Inspection Updates
Common observations: GMP Compliance for Biologicals and Vaccines

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Outline

General Background

- Biological products and Vaccines
- Regulatory expectations
- GMP Inspection principles

Observations from WHO GMP Inspections

Challenges due to Pandemic situation

Achievements

Biological products

Biological products can be defined according to

their source material and method of manufacture

Biological products are derived from cells, tissues or microorganisms and reflect the inherent variability characteristic of living materials

- **Vaccines**
- **Animal immune sera**
- **Monoclonal antibodies**
- **ATMPs**
- **Cytokines**
- **Products of fermentation**
- **….**

Biologicals versus chemicals

Active substances often too complex to be fully characterized by physicochemical testing methods alone

- In vivo testing (using animals)

More fragile, thermolabile

- Storage at low temperatures

Inherent variability/Lower reproducibility

Complex impurities profiles

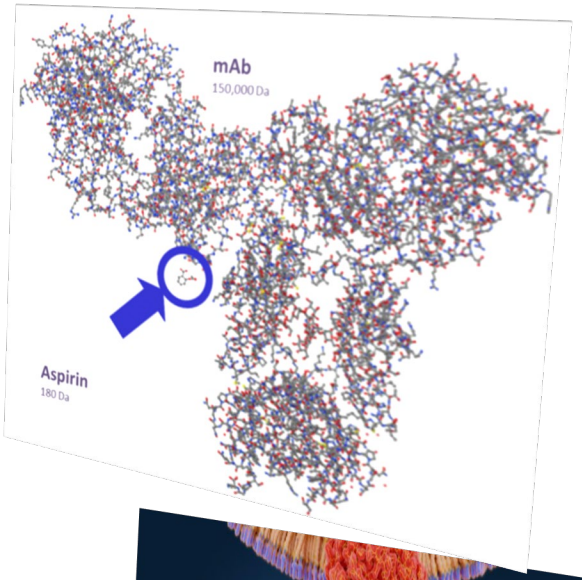
- Biological residues, By process residues

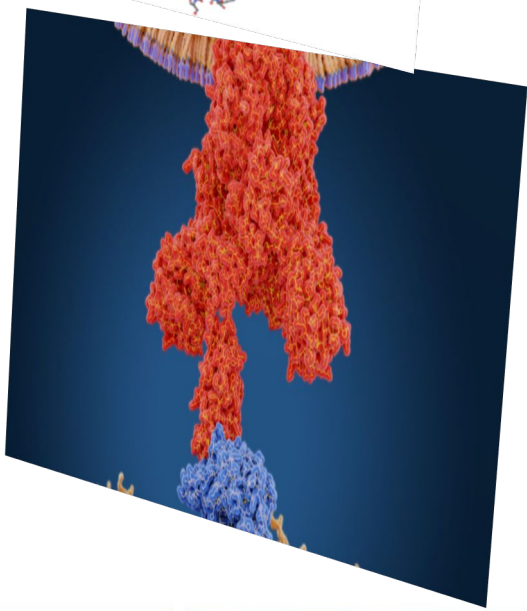
High risk of viral, BSE/TSE contamination

Overall injectable

Prone to high risk of contamination

- Media and reagents, manual processing, …





The opportunities for contamination and cross contamination

Biological processes are susceptible to microbial growth

Cell culture processes are susceptible to adventitious contamination

Bioburden can increase endotoxin levels

Contamination of biological products and intermediates can **lead to degradation, loss of potency, immunogenicity, heterogeneity, change impurity profiles and lead to inconsistent processes**

Source of contamination and cross contamination

Starting material/processing materials: Complex raw materials (serum, peptones, growth factors, enzymes, … etc), Reusable resins and filters, Cell substrates, …

Process (Open versus Closed, Hold times…)

Equipment: Assembly, cleaning, hold times Sterilization/sanitization, …

Facility: Dedicated versus shared, …

Utilities: Air, Water, Process gases, …

Personnel

Type of contaminations

Microbial:

