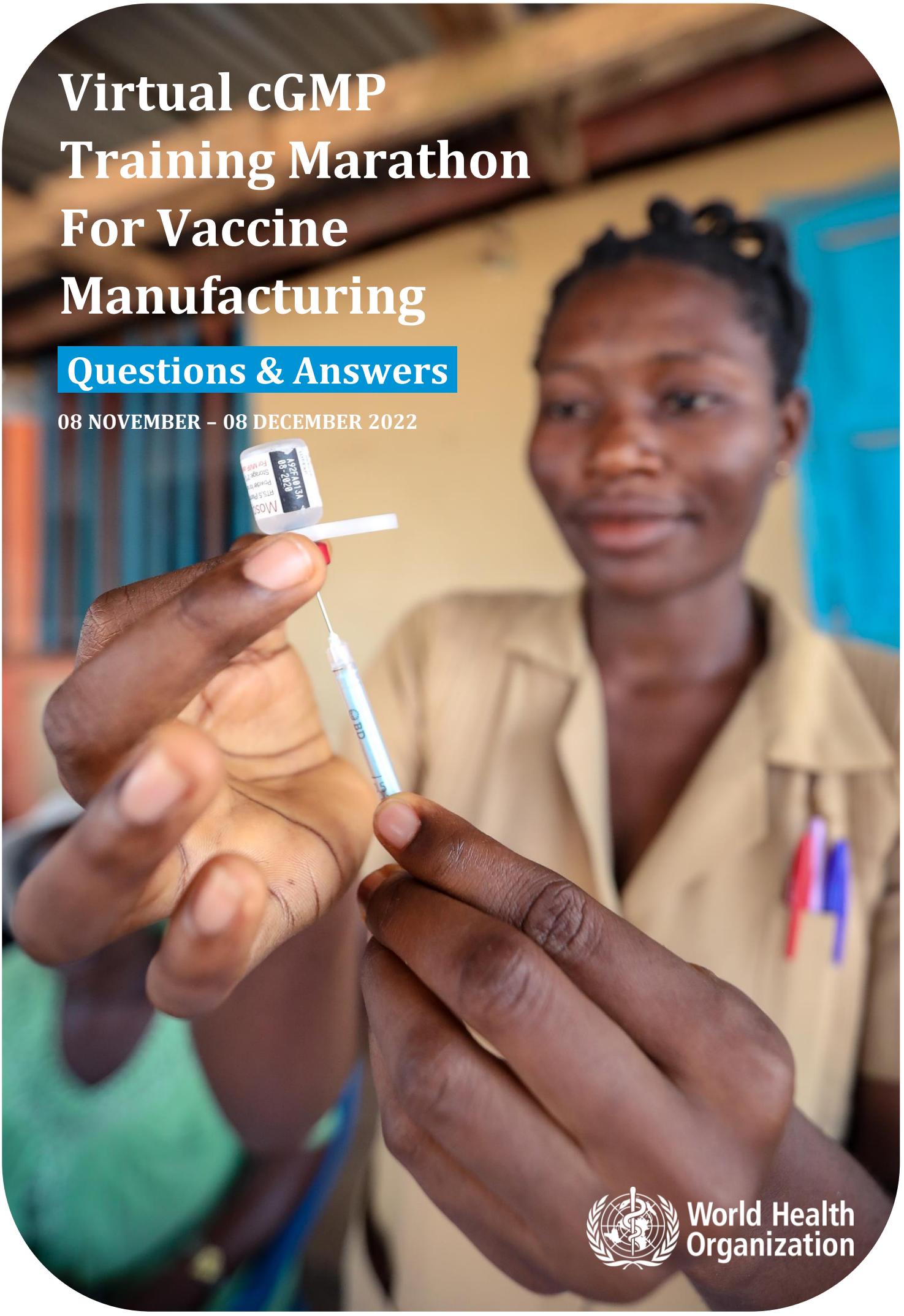
Virtual cGMP Training Marathon For Vaccine Manufacturing

Questions & Answers

08 NOVEMBER – 08 DECEMBER 2022



World Health Organization

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ABBREVIATIONS

ACPH	Air changes per hour
ADE	Acceptable daily exposure
AMT	Analytical method transfer
API	Active pharmaceutical ingredient
APS	Aseptic process simulation
AQL	Acceptable quality level
ASTM	American Society for Testing and Materials
ATP	Adenosine triphosphate
BCG	Bacillus Calmette–Guérin
BIBO	Bag-in bag-out
BMS	Building management system
BSE	Bovine spongiform encephalopathy
BSL	Biosafety level
CAPA	Corrective action and preventive action
CCIT	Container closure integrity testing
CCS	Contamination control strategy
CFU	Colony-forming unit
cGMP	current Good Manufacturing Practices
CIP	Clean-In-Place
CNC	Controlled non-classified
Cpk	Process capability index
CPP	Critical process parameters
CPV	Continued process verification
CQA	Critical quality attributes
DI	Data integrity
DPB	Dynamic pass box
EM	Environmental monitoring
EU	European Union
FDA	Food and Drug Agency
FMEA	Failure modes effects analysis
FMECA	Failure modes effects criticality analysis
FPP	Finished pharmaceutical product
GDocP	Good documentation practices
GLP	Good laboratory practice
GMP	Good manufacturing practice
GxP	Good practice
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPC	In-process control
IPR	Intellectual property rights
LAF	Laminar air flow
LCL	Lower control limit
LMIC	Low- and middle-income country
LPA	Local Production and Assistance Unit in WHO
MA	Marketing authorization
MAH	Marketing authorization holder
MAL	Material air lock
MAP	Mouse antibody production
MCB	Master cell bank
MKT	Mean kinetic temperature
MMR	Measles, Mumps, and Rubella
mRNA	Messenger ribonucleic acid
MSL	Master seed lot
NVPC	Non-viable particle count
OD	Optical density
OOT	Out of trend
PAT	Process analytical technology
PB	Pass box
PDA	Parental Drug Association
PIC/S	Pharmaceutical Inspection Co-operation Scheme
Ppk	Process performance index
PPQ	Process performance qualification
PQ	Prequalification
PV	Process validation
PVC	Polyvinyl chloride
QC	Quality control
QMS	Quality management system
QRM	Quality risk management
R&D	Research and development
RABS	Restricted access barrier system
RMM	Rapid microbiological methods
RMT	Risk management tools
RODAC	Replicate organism detection and counting
RPM	Revolutions per minute
RPN	Risk priority number
RPQ	Regulation and Prequalification Department in WHO
RRF	Risk ranking filtering
RU	Receiving unit
SAL	Sterility assurance level
SIP	Sterilization-In-Place
SOP	Standard operating procedure
SU	Sending unit
TeNT	Tetanus neurotoxin
TFF	Tangential Flow Filtration
TRS	Technical Report Series
TSE	Transmissible spongiform encephalopathies
TT	Technology transfer
TTP	Technology transfer program
UCL	Upper control limit
UDAF	Unidirectional air flow
USFDA	US Food and Drug Administration
USP	United States pharmacopeia
VHP	Vaporized hydrogen peroxide
VMP	Validation master plan
VPC	Viable particle count
VQR	Vaccine quality and regulations
WCB	Working cell bank
WHO	World Health Organization
WSL	Working seed lot
WVSB	Working viral seed bank

INTRODUCTION

The Local Production and Assistance (LPA) Unit, in the Regulation and Prequalification Department (RPQ), WHO headquarters, supports Member States, particularly low- and middle-income countries (LMICs), to strengthen local production toward quality assurance and sustainability to improve access to essential medical products. The LPA Unit provides assistance and support in a holistic manner to Member States in strengthening sustainable quality local production of essential medical products, such as conducting ecosystem assessments for sustainable local quality production, developing strategies/roadmaps and tools, providing capacity building and WHO Prequalification (PQ)/Emergency Use Listing (EUL)-related specialized technical assistance, and facilitating technology transfer.

In response to Member States' requests for capacity building in the local production of quality-assured pharmaceuticals and vaccines, the LPA Unit has been organizing the Virtual cGMP Training Marathon for three consecutive years since 2020. A selection of key current good manufacturing practices (cGMP) topics was delivered virtually in a marathon fashion for several consecutive weeks with content based on current WHO GMP guidelines. The first Virtual cGMP Training Marathon in 2020 strengthened foundational knowledge of WHO cGMP for pharmaceutical manufacturing. The second Virtual cGMP Training Marathon in 2021 focused on building the fundamentals of cGMP for vaccine manufacturing.

The 3rd Virtual cGMP Training Marathon for Vaccine Manufacturing was delivered virtually by the LPA Unit in a newly designed format from 8 November to 8 December 2022. Part 1 delivered in-depth content on facility design, technology transfer and advanced concepts of GMP for quality vaccine production; Part 2 was a hands-on group work for a small group of participants to solidify their learning and skills using real-life scenarios and pre-selected Quality Risk Management tools. More than 1200 vaccine and biopharmaceutical manufacturers and officials from national regulatory agencies and government ministries/institutions from around 80 Member States in the six WHO regions successfully completed Part 1 of the training marathon.

The most frequent questions raised in Part 1 of the 3rd Training Marathon have been assembled in this Question & Answer (Q&A) document with answers from GMP experts with long and rich experience in the pharmaceutical & biopharmaceutical industry, national regulatory authority, and other organizations. This is the 2nd Q&A document released for the series of Virtual cGMP Training Marathons organized by the LPA Unit; the 1st Q&A document was released following the Virtual cGMP Training Marathon for Vaccine Manufacturing in 2021. Its format allows the reader to easily refer to the questions under each specific session and topic. This is a continuous learning resource for participants and other relevant stakeholders to acquire new capacities to strengthen their local production of safe and quality vaccines.

SESSION

1

Quality risk management implementation on vaccine manufacturing

08 November 2022

1 Are multiple tools needed for risk assessment, or can a single tool be used to identify risk?

It is not necessary to use multiple tools for risk assessment (which includes 3 steps, i.e., risk identification, risk analysis, and risk evaluation). However, depending on the case, the tools should be selected based on the process' type and stage being analysed and the knowledge of the quality risk management (QRM) team. A single tool can be used for hazard identification. Some QRM tools such as Ishikawa diagram and Mind mapping are very useful for hazard identification.

2 What is the major difference between failure modes effects analysis (FMEA) and failure modes effects criticality analysis (FMECA)?

