Standard Operating Procedure **SOP050**

Title: CORRECTIVE AND PREVENTATIVE ACTION (CAPA) PROCEDURE

Location: CBE Laboratories

1. PURPOSE

This procedure establishes the process to identify, investigate, correct and/or prevent the causes of non-conformances or adverse events. The cornerstone of corrective and preventative action is written and retrievable documentation of actions taken and follow-up monitoring to determine that corrective and preventative actions have been documented, implemented and effective.

2. SCOPE

This standard operating procedure describes the procedure for recording and correcting the causes of non-conformity or adverse event, including but not limited to occurrences of microbiological contamination. The procedure is applicable to the laboratories of the Centre for Biological Engineering (CBE) and its personnel.

DEFINITIONS AND TERMS

- Corrective action - According to International Standards Organization (ISO), a corrective action is one undertaken to eliminate the causes of an existing non-conformity, defect or other undesirable situation in order to prevent recurrence. The term "correction" usually refers to the repair, rework or adjustment made to the product, process or quality system as part of the disposition of an existing nonconformity. A nonconforming product/process/quality system is one that does not meet the specified requirements. The corrective action relates to the elimination of the causes of nonconformity.

- Preventative action – According to International Standards Organization (ISO), a preventive action is an action undertaken to eliminate the cause of a potential non-conformity, defect or other undesirable situation in order to prevent its occurrence. The term "prevention" usually refers to the diagnosis of the root cause of the situation that caused or will cause nonconformities

- Corrective and Preventative Action (CAPA) report form - is used to initiate, track and complete identified corrective and preventative action.

- Non-conformance - This is non-fulfilment of a specified requirement of the Quality Management System or of a quality work product.

- An adverse event is an unanticipated problem involving “risk” to health and safety of workers or to the quality of work (impact on time, cost or quality of outcomes).

- Cause - A cause is a fundamental deficiency that results in a non-conformance or adverse event and is to be corrected to prevent recurrence or occurrence of the same, or similar, non-conformance or event.

3. RESPONSIBILITES

3.1. Person observing or detecting the adverse event/non-conformity

(i) Establishes the CAPA report form. Complete Section A of the CAPA form.

3.2. Person affected

(ii) Perform and document the immediate remedial action (section B of the CAPA form).

(iii) Investigate and document the cause of the adverse event/non-conformity (section C)

(iv) Assign and document the corrective and preventative actions to be taken (section D).

(v) After completion of Sections A to D, submit the CAPA form to the Quality Manager (QM) or Management Representative (MR)

3.3. Quality Manager (or Management Representative)

(vi) Review and verify the corrective and preventative action to be taken (section E of the CAPA form).

(vii) Follow up the progress and status of corrective and preventative action taken (section F of the CAPA form).

(viii) Review and verify the effectiveness of the corrective and preventative action implemented (section G of the CAPA form).

4. EQUIPMENT AND MATERIALS

None

5. PROCEDURE

5.1. Process

The corrective and preventative action process is illustrated in the flow chart (Figure 1). The steps are as follows

(i) When a non-conformity or adverse event is detected or observed, evaluate the situation and take immediate remedial action if practicable and safe to do so.

(ii) Report the adverse event or non-conformity to the Laboratory Manager and initiate a CAPA

form. Complete Section A of the form.

(iii) Document the remedial action in Section B of the CAPA form.

(iv) Begin investigation to identify the root cause of the adverse event or non-conformity and identify solutions for its resolution, noting observations, suggestions and the major areas/situations investigated. Complete Section C of the CAPA form.

(v) Identify the corrective and preventative action to be taken. Assign an action number and document in Section D of the CAPA form. Submit the CAPA form to the QM (or MR).