- Bacteria
- Molds
- Virus
- Mycoplasma

Physical particulate

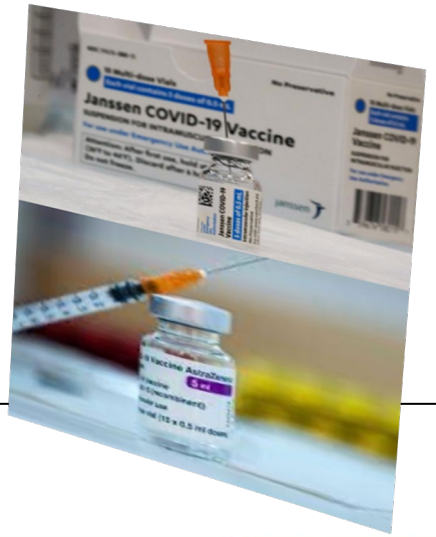
- Hair, skin, nails
- Foreign materials
- Dirt
- Dust

Chemical/residuals

- Chemical agent/Metal ions
- Lubricants
- Extractible & Leachable
- rHCP/rDNA/rProt

Cross-contamination

- Carryover (viable/non-viable)
- Foreign materials



Vaccines as an example

Each vaccine is an unique product

Different strains of bacteria/viruses used by different manufacturers for the same vaccine

- Measles: Schwartz or Edmonston Zagreb

Different Technologies and Platforms used by different manufacturers for the Sars-Cov2 vaccines:

- mRNA
- Inactivated adjuvanted vaccines (Vero cells)
- Adenovirus based vaccines (HEK293, Vero cell)
- Recombinant protein (CHO cell lines)

Different processes

- Different formulations
  - Use of different stabilizers, different excipients, …

Different equipment

- Different vessels/containers
- Different manufacturing lines

Different Testing methods

Regulatory Expectations

Irrespective of type of vaccine

Irrespective of type of submission

- Candidate vaccines WHO EUL procedure
- Candidate vaccines WHO PQ procedure

GMP requirements apply and GMP Compliance is required for all manufacturing sites

Quality is built into the product and not only tested into the product.

GMP Inspection

What ?

- GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial or product specification.

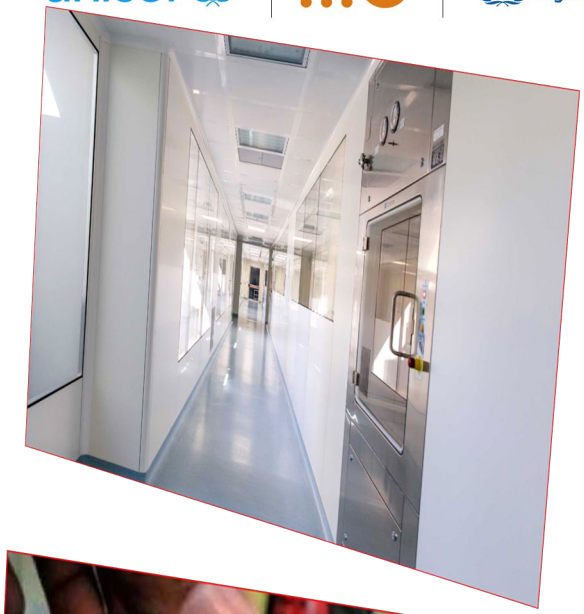
How ?

- Effective QMS.
- Adequate facility and equipment.
- Qualified personnel.
- Appropriate quality raw materials.
- Adequate validated operating procedures.
- Identity, quality and purity of products by requiring adequate control of manufacturing operations.
- Prevention of contamination, cross-contamination and mix-ups.

GMP Inspection Approach

Assessment at company level:

- Compliance of production with **WHO GMP** guidelines
- Existence of adequate **pharmaceutical quality system**
- Existence of adequate **labelling** and **packaging**
- Existence of **stability program**



Assessment at product level:

- Compliance with WHO guidelines for production and quality control (**product specific TRS**)
- Conformity with **UN specifications for tender** (which reflect the needs of the immunization programmes at country level)
- Implementation of **Vaccine Vial Monitor** (when required)

GMP Inspection references

- Technical Report Series: GMP related
  - **GMP Main Principles**: TRS 986 annex 2 (2014)
  - **Biological products**: TRS 999 annex 2 (2016)
  - **Sterile products**: TRS 986 annex 6 under review
  - **QRM**: TRS 981 annex 2
  - **Guidelines on validation**: TRS 981 annex 2 WHO (2019)
  - **Guideline on data integrity**: WHO TRS No. 1033, Annex-3 (2021)
  - ……

GMP Inspection Coverage

Scope

GMP Main Principles:
TRS 986 annex 2 (2014)