FMEA will evaluate the risk and is reported as risk priority number (RPN) as a quantitative evaluation, while FMECA will determine 'criticality' of the risk based on those RPNs as a qualitative evaluation. In short, FMECA is FMEA with the addition of a criticality analysis step at the end.

3 Are 0.22 micron (µm) sterilizing filters considered the golden benchmark for sterilizing filters, or are there any sterilizing filters below 0.22 µm? Also, how are these sterilizing filters validated?

A 0.22 µm filter is used for sterilizing filtration. 0.1 µm filter can be used to enhance removal efficiency for Mycoplasma species. 0.22 µm filters are qualified by bacterial retention test, i.e., challenging with appropriate bacteria such as *Brevundimonas diminuta* (minimum load of 1 x 10^7 colony forming units/cm^2 effective filter area) standard test method (ASTM 838-05). In addition, they are also qualified for compatibility with the vaccine, in terms of leachables, extractables and antigen retention.

4 Is there a specific QRM tool for management and classification of deviations?

For classification of deviations, please refer to the (draft) "Deviation Handling and QRM: A note for guidance for the manufacture of prequalified vaccines for supply to United Nations agencies July, 2013" - Vaccine Quality and Regulations (VQR), Essential Medicines and Health Products -World Health Organization (WHO), Geneva, Switzerland as a guide. The suggested tool is a simple questionnaire based on decision tree provided.

5 What are the risks associated to documentation?

The associated risks are poorly updated and non-good manufacturing practice (GMP) or non-regulatory compliant prescriptive document. Records may not comply with good documentation practices (GDocP) and data integrity (DI). QRM is expected to be integrated into the quality management system (QMS), such as to review current interpretations and application of regulatory expectations, to determine the desirability of and/or develop the content of standards operating procedures (SOPs) and guidelines to develop a good record form to enable GDocPs.

6 How is knowledge management considered in the QMS?

According to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q10 clause 1.6.1, "Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer (TT) activities; process validation (PV) studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities." It is expected that knowledge from processes and systems is appropriately utilized.

7 In risk management, what determines whether single or multiple chromatography stages are needed?

The design of the purification process depends on the product to be purified and prior knowledge about the product and process. In general, the purification process should be simple but efficient. Fewer steps are preferred.

8 What are the stages for the performance of a proactive risk assessment?
Proactive risk assessment is performed to identify and control potential quality issues of the product and the process before they arise. It is used to manage the risks associated with process effectiveness and product quality. Effective and proactive QRM can facilitate better, more informed, and timely decisions throughout the product life cycle, starting from pharmaceutical development to TT, and from commercial manufacturing to product discontinuation.

9 How is quality risk assessment applied in out-of-specification (OOS)?
QRM is used for investigation and impact assessment of the OOS to product quality and for corrective action and preventive action (CAPA) identification.

10 How can risk control mechanisms be applied at aseptic downstream processes, like the cell banking in deep freezer and onward purifications?
In a first instance, process steps (process flow diagram) need to be defined, and then the risk assessment, including hazard identification, risk analysis and risk evaluation, on each unit operation should be performed by using appropriate QRM tools. Later, risk control measures will be determined for the processes which are not acceptable when compared with the acceptance criteria.

11 On zoning of the water system, how to determine if a loop separation of the biopositive area (live bacterial area) and the bionegative area is required?
QRM must be applied for the design of premises, facilities, and utilities to prevent cross contamination between the biosafety and non-biosafety zones. However, it is common industry practice and a typical regulatory expectation that separate water loops are available for live and non-live areas.

12 What are the risks related to batch release assessment? What are the key issues to be considered if the National Regulatory Authority (NRA) performs release of batches based on overseas certification?
The risk would be the release of a substandard batch. The key issue to be considered is how reliable is the received batch release certification. The local NRA should have enough documented evidence to ensure that the batch meets the quality standards. In addition, some simple tests (such as visual inspection) could be carried out to verify the product's quality.

13 Can all the risks in vaccine manufacturing process be controlled by a validation study of each process?
Control strategy can include various control measures, one of which is process validation (PV). However, there are other control measures which should be additionally implemented such as specification and testing of the starting materials, intermediates, and final product. Please refer to ICH Q8 for more information.
Contamination control strategy (CCS) shall be implemented to minimize contamination of microorganisms, pyrogens/endotoxins and particulates in the vaccine product. Several elements should be included in the CCS and control measures should be implemented for design of the plant and processes, premises and equipment, personnel, utilities, product containers and closures, vendor control, outsourced activities, validation of sterilization processes, preventive maintenance, cleaning, and disinfection, monitoring systems for environment and utilities, etc. Please see more details in Pharmaceutical Inspection Co-operation Scheme (PIC/S) and European Union (EU) GMP Annex I (22 August 2022).

14 Is it acceptable to reduce severity during RPN's determination?
QRM is a systematic process to assess, control, review and communicate the risks to medicinal products' quality. The evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient. The QRM tool used should minimize subjectivity for risk analysis and evaluation. To reduce severity score during RPN determination, you need to be sure that the pre-determined scoring criteria has been well described and applied and you have enough scientific supportive information. Normally, severity score cannot be reduced.

15 What is the approach to periodic risk review? Should there be a mandatory prescribed period in the SOP?
A mechanism to review the risks/events should be written in a formal document, such as a quality manual, quality policy, guides, etc. The output and results of the risk management

process should be reviewed to take into account new knowledge and experience. Risk review should be done on events that might impact the original QRM decision, whether these events are planned (e.g. results of product review, inspections, audits, change control) or unplanned (e.g. root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk.

16 Is detectability correlated to a higher risk or severity? When risks are detectable and can be controlled, will the risk be at a minimum?
Increased detectability will reduce the risk.

17 What are the recommendations on risk assessment and cleaning validation for research and development (R&D) phases?
Please refer to the ASTM document "Standard Guide for Science-Based and Risk-Based Cleaning Processes Development and Validation" for guidance. However, please note that macromolecular therapeutics and peptides can easily degrade and denature when exposed to extreme pH or heat and may become pharmacologically inactive. A toxicological evaluation (severity based on acceptable daily exposure (ADE)) may therefore not be applicable in these circumstances.
Please also refer to WHO Technical Report Series, No. 1033, 2021, Annex 2.

18 How to deal with subjectivity during FMEA?
The scoring definition and criteria must be clearly written and the risk acceptance must be predetermined. The use of diverse risk assessment teams, being aware that uncertainty may be present while analysing risks and establishing a likely range of any risk rating that is difficult to assess and basing risk assessments on scientific facts, historical and experimental data/ information can help to reduce subjectivity during FMEA scoring.

19 Why FMEA is not considered a qualitative method?
FMEA itself gives the RPN score which is a quantitative output. However, the FMEA colour code system provides a partial qualitative output.

20 Is it possible to score probability based on historical data or brainstorming?
Probability score could be determined from historical data and scientific knowledge.

21 Are there any risk management tools (RMT) used to categorize dossiers for evaluation according to their risks?
There is no specific tool available. However, the risk ranking filtering (RRF) tool can be considered.

SESSION

2

Key facility design: aspects to facilitate compliance (including biosafety)

10 November 2022

1 Can different vaccines, or vaccines and other sterile preparations, be manufactured in the same facility with proper change-over procedure in place?
It is all with the nature of the vaccine(s): whether they can be considered as containing live (attenuated) organisms or if they are killed organisms or fractions of it. As a rule, it is better to separate biologicals (including vaccines) from general (chemical) entities. In any case, a fully validated cleaning and change-over procedure should be in place. Also, the type of operations to be carried out should be considered: a) in general, different antigens fermentation methods may need different fermentation or purification equipment and technology or even dedicated facilities, especially for spore forming toxoids; b) in contrast to form and fill operations those are broadly similar, yet there are still restrictions regarding which vaccines can share facility for safety reasons.

2 When a drain cannot be placed in class A/B, how is the outlet for the Clean-In-Place/Sterilization-In-Place (CIP/SIP) from the filling machine handled?
When good manufacturing practices (GMP) guides for sterile products mention "no drain in class A/B" it translates into: no classical (open) drain in the A/B room(s). Closed pipes/vessels that are to be connected with the CIP/SIP drainage are authorized when kept tightly closed during preparation and manufacturing operations. Only after operation and removal of the last filled unit, the pipes/vessels can be connected to the drainage(s). It should be noted that the discarding vessels should not be in overpressure to the class A/B (but instead in low pressure).

3 Is it possible to implement a ballroom cleanroom concept for vaccine manufacturing?
While designing a facility for bioprocessing, quality risk management (QRM) principles shall be applied taking into consideration process definitions, product risk profile, operational technologies used, degree of manual operations, degree of closed system security and the GMP/ biosafety level (BSL) requirement so that the scope of risk assessment and potential impacts are clear. If risks are considered manageable for some process steps, ballroom concepts may be advantageous from a flexibility, cost, and capacity perspective. Commonly, the ballroom concept is considered very risky. We (our parents) learnt it with the classical chemical manufacturing in the 50s in relation with the risks or errors and cross contamination. However, the modern techniques (with tight connections and, for example, poka-yoke solutions) can be qualified for working in ballrooms. Where this could have been chosen as an option, once again BSL should be considered, and applied only for BSL2 as a general rule.

4 Can risk assessment be performed to allow movement of pieces of equipment, such as an environmental monitoring (EM) device, between different production areas?
Movable equipments have a higher risk of contamination. Two types of contamination risks can occur: cross-contamination and microbiological contamination. Therefore, the good practice (GxP) is to avoid moving equipments and instruments in between different cleanliness classes and especially in between upstream and downstream areas.

5 What is the best containment approach and required air changes per hour (ACPH) for a vaccine manufacturing facility?
The risk associated to the organisms' nature will be taken into consideration to design the ACPH value. Key points to consider are: a) that the ventilation is permanent during the production process until fumigation is needed; b) that the relative air pressure designed from a room to another is maintained; c) that there is an effective flush of the room by the air, as visualized by air flow pattern studies. The higher the ACPH, the easier the adjustment, and higher are the investment and running costs. However, as a very rough indication, it is possible to consider a minimum of 20 ACPH (the higher the ACPH, there will be better elimination of contaminants).

6 What is the reason for sampling incoming material at the time of receipt?
Except if the manufacturer has a full control over materials that are supplied and delivered, it is necessary to check and ensure that the expected specifications are respected for each delivery. Moreover, the possible degradations occurring during transportation should not be neglected. In any case, all containers of incoming materials should be tested for identity.