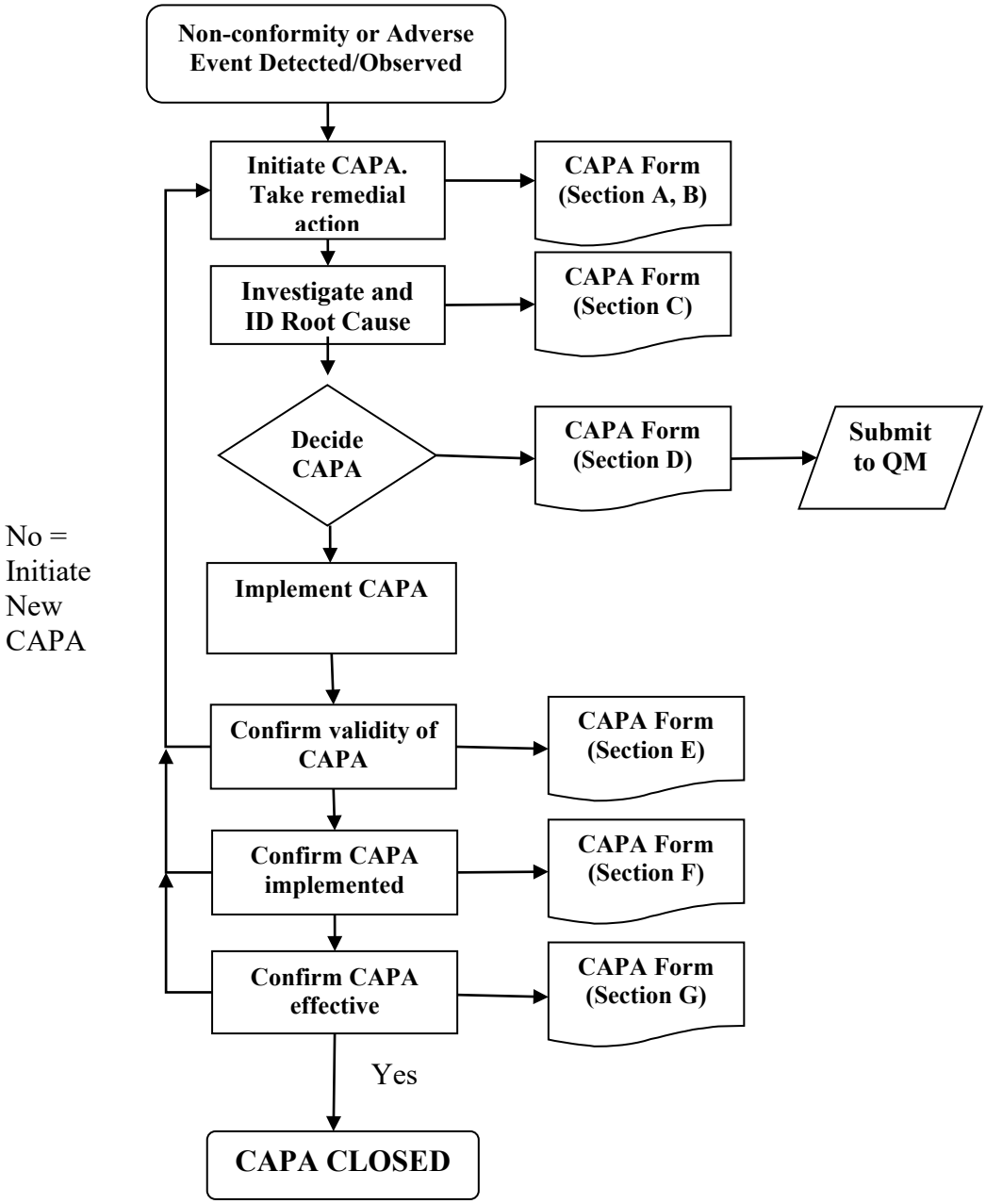
(vi) Implement the corrective and preventive action.

(vii) Review and verify the validity of the corrective and preventative action to be taken. If not valid, issue a new CAPA form.

(viii) Follow up the corrective and preventative action to confirm that they have been implemented. If not implemented, issue a new CAPA form.

(ix) Review and verify the effectiveness of the corrective and preventative action. If not effective, issue a new CAPA form.

Figure 1: Flowchart – Corrective and Preventative Action Process



5.2 Implementing Corrective and Preventative Action

5.2.1. Accountability for Corrective and Preventative Action

(i) The Quality Manager serves as a focal point for data quality, instrument/equipment problems, report and action quality and for feedback on corrective and preventative action taken.

(ii) Corrective and preventative action at the technical level is initiated and carried out by the laboratory worker. The person who 'created' the problem or the person that the problem affects fixes it.

(iii) The Laboratory Manager and the Quality System Manager detect and correct systematic problems which may occur in the course of daily work by maintaining surveillance over stated quality objectives, requirements and inspections/audits.

(iv) A sequential number for the CAPA form will be issued by the QM and serves as a tracking mechanism.

5.2.1. Initiation and Completion of Corrective and Preventative Actions

(i) The investigation of suspected quality problems is initiated as a result of quality control criteria being exceeded, specified requirements not being met, audit/inspection findings indicating systematic problems, or as a result of an observed/detected non-conformance or adverse event.

(ii) Corrective actions are of two kinds:

- On-the-spot or immediate remedial action to correct or repair non-conformance or adverse event, i.e. that are actions routinely made by laboratory staff; and

- Long-term corrective action to eliminate causes of non-conformities, adverse events or a complex deficiency i.e. that are actions normally identified by audits/inspections.

