected in the final product ABC cough mixture release testing, exceeding microbial limits

Investigation (Part IB)

- Microorganism related to quality of water
- Initial lab. Investigation performed concluded test results are valid as per 5M
- QA/ contract giver/ production informed

Initiation of Manufacturing and laboratory investigation (II)

- Contract lab: Concluded no abnormality, OOS confirmed
- Manufacturer: Cross functional team formed to investigate:
  - ❑ Production process reviewed and no abnormality found;
  - ❑ QA noted abnormal trend for water system monitoring results.

Investigation of Microbiological OOS and follow-up actions

Potential Assignable causes

- Water monitoring results showed high counts of microbes (within alert limits), investigation test results ID confirm presence of *B. cepacia*
- UV lamp was not replaced and used passed the recommended hours
- Sanitization not performed for 2 months due to reduced production volume

Impact Assessment & batch disposition

- Notify authority
- Batches in the market, prior to release, future batches
- Other products

CAPAs

- Change UV, update maintenance system to include periodic change
- Intensive sanitisation for 1 month, weekly sanitisation for 2 years
- Monitor microbial count (increase or decrease frequency)

References & Acknowledgement

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Thank you for your attention