7 For a quality control (QC) laboratory, is it acceptable to have a shared heating, ventilation and air conditioning (HVAC) system with the production area, or should it be separated?
WHO GMP general guide, Technical Report Series (TRS) 986, Annex 2, clearly states in paragraph 12.35 that HVAC should not be shared between QC laboratory and production areas.

8 Why Bacillus Calmette–Guérin (BCG) related materials cannot be produced with other biological products in the same facility?
BCG being a Bacillus tends to form spores. As spores are extremely resistant, the existing regulations do not allow other products to be manufactured in the same facility (at least for the next thirty years or more).

9 Are dedicated autoclaves required for deactivation and sterilization of equipment?
Definitively yes, two different autoclaves should be used for sterilisation (flow-in) and destruction (flow-out) in the vaccine facilities. This is a strong WHO recommendation from TRS 961, Annex 2, Paragraph 4.3.5.4.

10 Why is the centrifugation process deemed as highly contaminating?
The use of centrifugation equipment tends to be accompanied by the creation of aerosol drops. These drops contain organisms, creating a higher risk of contamination.

11 Between the dynamic pass box (DPB) and material air lock (MAL), which is the preferred option for a better control?
The criteria to decide between pass box (PB) and MAL is often the size of the item(s) to be entered in, or removed from. PBs are generally less expensive than airlocks and represent a lower risk than MALs. Another advantage is that it is possible to "superpose" two PBs: one for entry (upper PB) and one for exit (lower PB).

12 Can mechanical door closures be placed in an airlock opening to negative pressure side?
Closure mechanisms should be strong enough to maintain the door closed against the pressure force. Movement of the door can be ensured by the mechanism (if sufficiently strong) or by the personnel. The most important is to keep the doors closed.

13 What does bag-in bag-out (BIBO) housing means?
BIBO is a system into which the used filter(s) containing organisms or other undesirable particles are directly introduced in a flexible plastic sleeve which is almost instantly sealed to keep the dirty or contaminated filter(s) in a closed bag. These bags are then destroyed (usually by incineration).

14 What is the degree of segregation needed in multi-product facility?
Segregation is led by: a) the BSL classification of the organisms and b) by the process technology being used.

15 Which temperature range , 16-25 ºC or 19-23 ºC, should be considered in a manufacturing site setting?
There is no standard requirement with the temperature in manufacturing rooms. However, the temperature range that should be considered mainly depends on specific product and process requirements, including those of the product specifications. Then, considerations should be given to provide the most possible comfortable conditions for the operators. In general (not a strict rule), one can find two different targets: 18°C$\pm$2°C and 21°C$\pm$2°C.

16 Is fumigation allowed in a production area, especially class A?
Fumigation (or fogging) necessarily involves hazardous chemicals with different levels of toxicity and aggressivity. For example, formaldehyde is toxic to humans, hydrogen peroxide (currently the most popular agent) is damaging to several surfaces. Both are allowed for decontamination of clean rooms including but not limited to class A environments.

17 Is it a requirement for BSL3 and BSL4 areas to have a negative air pressure relative to the environment? What air or HVAC classification is needed for this environment?
It is a requirement that BSL3 and BSL4 areas are maintained under a negative pressure compared to the surrounding areas and, if possible, in a lower air pressure than the atmosphere. The reason is to keep the (pathogenic) microorganisms inside these areas. The air exiting these areas is high-efficiency particulate air (HEPA) filtered. Air classification (A, B, C, D) is a different topic; it depends on the operations to be carried out in these areas. For example, the manufacture of

non-sterile preparations will not be as demanding as the manufacture of sterile injectable preparations.

18 Can a laboratory be functional without a controlled environment?

No. Testing biologics in a non-controlled environment is definitively not testing in GMP conditions.

19 In which class does the inoculation of eggs occur?

There are two conditions for inoculation of egg-based vaccines: a) from a microbiological point of view, the inoculation should be performed under a protective laminar air flow (LAF)/ unidirectional air flow (UDAF) to avoid contamination with other organisms, b) from a biosafety point of view it depends on the BSL or the inoculated virus (Influenza is BSL2; Yellow Fever is BSL3).

20 Which guideline describes the recommended cleanroom classification for the different stages of vaccine manufacturing?

The 3rd edition and the 4th edition of the WHO "Laboratory Biosafety Manual" in addition to WHO TRS 961-Annex 6 (GMP for sterile pharmaceutical products) and WHO TRS 986-Annex 2 (Main GMP principles) are among recommended guidelines.

SESSION

3

Basis for a sound environmental monitoring program in vaccine manufacturing

15 November 2022

1 Is there any guideline for the environmental monitoring (EM) of the isolator system, where the filling is carried out in grade A and in background grade C?
United states pharmacopeia (USP) 1116 mentions values inside the isolator, as well as monitoring frequencies, independently from the background classification.

2 What should the background environment of an isolator be? Which WHO guidelines refer to this requirement for production of vaccines and biosimilars in isolator with its corresponding background environment?
WHO Technical Report Series (TRS), No. 1044, 2022, Clause 4.20 (i)(a) recommends the following for isolators: "a) The background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should be based on risk assessment and justified in the contamination control strategy (CCS)."
Canadian CDN GUI 0119 recommends a class D at least whereas the Annex 1 of the EU Guidelines (2022) states that the background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should be based on risk assessment and justified in the contamination control strategy (CCS).

3 What is the WHO Sterility Assurance Level (SAL)?
SAL gives a probability. Mathematical probabilities range from 0 to 1, where a probability of 0 means there is a 0% chance of an event occurring, while a probability of 1 means there is a 100% chance of an event occurring. Since it is impossible to ensure a sterilized piece of equipment is completely free of microorganisms, the SAL can never equal 0. However, the value of SAL can be very small. The accepted value is 1 in one million (10^{-6}) and there is no specific WHO value.

4 What is the difference between media preparation and buffer preparation? Does the sequence in processes matter?
It is a pure terminology matter: we use the word media when the products are used in the upstream phase and buffer in the downstream purification phase. Media are used for growing, washing, detaching and protection of microorganism and cells.

5 Is non-viable particle count (NVPC) monitoring required during open operations where viable particle count (VPC) is also carried out?
NVPC and VPC look at different types of contamination, and guidelines recommend that both types of measurements should be implemented.

6 In a passive EM program, what is the rule of thumb for the number of 90 mm plates that should be exposed? Is it the square root of the area of the room or the square root of the volume of the room?
There is no rule of thumb and certainly no relationship to the surface or volume of the room: the user must consider where the product or the open containers are at risk of particle or microbial contamination and place the monitoring devices in the immediate vicinity of those points, whilst ensuring that monitoring and sampling activities will not compromise the quality of the product.

7 Is environmental classification synonymous with environmental qualification?
Environmental qualification includes all environmental parameters (non-viable particle (NVP), viable particle (VP), humidity, temperature, light, pressure, etc.) whereas the air grade classification is done according to ISO 14644 and involves NVP only. As described in WHO TRS, No. 1044, 2022 and in EU Annex 1 2022, classification should be carried out "at rest" and "in operation" states. Classification is part of the qualification process of clean rooms.

8 For a production filling process room that had 10 sampling zones (equivalent to 10 sampling locations) for classification purpose, a risk analysis outcome defined less than 10 sampling locations can be used for monitoring. Is this acceptable?
The number of locations for classification is fixed on a geometric base, while the number of locations for monitoring is fixed on a risk base: consequently, the 2 figures do not have to match and you could have more or less points in monitoring, depending on the activities in the room and the criticality of the process, including type of equipment (e.g. open filling or restricted access barrier system (RABS).

9 Should the CCS and planned set of controls be identified and put together in a unique document?
To gather standard operating procedure (SOPs), policies, and other guidelines on CCS in a separate document makes sense. It would be like a validation master plan (VMP) or a water quality manual.

10 Does all 4 methods for monitoring of viable particles need to be performed?
Active sampling, passive sampling and surface sampling (replicate organism detection and counting (RODAC) or swabs) cover different purposes and are specific for certain situations: e.g. to monitor gowning, RODAC plates are the suitable method, while swabbing is best adapted for difficult to access areas.

11 Should EM, including surface and personnel, be applied in air cabinets (laminar air flow (LAF)/ biological safety cabinet (BSC)) in non-classified laboratories?
It depends on the application: for instance, for bacterial limit tests, it is important to know if the observed values come from the product or from the environment in which the tests are performed.

12 What is the bioburden limit for drug substances before filtration? If drug substance sterility fails after filtration, is refiltration or reprocessing recommended?
In the case of a sterile drug substance, the limit of 10 CFU/100 mL is specified (see EMA document EMA/CHMP/CVMP/QWP/850374/2015). If drug substance sterility fails after filtration, a renewed filtration may be possible, but only after an investigation of the earlier failure.

13 How is process mapping used to determine the level of EM in manufacturing units?
The mapping outlines the current state of the process steps and any gaps or issues with the current mode of operation (in this case contamination possibilities and negative influence on quality). Once the process is mapped out and possible improvements are studied and implemented, the user can evaluate the remaining risk and define the necessary level of monitoring.

14 The rapid methods based on adenosine triphosphate (ATP) have had difficulties to be implemented as they are not covered by a regulation that indicates acceptance parameters, but also because it is difficult to find a relation with the colony-forming unit (CFU) parameter. How could these methods be used and how can they be implemented with better acceptance?
Correct, there are no guidelines at this moment, and rapid microbiological methods (RMM) are more often used for quick results than for final decisions on quality. Nevertheless, it is interesting and rewarding to evaluate both methods in parallel to anticipate the upcoming guidelines. The appropriate pathway for rapid microbiology submissions to the Food and Drug Administration (FDA) is best determined through direct dialogue with the agency, as the process analytical technology (PAT) initiative recommends discussion with the FDA regarding all aspects of implementation for new process analytical methods, and this can apply to RMMs as well.
The currently available guidance on RMM validation can serve as a starting point for discussions and can include the revised parental drug association (PDA) Technical Report No. 33 (2013), and the current versions of USP Chapter 1223 and Ph. Eur. Chapter 5.1.6. However, a firm may also develop its own validation strategy, if it is scientifically sound and defendable.