- essential GMP elements

1. pharmaceutical quality system
2. good manufacturing practice
3. sanitation and hygiene
4. qualification and validati
5. complaints
6. product recalls
7. contract product, a sis and other activities
8. self-inspection lity/supplier audit and approval
9. personnel ing and personal hygiene
10. premise
11. trainin
12. pers l hygiene
13. eq ent
14. rial
1. cumentation
2. good practices in production
3. good practices in quality control

Systemic but risk based approach

Inspection coverage

Scope

Biological products: TRS 999 annex 2 (2016)

- specific GMP elements

1. Introduction
2. Scope
3. Terminology
4. Principles and general siderations
5. Pharmaceutical quali stem and quality risk manag t
6. Personnel
7. Starting materi
8. Seed lot and bank
9. Premises equipment
10. Contain
11. Clean s
12. Proc on
13. Ca ign production
14. lling
15. idation
16. Quality control
17. Documentation
18. Use of Animals

Emphasis on Quality Risk Management and control trategy

Manufacture of Sterile Medicinal Products
WHO TRS 986 annex 6 vs. Annex 1 (under Finalisation/Adoption)

Section Number	General overview
1. **Scope**	Includes additional areas (other than sterile products) where the general principles of the annex can be applied.
2. **Principle**	General principles as applied to the manufacture of sterile products.
3. **Pharmaceutical Quality System (PQS)**	Highlights the specific requirements of the PQS when applied to sterile products.
4. **Premises**	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Barrier Technology.
5. **Equipment**	General guidance on the design and operation of equipment.
6. **Utilities**	Guidance regarding the special requirements of utilities such as water, gas and vacuum.
7. **Personnel**	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance regarding the qualification of personnel.
8. **Production and specific technologies**	Guidance on the approaches to be taken regarding aseptic and terminal sterilization processes. Guidance on the approaches to sterilization of products, equipment and packaging components. Also guidance on different technologies such as lyophilization and Form-Fill-Seal where specific requirements apply.
9. **Environmental and process monitoring**	This section differs from guidance given in section 4 in that the guidance here applies to ongoing routine monitoring regarding the design of systems and setting of action limits alert levels and reviewing trend data. The section also gives guidance on the requirements of Aseptic Process Simulations (APS).
10. **Quality control (QC)**	Guidance on some of the specific Quality Control requirements relating to sterile products.
11. **Glossary**	Explanation of specific terminology.

Manufacture of Sterile Medicinal Products
WHO TRS 986 annex 6 vs. Annex 1 (under Finalisation/Adoption)

Key changes in summary:

- Emphasis of **Quality System** and **QRM**,
- Need to have a documented **contamination control strategy**,
- Based on QRM, **design is paramount to risk reduction**,
- Need to **use current technologies** (e.g. RABS, Isolators, robotics, …),
  - Old technologies such as **open "grade A" or curtains will not be tolerated going forward**,
- Needs to be designed to keep **operators outside of the Grade A**,
- …

GMP Observations

GMP Inspection Outcome

- deficiencies
  - non compliance with GMP requirements
  - origin
    - defective system
    - failure to comply with system
  - classification
    - critical: potential risk/harm to user
    - major: major deviation from GMP
    - other: departure from GMP
  - risk-based approach for definition and classification

GMP compliance lead to Prequalification/Emergency Use Listing

Serious non-compliances can lead to:

- ✓ **notice of concern;**
- ✓ **notice of suspension;**
- ✓ **de-listing**

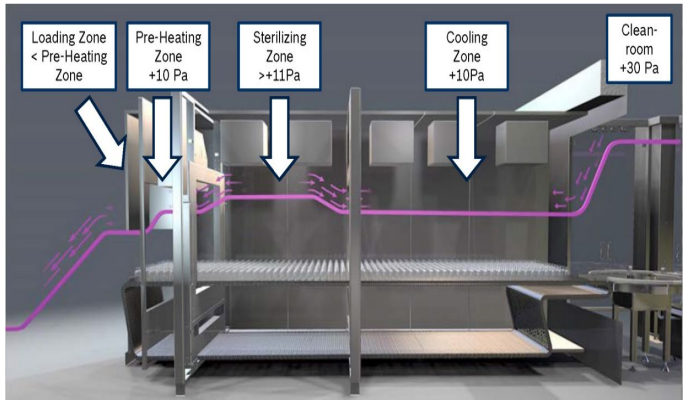
Common GMP observations for Vaccines

No and/or Incomplete Validations

- Master/Working Seeds and cells establishment
- Manufacturing Processes (DS, DP)
- Purification processes
- Stability studies
- Sterile filtration
  - Filtration not close to final filling
  - PUPSIT not in place
- Viral inactivation (When required)
- Holding storage periods of media, buffers and intermediates.