(iii) Preventive action plans are part of a proactive process for improvement rather that a reaction to problems. Preventive action includes the use of sources of information such as processes and work operations which affect quality, audit/inspection results, quality records to detect, analyze and eliminate potential causes of non-conformance or adverse event. Where practicable, the laboratory performs function verification and preventive maintenance on instrumentation. Service contracts with periodic manufacturer maintenance may be in effect for identified instruments.

(iv) A CAPA form is used to report the non-conformity or adverse event. This form provides the steps for a **closed-loop** process.

(v) Work is suspended if necessary e.g. in the event of a detected mycoplasma contamination. Action is taken to identify the causes of the problem and begin investigation to resolve the problem.

(vi) The findings are recorded on the CAPA form. Examples of findings or causes include but not limited to:

- equipment failure;
- incomplete or nonexistent procedures;
- non-compliance with procedures and regulations;
- improper collection, storage, handling, or preparation;
- calculation errors or transcription errors; and
- lack of training.

(vii) The cause and, if possible, the root cause is determined to correct recurrence of the problem and/or prevent occurrence of the problem and provide a permanent solution.

(viii) The conclusions and actions to be taken are recorded on the CAPA form. Examples of conclusions and actions include but not limited to:

- equipment repaired,
- procedures revised or created,
- product reworked to comply with procedures or regulations,
- correct calculation employed or transcription error corrected, and
- proper training given.

5.2.3 Submission to Quality System Manager and Follow up

(i) After completion of Sections A to D, CAPA forms with supporting documentation are submitted to the Quality Manager for review within an assigned number of days of the date the action was initiated (usually 30 days).This completion date is assigned by the Quality Manager.

(ii) The Quality Manager verifies the validity of the corrective and preventative action to be taken

(iii) The Quality Manager follows up and confirms that the CAPA has been taken

(iv) When there is objective evidence that the corrective and preventative actions are completed and effective, the Quality Manager approves and closes out the CAPA form.

(v) Monitoring the effectiveness of the corrective and preventive action is accomplished by for example following:

- Statistical process control charts;

- performance measurements and training;
- customer inputs;
- employee suggestions and inputs;
- audits, inspections and management review; and
- management, Health & Safety, laboratory meetings

6. DOCUMENTATION

The following records are outputs of this SOP:

i) FSOP050.1 Corrective Action and Preventative Action (CAPA) Form (available on CBE website)
ii) FSOP050.2 Cell Culture Investigation Form (available on the website)

These records shall be filed and stored in the CBE Office or otherwise archived for future review or retrieval.

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Appendix I (To be displayed in the CBE Laboratories for Guidance)

Corrective and Preventative Action Procedures Guidance sheet : Contamination

What do I need to consider?

1) What equipment have I used?
2) Which BSC(s), pipette fillers, pipettes, microscopes, water baths, and incubators have you used?
3) Do we need to quarantine the lab and who will be responsible for this?
4) Have you cultured this material before, in which lab(s)?
5) Has it spread? Who else is at risk? Do we need to extend quarantine area?
6) Who have you worked with?
7) Did it come from a vial or the cryobank (had it been previously banked?). If so, who else uses this cryobank? Who else is at risk? – what do we need to thaw and test.?
8) Cryostores – which banks/racks at risk?
9) Do we need to restrict access to the lab? Do we have enough disposable lab coats?
10) Have the Quality Manager and PI been informed?
11) Is there a common link? Repeat infections?
12) Can we confirm it has been dealt with? (monitoring?)

How do I deal with a Contamination?

1) Do I know what the organism is (e.g. rod-shaped motile bacteria, or fungal hyphae)?
   Yes – destroy (step 2)
   No - Take a Sample
   a. Take a sample of the medium (or samples, if multiple flasks) and place into a sealable centrifuge tube.
   b. Wipe the outer surface of the centrifuge tube(s) with 1% Virkon, then with 70% IMS.
   c. Seal the centrifuge tube(s) with parafilm then keep them in the cold room in a secure secondary container.
   d. Ensure the container and tube are properly labelled with the date, user, and cell line identity and that the contents are contaminated.