15 The EM's risk-based design is a live thinking design that needs to be updated regularly, either based on the previous EM data trend, criticality process, new activity, etc. A risk-based design can sometimes be different from personnel to personnel depending on their maturity to analyse the risk and identify it. Is it a requirement to perform a periodic re-assessment?
There is always a part of subjectivity in risk evaluation, but on the other hand, such evaluations are performed by a group of stakeholders belonging to different disciplines. Like for any other document, regular updates are necessary, considering findings from direct measurements or from data collected in the annual product review and in batch records. QRM process states that remaining risk should be monitored and reviewed periodically, and trends assessed for improvement (ICH Q9).

16 How is data integrity (DI) maintained if the bioburden test plates with the bioburden colonies, referred to as raw data, are discarded?
The original recorded results should be maintained according to the manufacturer´s documentation system. If it is a manual entry, then the record sheet or logbook should be kept. In this case, photographs may be taken, dated, and signed, and these should form part of the record. In all cases, data integrity is defined by the ALCOA+ principles: Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available.

17 Does EM also apply to vaccine quality testing laboratories (seed testing, virus neutralization test, etc)? Should test laboratories be categorized as a clean room or biosafety level (BSL)? How is EM program applicable in laboratories?
Monitoring and BSL are different issues. Each laboratory will have a certain BSL according to the organisms being handled. For sterility testing, monitoring is required as it deals with an A in B area (different rules apply of course if there are sterility testing isolators). For the other activities, monitoring of adventitious organisms is important as you want to keep strains and cell lines clean.

18 What is the rationale to expose the settle plate for 4 hours?
Experience shows that plates exposed for more than 4 hours tend to dry, and so the growth promoting effect is gone.

19 What is the frequency of identification of microorganisms?
Regular update of house isolates (yearly suggested) and ad hoc identification in case of abnormal quantities.

20 Does the continuous pressure differential trending require minute-by-minute data? Is it acceptable to have 10 minutes interval for data trending?
Regular intervals close enough to catch deviations are needed. Minute by minute data is not required. In more modern factories, building monitoring systems (BMS) will monitor this parameter on a continuous basis.

21 Is there any recommendation on the frequency to review alert limit and action limit of EM data?
Reviews are done on regular intervals, often yearly, but if new contaminants are discovered, an earlier modification to protocols must be foreseen.

22 Does a deviation need to be raised when the temperature is out of limit (25-30 °C) but the mean kinetic temperature (MKT) is 25 °C during temperature mapping?
Temperature mapping is done during specific periods (to study for instance seasonal variations) and MKT can be calculated for those periods. However, if deviations occur outside those periods, MKT must be recalculated based on the accumulated historical data. In regulatory documents, there is a wide consensus that MKT can be used to assess temperature excursions outside specified storage conditions of refrigerated and room temperature products.

23 What kind of EM is required for a dynamic pass box (DPB) ?
DPB should show the same class characteristics as the class they are leading to. Normally, particle counts and microbial counts are sufficient.

24 What is the acceptable value for MKT? How is MKT used for a vaccine with a storage requirement of 2-8 °C, which showed that a temperature excursion occurred during transport?
MKT is a weighted average temperature (one single number) which summarizes or simulates the thermal challenge that a drug substance or drug product would experience over a range of various temperatures for a defined period. The MKT is higher than the arithmetic average temperature since it takes into consideration the Arrhenius equation, but it should still be within the specified range. Important: MKT should be used to evaluate temperature excursions but not to compensate for earlier excursions.

25 Is a portable particle counter acceptable in the grade A area during monitoring of a short process period?
Yes, fixed counters are preferred if you have repeated, long measurement periods but portable ones are fully acceptable, if properly calibrated and the associated risks related to the placement and operation of the portable counter evaluated.

26 How to define the alert limit in EM? Is there any statistical rule that exists, and should it be a tighter limit than the previous year?

Alert and action limits are closely related to actual value; an easy way to determine them is to calculate the average contamination; for example, when a significant number of CFU are found (e.g., class C or D) an average + 2 σ (standard deviations) would be your alert limit, average + 3 σ would be your action limit.

27 What is the frequency of fogging?

Fogging is a part of the cleaning program, and its frequency will be determined empirically by evaluating the surface contamination; with short intervals at the beginning and larger ones at a later point, based on those measurements.

28 How to define the extent of NVPC monitoring in grade B? Is it performed continuously?

Please refer to the latest Annex 1 of the EU GMP: 9.17 The grade A area should be monitored continuously (for particles ≥ 0.5 and ≥ 5 µm) and with a suitable sample flow rate (at least 28 L (1 ft^3) per minute) so that all interventions, transient events, and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.

It is recommended that a similar system is used for the grade B area although the sample frequency may be decreased. The grade B area should be monitored at such a frequency and with a suitable sample size that the program captures any increase in levels of contamination and system deterioration. If alert levels are exceeded, alarms should be triggered.

SESSION

4

Technology transfer of vaccines

- The ecosystem for successful technology transfer
- Main GMP aspects to consider and typical pitfalls

17 November 2022

1 What are some examples of different technology transfer (TT) models?
Some examples of TT models include bilateral agreements, joint ventures, acquisitions, de novo manufacturing and TT hubs.

2 Within the context of TT and business models, to what extent are intellectual property rights (IPR) protected?
The protection of IPR is governed by the national intellectual property (IP) regime as established by national legislation. The IP regime and the extent of IPR protection in each country will vary. IP/patents are commonly part of a TT agreement. Understanding the national IP regime and its effect on a TT could help in the negotiations with the technology holder for a transfer.

3 If the analytical methods are validated at the TT sending site, is it required to perform the analytical method validation again at the receiving site?
If the analytical methods have been validated at the sending unit (SU), there is no need to repeat the validation, although the ultimate decision depends upon the risk of any essential changes in equipment or reagent sources used. Normally, a comparative assay study, which in fact is a simplified validation study and comparison of results, is sufficient.

4 What is the qualification and eligibility criteria that TT receivers should have?
There is no absolute qualification and eligibility criteria defined, however, there are essential requirements the receiving unit (RU) should have such as the appropriate manufacturing licenses. Each TT case should be treated separately, and the criteria be clearly stated and documented.

5 Should both parties, SU and RU, prepare the quality risk management (QRM) documentation before the transfer?
The QRM documentation is developed by both the SU and the RU, including the marketing authorization holder (MAH) if this is an additional party.

6 What feasibility studies are recommended to assess the value of TT?
A typical feasibility study may be based on due diligence, which could include the market opportunities of a chosen product.

7 Could critical process parameters (CPPs) or critical quality attributes (CQAs) change during the TT process impacting the manufacturing process? For example, do the critical parameters change from research and development (R&D) to commercial plant?
As part of a TT process, the CQAs should not change, however, the CPPs may change depending on the production technology used at the SU and RU, especially if the SU is a R&D facility. This should be captured as part of the TT gap analysis.

8 Based on the principles of TT can the RU use the SU's validation and stability studies for their marketing authorization (MA) product dossiers?
The RU should generate their own validation and stability data for their dossier and MA. However, usually the SU data supports the pharmaceutical development section of the dossier. The information gained during validation and stability in the SU is supporting documentation. Also, clinical studies will most likely have been performed using batches made by the SU and so this data will be essential to any comparability study. That said, the RU is required to generate confirmatory stability studies and validate the RU commercial equipment and process, such as media fills, etc.

9 If the scope of TT is filling a bulk vaccine, should the SU provide the R&D documentation?
Any relevant documentation and information should be transferred to the RU to achieve a successful TT.

10 When considering TT, does the RU have to undergo a due diligence and gap assessment visit to the SU?
It is possible to carry out a due diligence to the RU and the SU, however, usually the due diligence is performed by the SU to the RU to evaluate its capacity. The TT gap assessment will be the responsibility of both units.

11 What is the difference between TT and contract manufacturing?
TT is a regulatory good manufacturing practices (GMP) requirement for all pharmaceutical manufacturers aimed at transferring any process together with its documentation and professional expertise, experience between development and manufacture or between manufacturing sites.

Contract manufacturing is the activity of outsourcing a manufacturing activity to a third party. All contract manufacturing includes a technology, and the contract manufacturers are considered the RU.

12 Who is responsible of the technology transfer program (TTP) execution after the protocol is set and planned?
The TT team should identify the person responsible to manage the project and meet the expected goals in the defined timeframe. The sponsor is ultimately responsible, including assigning responsibilities to the TT team, and the project manager should track the day-to-day tasks accordingly.

13 How is it possible to mitigate the risk of TT if there is an ecosystem gap between the developed country to the developing country?
To mitigate the risk of TT from a developed country to a developing country, it is essential that the performed gap assessment covers not only the technical aspects. For example, the differences in equipment and key process parameter settings or the availability of equipment should be identified, and their potential impact should be assessed by the TT team. The availability of human resources, technical support from vendors and spare parts stocks, and organizational quality culture should also be considered and assessed.

14 How should a successful analytical method transfer (AMT) and acceptance criteria be defined?
The transfer procedure is a documented process to qualify the receiving laboratory, RU, to use an analytical method originated in another laboratory, the SU.
The AMT assures that the RU has the required knowledge of the analytical method which was transferred and the capacity to perform it. The acceptance criteria will be defined based on the performance and validation of the analytical method from the SU.

15 Are incomplete validated methods eligible for AMT?
Yes, incomplete validated analytical method may be eligible for transfer. In this case, a simultaneous validation (i.e. co-validation) study between the SU and RU is the recommended practice.

16 When the analytical method is transferred from R&D unit to quality control (QC), which step should the validation be performed?
In this case, the R&D unit is the SU and all TT requirements are applicable, such as a gap assessment covering all the product and process key information.

17 Is the analytical method development required in TT of new products?
The analytical method development is an activity carried out by the SU; therefore, the RU is not supposed to perform.

18 If the TT is done from a research institute to a manufacturing company, what kind of documentation is required?
In case a TT is done between a research institute and a manufacturing company, a complete development report is expected to be received by the RU including all CQA, CPPs, accelerated stability data, QRM, target product profile, raw materials and active pharmaceutical ingredients specifications and source, among other key information related to the design space. There should really be no difference between a research institute and the R&D unit of a SU but usually a research institute has good laboratory practice (GLP) in place, however, may have limited GMP knowledge and implementation.

19 Between SU and RU, does the equipment need to be from the same model, size, etc. (equipment equivalence)?
No, equipment could differ in terms of size, make, and model, but it is best if changes are minimized. All possible differences should be captured and assessed as part of the TT gap assessment.