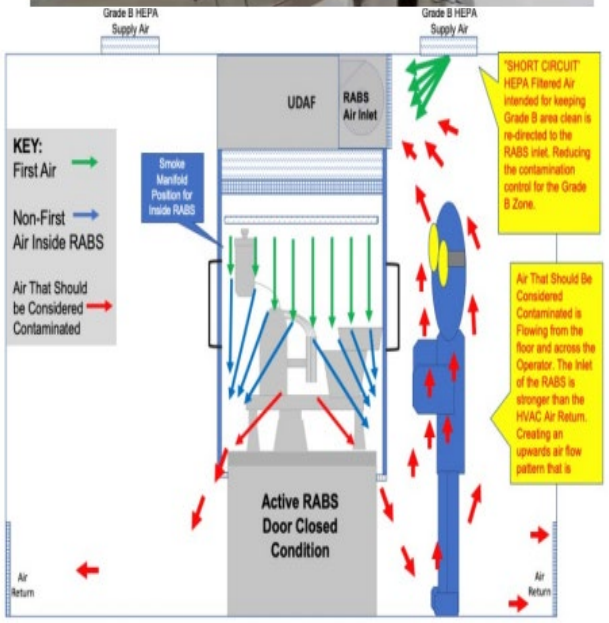
Facilities and equipment

- Inadequate design of:
  - Facility
    - Inadequate segregation (including live/non live areas
      - Shared equipment
      - Shared HVAC systems
      - Inappropriate pressure cascade
      - Cross flows
  - Equipment
    - Manuafcturing vessel (Not SIP/CIP)
    - Depyrogenation tunnel
      - Not adequately controlled
      - Not protected from contamination after interventions
    - Autoclaves (Types, applications and qualifications)



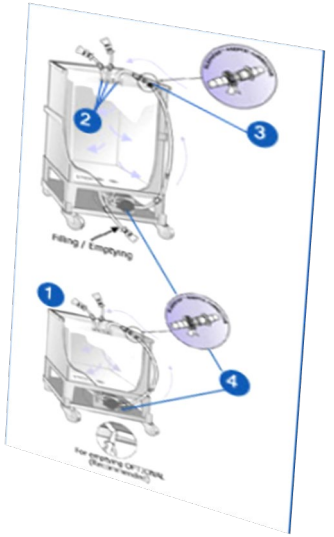
Facilities and equipment

- Filling machines/lines
  - Design failure and Technical limitations
    - Extensive manual operations within grade A
    - Critical parts of fill machine against the wall
      - Unmitigated risks for contamination
    - Inadequate access (Fill line in L or U shape)
      Prolonged time for access and set up
    - Inadequate airflow patten
      (Designed for turbulence !)



Facilities and equipment

- Single Use System (SUS)
  - Poor qualification and validation
  - Inappropriate scale up from hard vessels to SUS
  - Integrity to preserve sterility not considered
  - Leachable and extractibles not considered



Laboratory control system

- Inadequate test methods
- Incomplete validations
- Lack of qualification of in-house reference material
- Samples management
  - Huge numbers of samples and tests placing stresses on essentially manual tracking systems
- Personnel comfort (huge workload)
- Data integrity (ALCOA principles)

Laboratory control system

Environmental monitoring program:

- Performed during set up of the filling machine
- Risk assessment based
- EM devices of adequate design
- Media containing appropriate neutralizers
- Personnel garments and gloves monitored after manufacturing operations in grade A/B areas
- Investigation of contamination, root cause and product impact analysis
- Sampling/testing of utilities

Data Integrity

… The data on which … decisions are based should … be **complete** as well as being **attributable**, **legible**, **contemporaneous**, **original** and **accurate**, commonly referred to as "**ALCOA**".