2) Dispose of samples/flasks - Use an autoclave (cycle 5), or submerge samples/flasks in 1% Virkon and leave overnight.
3) If culture solutions (e.g. culture medium, wash solutions, enzyme solutions) remain unused, then sample them under quarantine (in a Biological Safety Cabinet), place 5 ml of each into sterile T25 flasks, then put them in an incubator. Inspect the flasks the following day for signs of contamination.
4) Change your lab coat (or change all lab coats if major contamination (mycoplasma) is detected).
5) Contain the laboratory area and prevent other users from using the same equipment (e.g. pipettes, pipette fillers, biological safety cabinets).
6) Inform laboratory management/PI/Lab users.
7) It is recommended that you discard any opened and unused culture solutions (including growth medium, enzyme solution, saline solutions, etc), pipette tips, tissue-culture flasks.
8) Deep clean of equipment used with 1% Virkon, followed by 70% IMS:
   a. Pipette fillers (including filter change)
   b. Pipettes
   c. Microscope stage
   d. Biological Safety Cabinet(s)
   e. Other items (e.g. shaker plates, cell counting equipment)
9) If a major contamination (e.g. mycoplasma) is suspected, a deep clean of the laboratory and a full investigation (CAPA) is necessary.
   a. Internal PCR testing (mycoplasma)
   b. External testing (mycoplasma)
      i. Unknown samples may be sent externally for identification.
10) Establish a monitoring period for future culture. Does the contaminant reappear? If so, consider that the cell bank(s) themselves may be contaminated.
11) Photograph what you see (e.g. camera-phone or microscope images), to help determine whether contaminants are repeatedly occurring.

Sources of contamination

1) The number 1 source of contamination is always the operator.
We harbour numerous bacteria, fungi and other microbes in and on our bodies. Without good cleaning and aseptic technique, these microorganisms will enter your cultures. Are you unwell? Is being in a rush resulting in lax aseptic technique? Do you feel sufficiently trained and confident in your aseptic technique?. Is the laboratory over capacity?..Has hair been tied back /facial hair covered?

2) Culture vessel(s)
The outer surface of flasks/plates will pick up environmental contaminants over time, which can enter the vessel if surface sanitisation is not performed properly. How thoroughly do you wipe down your culture vessels with Chemgene?

3) The laboratory environment
Dust and particulates are a ready source of microbes shed from humans and entering from the outside world. Mud and dust from roads, streets and fields adhere to clothes and boots alike. Collectively, the entire laboratory environment is contaminated to some degree. Have you sanitised your working environment properly? Have you checked that the biological safety cabinet is operating properly? . Is the air flow in the laboratories working correctly?

4) Liquid media (e.g. culture medium, enzyme solutions)
All liquid media, especially nutrient-rich culture media, are the perfect environment for growth of many microbes. Has the medium been prepared aseptically? Has it been sterile-filtered (note: will not remove viruses or mycoplasma). Have these solutions been used by other operators? Have you aliquoted your medium and tested it for contaminants before use?

5) Water bath
Water baths are good environments for microbial growth and exposed to the environment on a continual basis. When was this last cleaned? Has it been neglected over the last few weeks?

6) Disposables (e.g. pipette tips)

Frequently used disposables like pipette tips are repeatedly exposed to contamination even inside a biological safety cabinet. Have you disposed of old tips? Are you sure you are the only user of these tips? Would discarding them and using a new unopened pack be less risky for important work in future?

7) Cross contamination from other labs?

Other laboratory spaces may be used to culture microbial cells, or other mammalian cells. Ideally, activities should be contained within specific laboratory spaces. Has there been unusual movement of cell materials between laboratory spaces recently? .Has equipment been moved between labs (pipettes?)

8) Material used within cultures (metals/polymers/ceramic). Have they been sterilised correctly?

9) Is the external cell source of good quality? Are their contaminant screening tests up to scratch?

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SOP Version History

Version Reviewed	Date Revised/ Reviewed	Revision Summary	New Version Number
001	26.08.09	Minor editorial changes to the format of the Corrective Action Problem Report. Revised to include (i) a table (section D & 'follow up' section) to monitor action progress and (ii) an assessment of impact (section B). No alteration to procedure – database updated. Hardcopy not circulated.	002
002	21.07.10	SOP revised to combine corrective action procedure (SOP050) with preventative action procedure (SOP051). The CAPA form has been reformatted to provide clarity on reporting lines and to distinguish the actions as corrective or preventative. The procedure, driven by the form, has been upgraded and simplified.	003
003	01.10.12	Annual Review – Format revised. Submission process to QM clarified in sections 3 and 5	004
004	23.10.2017 C.Kavanagh	**i)**Annual Review ii)SOP revised to reflect changes to recording of Cell culture contaminations. Cell Culture contaminations will now be logged using a cell culture questionnaire (introduction of a new form FSOP050.2) rather than through the CAPA form FSOP050.1. This is has been done to encourage better reporting of contaminations to ensure patterns are identified. However, a CAPA may still be written for a contamination if root cause cannot be found and more investigation required. iii)Appendix added which contains guidance on how to complete the cell culture questionnaire form, what you need to consider if you discover a contamination and how to deal with a contaminations.	**005**
005	**20th April 2020 C.Kavanagh**	**Minor editorial changes only**	**005**
005	**18th January 2022 by C.Kavanagh**	**No amendments**	**005**

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