20 Should the RU use the same raw materials used by SU in production?
Yes, raw materials should be the same between the SU and the RU, but they could be of different sources. However, the sources of some biological materials and reagents are often critical to product comparability and consistency. Any changes in such materials should be avoided. Any difference should be captured and assessed as part of the TT gap assessment.

21 For transfer of analytical methods, does the in-process control (IPC) methods need to be validated at the RU?

In general, IPC methods are based on compendial pharmacopeial methods and are not part of the AMT (e.g. pH, fill volume, optical density (OD)). However, other IPC, such as at line container closure integrity testing (CCIT), should be validated.

22 During intra-company TT, what documents need to be transferred apart from batch manufacturing record, process validation (PV) and cleaning validation?

The information and documents required for an intra-company TT differ very little as compared to an inter-company TT. Besides the batch manufacturing record, PV and cleaning validation, other documents usually required are environmental conditions and monitoring, safety measures, equipment and technology used, personnel available, facility and equipment qualification. In some cases, the TT occurs between different regional subsidiaries of a corporation – in this case the TT is almost identical to TT outside the company.

23 If the RU decides to undergo all method validation according to the ICH Q2 requirements, in addition to the validation performed by SU, is it necessary to compare the results between the SU and RU?

This is an unlikely situation as it would be unnecessary, time consuming and costly to perform a full validation. However, if it is decided to go through that path, there should be an inter-lab (SU and RU) comparison study on a same set of samples.
In certain cases, it would be justifiable to partially repeat the validation of a certain characteristic of the method as an additional assay, before performing the comparative assay. For example, if it is determined from the gap assessment that the SU uses an automatic agitator for the sample preparation, including operational parameters such as revolutions per minute (RPMs), but the RU does not possess that exact piece of equipment but a similar one, then it would be reasonable that the RU performs an accuracy assay to adjust the parameters of the equipment being used. This action would help to achieve the recovery percentage defined in the validation.

24 Is it required to use the same brand of reagents on the method validation between SU and RU?

It is not mandatory to use the same brand of reagents, however, it is strongly recommended to do so. If different brands are used, the TT gap assessment should carefully examine the possible differences and their impact. Brands of reagents should be part of the TT gap assessment, including differences in their specifications and catalogue numbers considering that the same reagent may have different specifications according to their catalogue number.

25 Due to different pharmacopeia methods from a country to another, how to match the comparative results with different methods when TT is between a SU and RU from two different countries?

The pharmacopeial analytical methods are usually harmonized among the different countries. However, if differences are detected based on the required gap assessment, then the pharmacopeia of the RU should be taken as reference provided that the SU considers the RU´s test as equivalent.

SESSION

5

Process validation: current harmonized expectations based on knowledge management

22 November 2022

1 During process validation (PV), should all attributes or only critical quality attributes (CQA) be considered?
When there are many input parameters and attributes, an initial screening should be conducted based on risk and criticality assessment to identify critical process parameters (CPPs) that have the most important statistical effect on the product quality attributes. Critical parameters and attributes should be included in the control strategy. Other key parameters, that are essential to process performance but do not have an impact on product quality, should also be carefully controlled.

2 For PV, do the batches need to be consecutive or is it 3 batches randomly picked?
It is a regulatory requirement that performance qualification batches shall be consecutive. All guidance documents explicitly mention that process performance qualification (PPQ) successful batches need to be consecutive.

3 Is it a requirement to use different lots of active pharmaceutical ingredient (API) in the batch testing to assess batch variability as part of PV exercise?
Risk management approach should be applied in designing every aspect in the PPQ. PPQ batches should preferably originate from different drug substance batches. However, in case of neglectable risk and difficulty to realize, waiver justification can be developed and accepted. In case the risk assessment reveals that API and/or critical excipient lot can account for lot-to-lot variation, then different lots should be represented in the PPQ batches.

4 What is the difference between marketing authorization (MA) limits and batch release limit? Are MA limits the same as shelf-life specifications?
Release specifications are the in-house specifications established by the product manufacturer. These specifications are often tighter than MA specifications. These tighter specifications help the manufacturer to ascertain that the drug product shall continue to meet the specifications throughout its shelf life.
The performed stability studies provide information which could be considered to establish the tighter specification for finished pharmaceutical product (FPP) release. In case no change is reported, MA specification can be used for release purpose.

5 During equipment qualification, what are the criteria to be considered for the selection of equipment to be qualified?
Risk assessment determines which systems and system components have an impact on the establishment and maintenance of process parameters and conditions that affect product quality. This information helps develop system qualification plans, protocols, test functions, and acceptance criteria.

6 What is the difference between bracketing and matrix concepts?
Grouping in study designs may be considered for operations that involve similar or identical process operations or equipment. The bracketing strategy is used when a single process element can be varied while all other variables remain fixed. A matrix approach is appropriate for commercial manufacturing PPQ when configurations of the same process and product have more than one variable.

7 If the manufacturer changes the batch size in the same bulk tank, is 3 consecutive batches for PV required?
Scaling-up the batch is one of the changes that may impact the final product quality, hence it requires risk assessment of the changes and, accordingly, the extent of validation and the number of batches to be included in the PPQ needs to be determined.

8 How to set the out of trend (OOT) limit in trending?
Based on the statistical analysis of sufficient collected data from PPQ and enhanced continued process verification (CPV) batches that show the process is stable, control limits can be established considering the trend limits for the process as well as its capability.

9 What is the minimum number of data points required to establish trend limits?
There is no defined minimum number of data points identified to create the control or the run chart. Ideally there should be a minimum of 10 to 15 data points to calculate adequate control limits that reflect the process variability. In general, the more data points you have, the more accurate the calculated limits are.

10 How to determine upper control limit (UCL) and lower control limit (LCL)?
Control limits are calculated from the data set that is plotted on a control chart. They are placed approximately 3 sigma values away from the average line. They represent the process variation and help indicate when the process is out of control. To determine the UCL and LCL, firstly, the average (mean) and standard deviation for the data set needs to be calculated. Then, the standard deviation is multiplied by a constant (typically 3). By adding or subtracting this value (3 σ) from the average, the UCL and LCL are determined respectively. Also, they can automatically be obtained from a statistical software either from the control chart plotting command or descriptive basic statistics commands. Once the UCL and LCL have been determined, they can be used to monitor the process performance and identify any instances where the process falls outside the desired limits, indicating the need for further investigation or action. Regular monitoring and recalculation of the control limits are necessary to ensure they remain relevant.

11 How to determine the number of PPQ batches during the implementation of prospective PV when there is insufficient knowledge during the pilot stage?
Current Good Manufacturing Practices (cGMP) guidance does not specify a minimum number of batches to validate a manufacturing process. The required number of batches for demonstration of process reproducibility and consistency at scale shall be derived from the statistical and risk-based evaluation and based on the accumulated process and product knowledge obtained from historical data or development phase. For confirmation of process reproducibility and to show consistency, enough batches should be evaluated to demonstrate batch to batch variability which cannot be statistically achieved by two batches or less. The more knowledge and confidence the manufacturer obtains during design and development phase, the lower the number of PPQ required and vice versa.

12 Is it necessary to reach a process performance index (Ppk) = 1 in a biopharmaceutical process?
Ppk is a capability index. Ppk of value less than 1 indicates that the process is not capable. A Ppk of value more than 1.33 indicates the process is highly capable, and when a PPK value is ranging between 1 to 1.33 it reflects a marginal process capability and that further improvements are needed to ensure product conformance with established specifications.

13 During CPV, is it better to use process capability index (Cpk) or Ppk for the whole process to determine reduction in sampling?
In simple terms, the Cp/Cpk indicates the short-term capability and Pp/Ppk indicates the long-term capability of a process. Cpk and Ppk can be calculated from initial batches of stage 3 (continued process verification). After sufficient data demonstrates process capability and stability, it is possible to justify starting a less heightened routine CPV monitoring plan.

14 Is there any regulation or requirement for periodic revalidation process? For example, every 3 years or when there are changes of high-risk category in quality risk management (QRM).
In the new PV life cycle approach, CPV assures maintenance of the validated state, hence replaces periodic revalidation. In response to changes, manufacturers should assess the risk on process performance and capability and determine whether reperforming stage 2 (Process Qualification) or stage 1 (Process Design) is required.

15 Would a manufacturer require a validation master plan (VMP) for PV?
The VMP is a document that defines the PV scope and rationale, and that contains the list of PV studies to be performed. VMP depicting the conduct of PV is one of the expected deliverables from stage 1 and is important to make the transition to stage 2. It also outlines the validation strategy, supporting rationale, PQ, PPQ and CPV plan.

16 Is it mandatory to complete validation on all 3 bathes before release for commercialization? In cases of low market demand (2 to 3 batches per year), can one commercial batch validation be adopted before release to market?
In most cases, the PPQ study needs to be completed successfully and a high degree of assurance in the process achieved before commercial distribution of a product. In special situations, the PPQ protocol can be designed to release a PPQ batch for distribution before complete execution of the protocol steps and

activities, that is, concurrent release. The Food and Drug Agency (FDA) expects that concurrent release will be used rarely. Concurrent release might be appropriate for processes used rarely for various reasons, such as limited demand drugs' manufacture (e.g. orphan drugs, minor use and minor species veterinary drugs) or which have short half-lives (e.g. radiopharmaceuticals, including positron emission tomography drugs). Circumstances and rationale for concurrent release should be fully described in the PPQ protocol. Any lot released concurrently must comply with all cGMPs, regulatory approval requirements, product specifications and PPQ protocol lot release criteria.

SESSION

6

Aseptic process simulation (media fills) for vaccines: how to challenge the process based on risk assessment

24 November 2022

1 During aseptic process simulation (APS), does the operator need to be qualified in all interventions?

During APS, the operators do not need to be qualified in all the interventions. The APS is carried out by a team of people with different tasks described. This, and people trained for such tasks must be assessed. The APS needs to be carried in worst case condition, so it is not necessary to add many tasks for one staff to reduce the number of people. In operation, the number and skills of staff involved in production are covered by the number of staffs involved in the APS. If an operator is not qualified for some tasks, he will not be allowed to perform such tasks during the production. With this statement, you need to qualify your staff following a risk-based approach and allow flexibility in your facility.

2 During batch manufacturing, how long should a person stay in an aseptic area?

Clause 7.15 states that every operator entering grade A or B areas should gown into clean, sterilised protective garments (including eye coverings and masks) of an appropriate size at each entry. The maximum period for which the sterilised gown may be worn before replacement during a shift should be defined as part of the garment qualification.