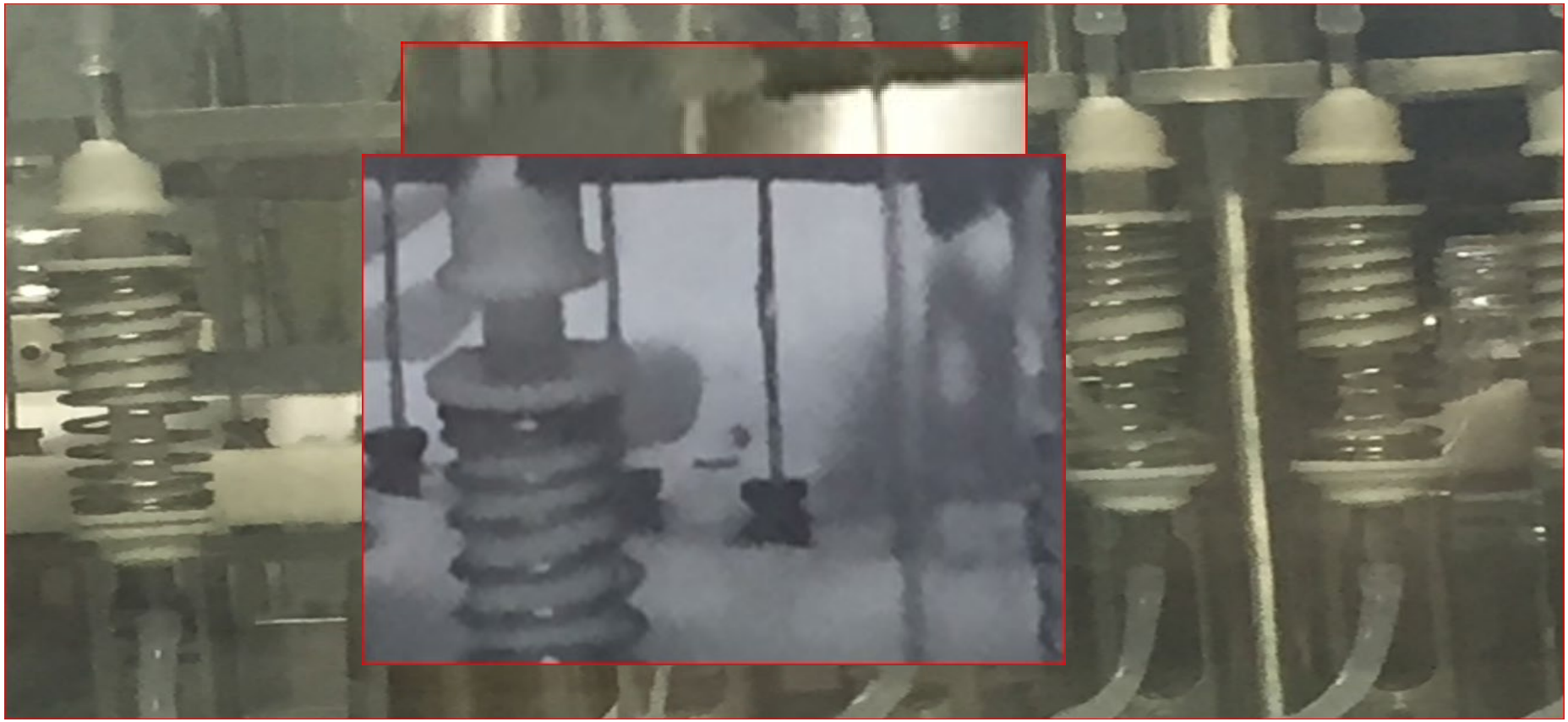
Data integrity issues on:

- ✓ **Computerized Systems – Quality control**
- ✓ **Computerized Systems – Manufacturing and utilities**
- ✓ **Microbiology including Environmental monitoring (EM)**

Several critical deficiencies were raised for no or false reporting of the integrity test of the sterilizing filters.

Several critical deficiencies were raised for no or false reporting of EM test results.