There is no requirement for how long a person should stay in an aseptic area. This needs to be assessed as part of the APS and comfort of operators. It is difficult to stay in aseptic conditions for more than 6 hours in a row. This will be a part of validation.

3 Is it possible to perform an aseptic campaign in restricted access barrier systems (RABS) or conventional filling line?

Aseptic campaigns could be made in RABS with appropriate procedures and organisation. Considering conventional filling lines, it seems constraints will not make the campaign possible. Isolators are best suited for campaign filling.

4 Does the sterile filtration of the viral vaccine need to be performed before filling?

The purpose of sterile filtration (generally performed using a 0.22 µm filter) is to remove any potential contaminants and microorganisms from the vaccine solution, ensuring that it is free from viable particles that could potentially compromise its sterility. This step is critical for maintaining the safety and efficacy of a vaccine. However, the choice of sterilization method for a viral vaccine depends on its nature (e.g. live attenuated vs. inactivated or a subunit vaccine), its manufacturing process and its formulation. If sterile filtration cannot be used for the filling operation of the vaccine, an alternative is to use sterile raw materials and form the vaccine under aseptic conditions. This approach involves using components and materials that have been sterilized before use in the formulation and filling of the vaccine. The acceptability of this approach is subject to the regulatory jurisdiction and requires rigorous control over the entire manufacturing process, including the sourcing, storage, and handling of the raw materials, as well as the formulation and filling of the vaccine. If sterile filtration of the viral vaccine is demonstrated to be the best method for the specific vaccine under consideration, it is typically performed as close to filling as possible to the filling needle to minimize the potential for contamination. However, in some cases, it may be necessary to store the filtered vaccine solution for a short period of time before filling and in such cases, it should be stored under conditions that are designed to maintain its sterility. To add, no terminal heat sterilization is possible for vaccines but only sometimes for their diluents, such as saline.

5 In a production process that uses a fermenter and two process temperatures are required, how should the APS or sterile hold test validation be carried out?

The process simulation should mimic the most critical production steps, and the temperature needs to be set to enhance any possible bacterial growth (e.g., 20 – 35 °C).

6 According to the aseptic processing guidance, what is the ideal aseptic filling time?

There is no ideal aseptic filling time. The ideal aseptic filling time is based on all parameters, risk assessment and information provided by the vendors' studies.

The answer to this question can be found in Clause 8.85 in Annex 1 Pharmaceutical Inspection Co-operation Scheme (PIC/S) good manufacturing practices (GMP) guide: "Unless using an isolator, filling times should normally not exceed one shift period, but it can be extended based on process validation (PV)."

7 Based on the concept of lifecycle approach to validation, can APS be assured on three batches only?

APS should be made with a minimum of 3 successful consecutive runs. The main point for initial validation is staff qualification with 3 runs as well. That means for initial validation, more than 3 APS will be required for each product and different content of filling, covering the highest risks.

Clause 9.38 states that APS should be performed as part of the initial validation, with at least 3 consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment which are assessed to have an impact on the sterility assurance of the product (e.g. modification to the heating, ventilation, and air conditioning (HVAC) system, equipment, changes to process, number of shifts and numbers of personnel, major facility shut down). Normally, APS (periodic revalidation) should be repeated twice a year, approximately every 6 months, for each aseptic process, each filling line, and each shift. Each operator should participate in at least 1 successful APS annually. Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.

8 While designing the APS program, is the lowest or highest fill volume simulated in the media fill?

Based on risk assessment, the design of the APS program should cover all formats and emphasize on the highest risks. Bracketing and/or matrixing can be used to reduce the number of runs.

9 According to Annex 1, separate simulations of individual unit operations should be avoided. Is this requirement also applicable if operations are carried out as routine in different days ?

Operations such as virus seed preparation, or bulk vaccine preparation before formulation could be carried out in separate operation. For long operations such as filling, lyophilisation should be simulated in 1 row and to simulate all operations carried out in the lyophilizer. For instance, starting from filling, lyophilizer loading, mimic of freeze-drying operations, closing, unloading the freeze dryer, and finally capping the vials.

10 Does the mechanical activity (e.g. light fixture) above the filling machine need to be simulated?

Such operation should not be carried out during production activities. If such risk is identified, then it should be a part of the APS design.

11 Should anaerobic media fill be performed with the same frequency as the aerobic media fill on the production lines (twice/year for aerobic media and twice/year for anaerobic media)?

The clauses mentioned below state that APS should be performed for aerobic bacteria. When anaerobic simulation is required by the process, then it needs to be carried out occasionally as APS is made to track aerobic potential contamination from operators or environment.

Clause 9.33 (iii) states that where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended. Clause 9.36 (v) states that the requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air unless anaerobic simulation is intended. In these situations, inclusion of occasional anaerobic simulations as part of the overall validation strategy should be considered (see paragraph 9.33 (iii)).

12 During the routine filling process, there are vials to be discarded either manually or automatically for fill volume stabilization process. Should these vials be considered for incubation during APS process?

If vials are going to be discarded, in the APS the number of discarded units should be the same than for routine production. See the clause below where discarded units should be incubated but the results not considered as part of the APS.

Clause 9.41: If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production standard operating procedures (SOPs) clearly specify that units must be removed under the same circumstances (i.e. type of intervention; line location; specific number of units removed). In no case should more units be removed during a media fill intervention than would be cleared during a production run. Examples may include those that must be discarded during routine production after the set-up process or following a specific type of

intervention. To fully understand the process and assess contamination risks during aseptic setup or mandatory line clearances, these units would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.

13 Is it required to incubate vials with sealing defects?

Vials with sealing defects should be considered and incubated for information but not incorporated in the results of the APS. See Clause 9.41.

14 Is APS needed after a change in primary packaging material to demonstrate container closure integrity testing (CCIT) by microbial ingress test (e.g. physical variation such as dimensional change of aluminium seals)?

APS is required to be performed after each change in production which could impact the aseptic process (e.g. primary packaging, raw materials, etc.).

15 In the revalidation of APS where no significant change has occurred, is periodic revalidation needed twice a year?

Yes, requalification is needed twice a year for grade A/B areas even if no changes occur. This is a requirement linked to contamination control strategy (CCS) and grade A and B areas monitoring.

16 What is the minimum duration to perform for APS if normal aseptic filling time is 8 hours and filling is continued for 24 hours during PV to validate the maximum time?

The duration of an APS is relative to the number of filled units based on risk management as defined by CCS. For a batch, it should be around 5000 to 10 000 units. If the batch is foreseen for several days, the number of filled vials could be more. With the selected number of filled vials, all production shifts will need to be covered, including beginning of the first day, the stop and shift changes, the last shift change and end of the filling.

17 Do all worst-case sizes of containers, that were simulated initially, need to be resimulated every 6 months?

Worst case container size(s) simulated during the initial aseptic simulation must be resimulated every 6 months, but it is not for all worst-case containers. It is possible to make a matrix which will cover all risks.
The answer can be found in the Clause 9.36 (ii): Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified.

18 For continuous manufacturing during APS, should the full batch size be mimicked every 6 months?

For each type of production, based on risk management and CCS, the highest risk should be covered including the highest risks during this process. The mimic should cover the most important steps of production and cover all the critical process steps identified based on scientific risk-based approach and CCS.
Clause 9.40 states that the number of units processed (filled) for APS should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the CCS. Typically, a minimum of 5000 to 10 000 units are filled. For small batches (e.g. those under 5000 units), the number of containers for APS should at least equal the size of the production batch.

19 If all staffs in a clean room must participate in 3 consecutive APS, is it a requirement to revalidate with 3 consecutive APS every time a new person is recruited?

Yes, this is a requirement which needs to be followed. Only qualified personnel can enter clean rooms and perform critical operations. A person will be qualified if he/she has completed 3 APS successfully.

20 Annex 1 mentions "Approximately every 6 months". If more than 6 months elapsed since the last simulation, how many runs should be performed?

The same number of batches should be done even with more than 6 months, the extension should be justified. Approximately 6 months per scope of the document, is considered as a maximum period.

21 What are the concerns of facilities and equipment risk contamination with the nutrient media?

When carrying out sampling on walls, floors and equipment with contact, media could remain on the parts and/or equipment. This is why quality risk management (QRM) must be considered. After sampling, cleaning should be done to avoid bacteria growth on the remaining media. A complete disinfection of the line/sterilisation of line components is necessary after an APS.

22 PIC/S Annex 1 section: 6.2: 1 contaminated unit should result in investigation, including consideration of repeat media fill. Could this section be explained in detail?

The expected result for APS is 0 growth, so with 1 unit contaminated the APS is considered as failed.
Investigation is required to find the root cause of the failure, make corrective actions if required and perform a new APS with at least 3 runs. All commercial batches produced before the failure and after the failure needs to be quarantined and investigated.

23 What action needs to be taken for failure of APS when the batches are already filled?

When an APS has failed, all batches made before and after should be reviewed and assessed after the investigation of the failed APS.
Actions are as following:

- Review of the failed APS make to investigate/ identify root cause;
- Propose corrective action;
- After corrective action implementation, redo APS with the necessary number of batches with at least 3 batches;
- Review all batches produced before failure and after failure. Quarantine and assess their status in regard with the failure investigation and make decision based on risk assessment.

24 Is APS required for working cell bank (WCB) and working viral seed bank (WVSB)?

Below is the Clause 5.32 from PIC/S GMP Annex 2 for master cell bank (MCB) and seed lots manufacturing. These are considered as aseptic processes; no new contaminant should be included in the product. Based on QRM and CCS, you should follow Annex 1 requirement.

Clause 5.32 Annex 2A PIC/S: As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, as well as maintenance and storage, should be performed under appropriate GMP conditions. This should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons. For all stages prior to the establishment of the master seed or cell bank generation, principles of GMP may be applied. For all pre-master bank stages, documentation should be available to support traceability. All issues related to components used during the development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development should be documented.

SESSION

7

Upstream and downstream vaccine manufacturing processes: challenges and deviations

29 November 2022

1 What is the difference between a seed lot and a working cell bank (WCB)?
Cell Bank is "a collection of a single pool of well-characterized cells of animal or other origin in appropriate containers whose contents are of uniform composition and stored under defined conditions". A seed lot is "a quantity of live cells or viruses which has been derived from a single culture (though not necessarily clonal), has a uniform composition and is aliquoted into appropriate storage containers from which all future products will be derived, either directly or via a seed lot system." (WHO TRS 999—Annex 2)

2 Is it important for population doubling/passage number to be specified in the product dossier?
Yes, details on the microorganism´s maximum population doubling/passage number should be mentioned in the product´s dossier.

3 Can half of the master cell bank (MCB) and WCB be stored together in 2 different locations? If not, why?
The requirement is to assure that the bank material is not lost in case of a major unwanted event. Therefore, any storage combination is possible provided that the objective is met.

4 Are optical density (OD) values used for WCB?
OD measurements are typically used during the fermentation process as an indirect measure of cell viability.

5 Is it a finding if the storage of MCB and WCB is in the same location but are well labelled and segregated? Please provide the clause/document to reference.
At least the MCB should be stored in a completely different location or site. Therefore, if a WCB is lost in one of the locations, a new one can be readily prepared. "Master seed lots (MSLs), MCBs, and preferably also working seed lots (WSLs) and working cell banks (WCBs), should be stored in two or more controlled separate sites to minimize the risk of total loss or due to natural disaster, equipment malfunction or human error. A contingency plan should be in place." (WHO TRS 999—Annex 2; section 8.10)

6 Is there any regulation to change the WCB having the same batch after 5 years?
There is no mention of expiration date of the cell banks in the regulations, provided the passages are not exceeded and the stability data demonstrates the bank has not changed its characteristics and specifications.

7 Which step of the cell bank preparation requires a working condition under the unidirectional air flow (UDAF)?
All steps where there is exposure of the cell bank material should be conducted under UDAF.

8 Is there any regulation to have a minimum number of counts per vial in MCB or WCB?
The regulations require that the concentration is determined during development and preparation of the cell banks. This cell concentration is usually high and depends on the process and microorganism of interest. In addition to the concentration, the time of incubation is also important to assure the organism is in the exponential growth phase.

9 During stability studies, could the information and results from each successful revival of production lot for WCB and each successful revival of WCB lot for MCB be considered?
For MCB and WCB stability studies, besides the successful revival of the microorganism or virus, it is necessary to prove that all other applicable specifications are met.

10 Please explain the viral test for cell bank.
ICH guidance Q5A Quality Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin includes specific information on viruses that could occur in the MCB, or adventitious viruses that could be introduced during production. MCB extensive screening for both endogenous and nonendogenous viral contamination should be performed on the MCB. Testing for nonendogenous viruses should include in vitro and in vivo inoculation tests and any other specific tests, including species-specific tests such as the mouse antibody production (MAP) test, that are appropriate based on the passage history of the cell line to detect possible contaminating viruses. Also, WCBs should be tested for adventitious virus either by direct testing or by analysis of cells at the limit of in vitro cell age, initiated from the WCB. When appropriate nonendogenous virus tests have been

performed on the MCB and cells cultured up to or beyond the limit of in vitro cell age have been derived from the WCB and used for testing for the presence of adventitious viruses, similar tests need not be performed on the initial WCB.

11 Is it recommended that 1 shift of personnel works with 1 set of cell bank for 1 bacterial or 1 viral propagation?
There is no specific good manufacturing practice (GMP) requirement on the matter, however, to address the risk of cross-contamination, there should be certain restrictions on the movement of all personnel handling live microorganisms based on quality risk management (QRM) principles, considering the risk of contaminating the non-live areas. Contamination control measures (e.g. clearly defined decontamination measures such as a complete change of appropriate clothing and shoes, and showering if applicable) should be followed by personnel handling live microorganisms.

12 For viral vaccines, how to inactivate the other virus?
A way to avoid the presence of other unwanted virus in viral vaccines is to check the mammalian cell source for virus, and check for possible routes of contamination through sick personnel.

13 Is oxygen or oxygen concentration a critical process parameter (CPP)?
Yes, oxygen is a CPP in aerobic cultures and fermentation processes.

14 Can live and non-live products be manufactured in the same filling line/facility if appropriate decontamination, cleaning, and controls are performed?
As per WHO TRS 999, 2016, Annex 2, WHO GMP for biological products, section 9.1, there is a restriction to manufacture products containing live microorganisms or live viruses in the same premises used to fill other pharmaceutical products (i.e. including other non-live vaccines, such as meningococcal vaccine), unless there are effective containment and decontamination measures, closed/disposable systems, campaign production, and a well-documented quality risk assessment. In the same line, as per WHO TRS 961, Annex 2, clause 4.22, in general, preparations containing live microorganisms should not be made, nor should containers be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms, the use of multiproduct facilities and a comprehensive QRM may be justifiable. As a general practical recommendation, it is always preferred to have dedicated areas to handle live and non-live microorganisms. In the case of tetanus neurotoxin (TeNT) production, separated and dedicated facilities are required.

15 How many passages are permitted before fermentation in a large-scale reactor?
The number of passages may vary depending on the microorganism and the process. Usually, eukaryotic cells have more passages that prokaryotic organisms.

16 Is addition of thiomersal acceptable in toxoid downstream?
Yes, thiomersal is acceptable in case of multidose vaccine presentations.

17 How to perform validation of cell storage in liquid or vapor phase nitrogen?
The validation of the cell storage would be achieved through stability studies.

18 In which cases is pressure considered a CPP for tangential flow filtration (TFF)?
In TFF processes, pressure is always a CPP.

19 In the cleaning of TFF, is it necessary to perform sterilization-in-place (SIP) or clean-in-place (CIP)?
After use, the TFF system is first cleaned using a CIP process, and the TFF filters are stored in a preservative solution. SIP is applied to the TFF components (tanks, pipes, etc.) but without the TFF filters, after which the TFF cassettes are placed.

20 What is the recommended strategy for knowledge management amongst production personnel to maintain the same level of process understanding and knowledge?
Appropriate communication channels and adequate personnel qualification are the basis for reducing the knowledge gap between the shop floor personnel and mid management. Also, a "Lean" manufacturing philosophy will greatly contribute to develop sound standard operating procedures (SOPs) and prevent

deviations.

21 What is the maximum number of years that the MCB can be stored in cryovials? When should we requalify the same?
The storage time depends on the viability of the cells and the storage temperature (i.e. the lower the storage temperature, the longer the cells may be stored). A requalification and stability program should be established and followed, defining test periods as in any other stability study for finished or intermediate product.

22 Can we manufacture live attenuated viral vaccine in non-biosafety level facility by providing classified area like grade A, B, C & D?
Production of live attenuated vaccine, such as measles, mumps, and rubella (MMR) vaccine, require an adequate biosafety level facility.

23 How many years is the stability program defined for WCB?
The long-term stability program for a WCB will require regular testing of the WCB during the estimated and actual period of use.

24 How often should the MCB, WCB, MSL and WSL be revived?
A cryovial of WCB or WSL will be revived for each manufacturing batch produced. A MCB or MSL cryovial will be revived every time a new WCB or WSL is prepared.

25 Are there any concerns about transmissible spongiform encephalopathies/ bovine spongiform encephalopathy (TSE/BSE) agent if the ingredient is of fluid material or secretions from the animal apart from it being an animal tissue origin?
Any material originated from an animal source has the risk of contamination with TSE/BSE, and should be avoided, if possible.

26 What is the validation process of chromatographic columns?
The reuse or recovery of chromatographic columns should be validated to prove that the procedure eliminates the residues. This would include among other aspects, testing of residues at maximum storage times.

27 How is a closed system achieved during drug substance sterile filtration?
A closed system may be designed using closed circuit connections, quick connectors and SIP-ed valves.

28 Why live products are filled under negative pressure whereas non-live products are filled under positive pressure?
For microorganisms BSL 3 or 4, negative room differential pressure (ideally, with reference to atmospheric pressure) is required to handle live products or potent toxins (e.g. TeNT) during the upstream, inactivation and purification phases of the process to avoid contamination of the environment. In the case of non-live microorganisms or proteins, such as recombinant Hepatitis B vaccine, there is no need to have negative pressure, and a positive pressure cascade is expected.

SESSION

8

GMP deficiencies for vaccine manufacturing: causes and successful CAPAs

01 December 2022

1 What are the monographs available on quality of vaccine?
Normally the legal minimum standards for a vaccine are defined in the Pharmacopeia's general and product specific monographs. The International Pharmacopeia, European and United States of America Pharmacopeia are the most common reference points, but the monograph required will depend upon the destination market. In the case of novel vaccines, there may not currently be an adopted monograph instead a draft guidance may be available for published monographs under development, such as PharmEuropa for the European Pharmacopeia. In addition, WHO Expert committees developed "Points to Consider" documents that give further guidance for many vaccines.

2 Is it acceptable to have vaccine, biotechnological, medicine and traditional medicine, such as methylprednisolone, manufactured in the same facility?
In most cases, vaccine biological drug substance is manufactured in segregated facilities dedicated for the specific type of vaccine under manufacture, for example bacterial or viral vaccines. There will be specific bio secure and bio-safe areas. The good manufacturing practices (GMPs) define that certain vaccines must always be made in dedicated facilities. In the case of filling of inactivated viral vaccines, subunit, and messenger ribonucleic acid (mRNA) vaccines, it may be possible to fill these using dedicated change parts and tanks on a line used for the filling of other sterile products depending upon the risks of cross contamination and ease of effective cleaning and decontamination. For example, season inactivated influenza vaccines are usually filled on lines that are used for other products outside of the flu season. In all cases, risk management plans need to be prepared and these should be discussed with both domestic regulators and the relevant authorities in the importing countries for exported vaccines.

3 For the prequalification (PQ) inspection in areas committed to development and GMP implementation, what is the risk-based evaluation to analyse the fulfilment of the essential elements, and what are the key points of inspection?
During a PQ inspection, all aspects of manufacture and control will be inspected by a team of 3 to 5 inspectors according to both the general pharmaceutical GMP and the relevant annexes, such as sterile products, validation, data integrity (DI), among others, as well as specific biological product annexes. The inspectors will also focus on the application related to integrity of data and studies submitted in the dossier for accuracy and completeness. Key risk areas would include the robust functioning of the quality management system (QMS) elements of change and deviation control and investigation, suitability of equipment and facilities, the contamination control strategy (CCS), and controls over asepsis of the process. For new products, the transfer of the product from development into commercialization and the comparability between the commercial vaccine and those used in clinical studies will be assessed.