Design for failure



Technical limitations can not be addressed with procedures

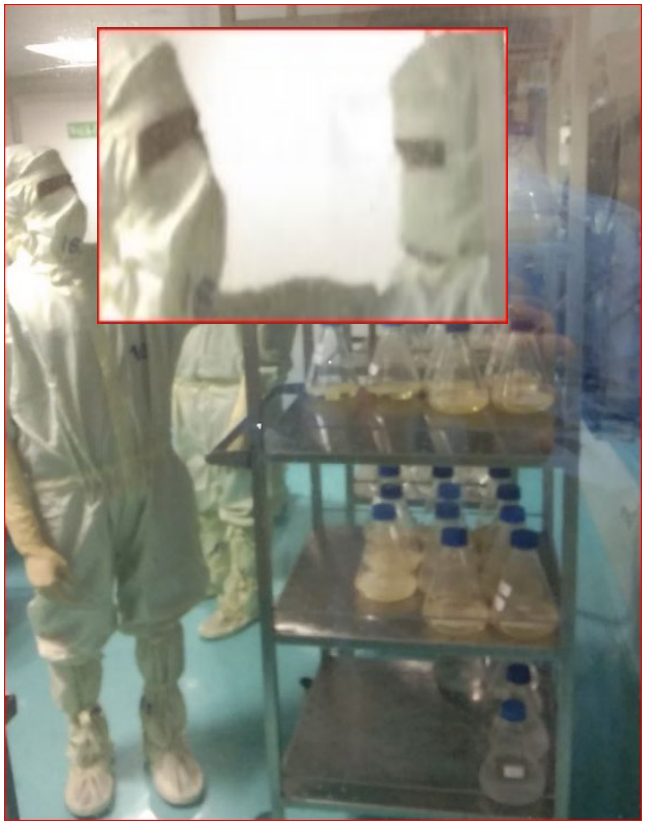
Design for Failure

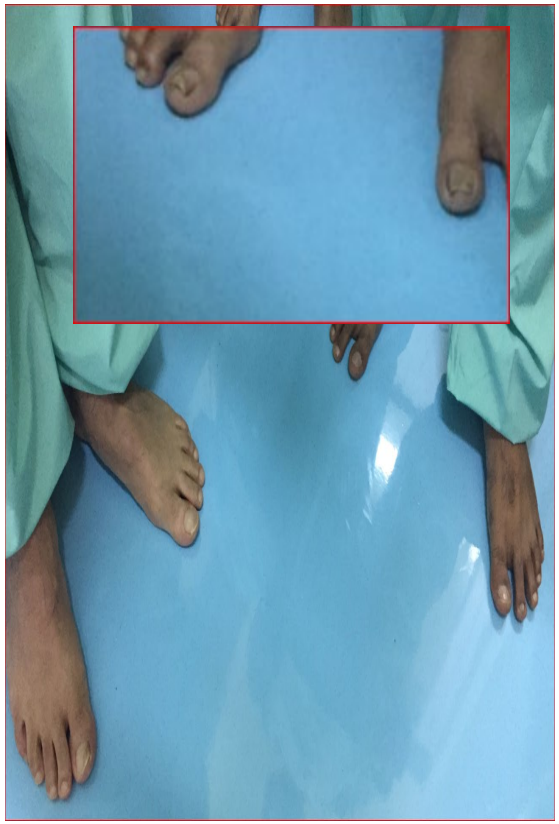
Design, restricted access barrier system, gowning and procedures are all together of paramount importance in aseptic processes including vaccines.

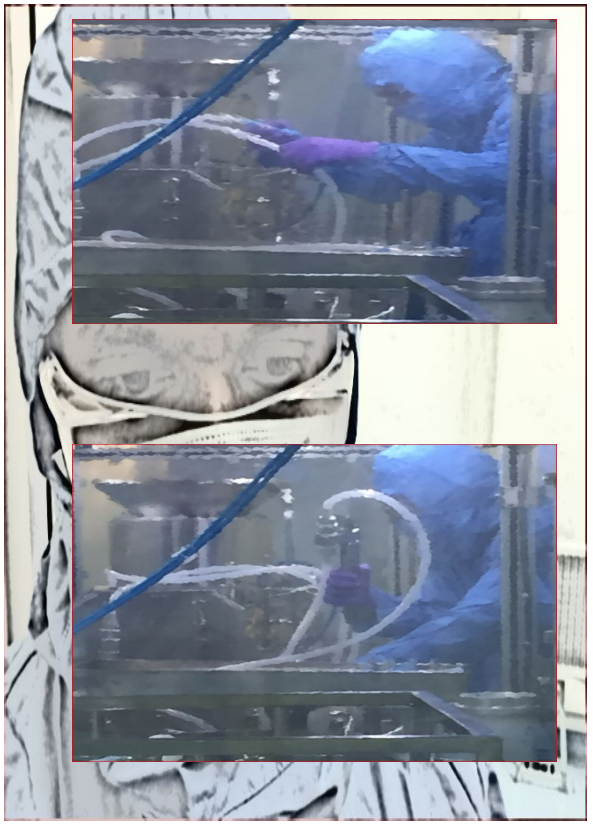
Design for Failure

Extensive manual human intrusions within grade A is too risky to appropriately mitigate.