4 How should risks be mitigated to enable controlled non-classified (CNC) operation?
All vaccines should be manufactured in facilities of the appropriate standard, and most vaccine manufacturing stages need classified clean room environments for delivering the required critical environment that are mandatory to provide to minimize risks of contamination, even though some less critical manufacturing activities like labelling and packaging can be conducted in CNC areas. The clean room standard depends upon the risks of contamination of the vaccine to be controlled. When raw materials and intermediates cross CNC corridors and other areas in closed containers, then transfer of containers must be risk assessed. The CCS should consider the transfer into the clean room, including but not limited to, the bio-decontamination methodology, the exposure time, the state of process technology, system closure integrity, connection types, among others, to evaluate process, environment and quality requirements.

5 Are there any commonalities when it comes to classifying non-conformances of the observations (critical, major, minor) made during GMP inspection?
Most but not all inspection authorities classify deficiencies, such as the United States Food and Drug Administration (USFDA) which does not classify them. The basis of classification is according to the actual or potential risk of the observation to the recipient of the product or in some cases the healthcare professional administering the product. A key consideration is that the inspecting authority should have a consistent mechanism using inspectors with sufficient experience to classify observations. The Pharmaceutical Inspection Co-operation

Scheme (PIC/S) has a guideline on classification of GMP deficiencies that is widely used or has been adapted into several national classification guidelines.

6 How to have an effective corrective action and preventive action (CAPA)?

CAPA can only be effective if the circumstances and background observations are fully investigated and understood, the potential impact(s) risk assessed, the root cause(s) identified, and then effective steps taken to prevent reoccurrence robustly implemented. The impact on manufactured products must also be assessed and appropriate actions taken to mitigate patient risk. This may involve rejection of work in progress, batches already completed, and in the most severe cases, recall of product already distributed.

7 What are the rules to escalate issues to management level?

There are no rules to escalate issues but the principle is that good practices' (GxP) issues should be reported to the level of management with the appropriate resources, knowledge, and expertise to resolve the issue and prevent their reoccurrence. In all cases, issues with the potential to influence quality must be reported within the quality system. WHO guidelines and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q10 give guidance to systems that should be periodically reviewed by management.

8 What is the procedure if the same issue reoccurs after finalization of CAPA?

If an issue reoccurs, then the CAPA implemented was ineffective either due to failure to determine the actual cause or failure to eliminate that cause by the correct fully implemented measures. The organization shall open 2 new deviations: first deviation is to re-investigate the original problem and to identify if there were further sources of variation or error that were not identified in the earlier case, and the second deviation should seek to find the reason why the investigation/CAPA system failed.

9 What are the 5 WHYs?

The 5 WHYs is a problem-solving method that explores the underlying cause-and-effect of problems. The primary goal is to determine the root cause of a defect or a problem by successively asking the question "Why?". Keep in mind that "5" is just a number. Ask "Why" as many times as you need to complete the process and take appropriate actions.

10 How can human error be controlled, other than retraining, to avoid related deviations? What are the proven analysis and implemented practices that can help reduce human error close to zero?

Retraining is rarely the sole answer to preventing human errors and making a process intrinsically less error prone. There are 2 ways to prevent human error from affecting performance. The first is to stop people from making mistakes (avoidance) or keeping the mistake from impacting (interception) the system. The preventive interventions require that the possible/potential errors be known before they occur. It is essential to learn by understanding the circumstances and chain of events that lead to an error historically occurring if it is to be prevented in the future. In most cases a procedure or process can be re-designed to make it more resilient to error. Human error investigation is a complex area that requires training and understanding of technologies and how humans interact with a process. There are many sources of information into the investigation and tools available for successful implementation - many from the aviation industry.

11 Given that smallpox was produced at a time when non-GMP was applicable, does WHO have specific guidelines on this matter?

Smallpox was eradicated at a time when modern GMPs were in development or just being implemented in the late 60s and early 70s. WHO launched an intensified plan to eradicate smallpox in 1967. Widespread immunization and surveillance were conducted around the world for several years. The last known natural case was in Somalia in 1977. In 1980, WHO declared smallpox eradicated – the only infectious disease to achieve this distinction.

See: https://www.who.int/health-topics/smallpox#tab=tab_1

WHO recommendations for the production and quality control (QC) of smallpox vaccines were first adopted in 1959 and revised in 1965. They were updated in 2003 in case new supplies of vaccine were required. This update includes production on cell substrates and introduces modern requirements for adventitious agent testing. Recommendations for the production and QC of smallpox vaccines is available in

WHO TRS 926, Annex 1.

12 Do findings from WHO inspections have to be recorded in site deviation forms?

Findings from both internal self-inspection and external audit and inspection should be recorded in the site QMS and the CAPA managed through that QMS. Industry common practice is to have separate categories for deficiencies identified in external/regulatory inspection separate from self-inspection findings.

13 Is a video recording mandatory for media fill execution and QC activities?

The purpose of video recording a media simulation is the recording of interventions made and to facilitate investigation should a problem be found with the best data available. So yes, good quality video recordings offer significant advantages and should be considered essential in any protocol.

14 If the root cause is identifiable through simple interviews, is it mandatory to use investigation tool such as fish bone, 5 WHYs, etc.?

No, it is not mandatory to always use investigation tools such as Ishikawa diagrams or the 5 WHYs etc., if the root cause can be readily identified through simple interviews. The choice of methods depends on the specific situation and the information available, with the degree of formality of the investigation and associated risk assessments reflecting the seriousness of the hazard and complexity of the situation.

Using interviews alone does, however, have heuristic risk. Humans are easily led to subconscious selective recall and exhibit « motivated reasoning » in their interpretation of events which may lead to unintentionally missing key and/or related or deeper factors as to why an event really happened. Furthermore, events often do not have a « single » root cause, but frequently occur when there has been a chain of errors. There is a risk that interviews alone may identify important parts of this error chain but not all factors, resulting in incomplete CAPA being implemented, and possibly repetitive incidents or similar issues in the future.

Using the simple and very basic tools, such as 5 WHYs, generally requires minimal organisational effort, can help ensure a more systematic and thorough investigation, and to mitigate these heuristic risks. For this reason, in many situations, using 5 WHYs is best considered as part of the investigation. Other investigation tools such as Ishikawa, can be introduced as situations become more complex, along with other more resource intensive risk assessment tools as needed.

15 What is a proper and sufficient justification for batch release of products found with suspected inherent particle? What happens to the rest of the batches that passed the visual inspection if the identified product with particles is discarded during the visual inspection?

After 100% inspection and the rejection of any container with inherent particles then the completed batch should be re-examined using a statistically valid acceptable quality level (AQL) sample using tightened limits for acceptance levels. If further containers with inherent particles are found then the whole batch should be re-inspected, where scientifically justifiable, and then a further enhanced sample for a new AQL test which is recommended to have tighter AQL limits. Such atypical trends should also be investigated as it may indicate manufacturing problems, especially, should the occurrence of units with visible particles be those not commonly observed. The re-inspection should be done according to approved standard operating procedures (SOPs) with defined number of allowed re-inspections and reject rates. It is common industry practice to set the number of inspections to a maximum of 3 times. USFDA recommends not more than 1 reinspection of batches found to have atypical defects. All inspection, reinspection and AQL testing steps should be evident in the batch documentation and considered in the release decision.

16 How many inspectors can be engaged for an inspection?

There should be sufficient inspectors and the length of the inspection should be long enough to cover the necessary scope depending upon product risk and inspection history of a site. Most authorities as well as WHO PQ typically will inspect a new site with 3 to 5 inspectors over a period of 5 to 6 days. Periodic re-inspection will typically involve 2 to 3 inspectors working independently over 4 to 5 days. In the case of serious non-compliance being found and investigated, additional resources may be necessary.

17 How and when CAPA verification should be made? What should be considered when establishing the timeline of effectiveness check for CAPA? Do we consider the number of batches produced, certain period after the implementation of CAPA, or are there other considerations?
The mechanism for verification of CAPA effectiveness and its timing depend upon the nature and risk if the issue reoccurs. The mechanism for checking CAPA effective implementation should not be limited to checks for revised documentation and training records. It should be extended to verify that implemented actions will prevent future recurrence through periodic checks, internal audits, verifications and validations, quizzes for training, process metrics and trending results if available. The timing of the verification checks shall be determined after all correction and corrective actions have been fully implemented and consider the required action criticality, urgency, risk of recurrence and difficulty of implementation.

18 Is the replacement of polyvinyl chloride (PVC) curtained zones expected everywhere in grade A or is it acceptable in active pharmaceutical ingredient (API) production operations (sterile by specifications) only?
Generally, the use of PVC curtains should be avoided as they are difficult to clean and maintain. They should be especially avoided in any areas where powders or aerosols are handled or a risk. In sterile API areas, it may be technically challenging to use restricted access barrier systems (RABS) so curtains may be unavoidable, however, in all cases the expectation is to eliminate open systems wherever possible.

19 Can vaporized hydrogen peroxide (VHP) be used in sterilization of lyophilizers?
Vaporized hydrogen peroxide (VHP) bio-decontamination is not considered to be a sterilization process. Equipment requiring sterilization should normally be steam sterilized before each use. VHP was used as a remediation in older lyophilizers that were incapable of steam sterilization as it was more effective than manual decontamination methods common in the 1980s and 1990s. The GMPs mandate that processes and equipment should be replaced as technologies evolve and become available. It would not be appropriate today to install a lyophilizer that could not be steam sterilized.

20 Is there a specific number for trial batches for biologicals? Can they use less than 5% of the batch size?
Trial batches should be sufficiently sized to achieve the outcomes of the experiments with suitable statistical confidence. In early laboratory studies, small experimental batches may be appropriate. For early stability studies, the trial lot size should always be justified. For final commercial process validation (PV) and for stability testing of commercial product, batch size should be close to the planned commercial batch size.

21 How many years can an equipment be maintained and used in the same process?
GMP requires that processes and equipments are periodically updated and improved as technologies evolve and become available to maintain compliance of equipment design with current GMP standards and updated regulatory expectations. Equipment must be maintained until retired. Experience suggests that most pharmaceutical equipments have a maximum working life of 15 to 20 years after which it will require hardware replacement. Most modern equipments have sophisticated electronic control systems that frequently require significant upgrading of their control systems earlier than the above intervals, due to non-availability of electronic components or software redundancy and withdrawal of software support by the supplier.