Design for Failure

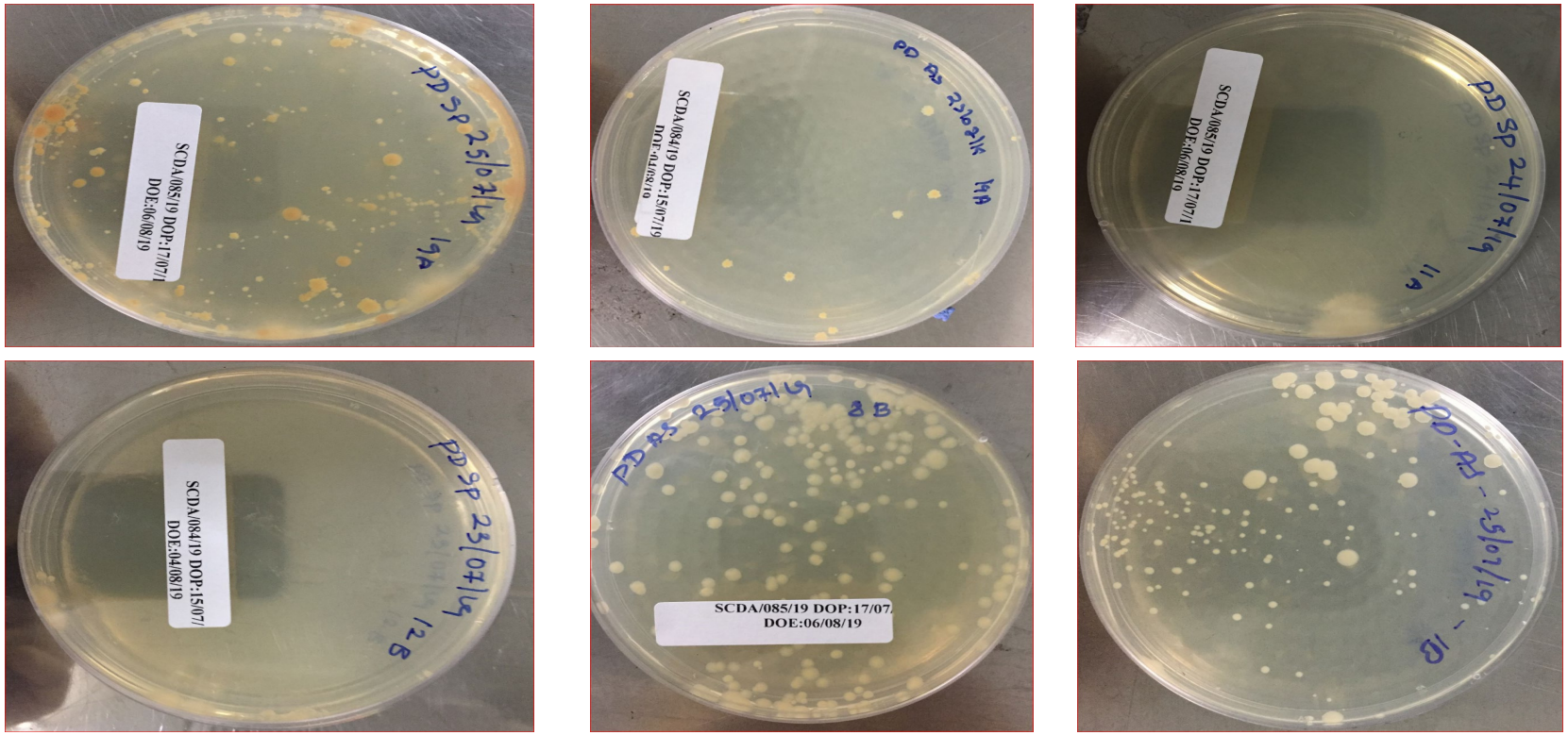






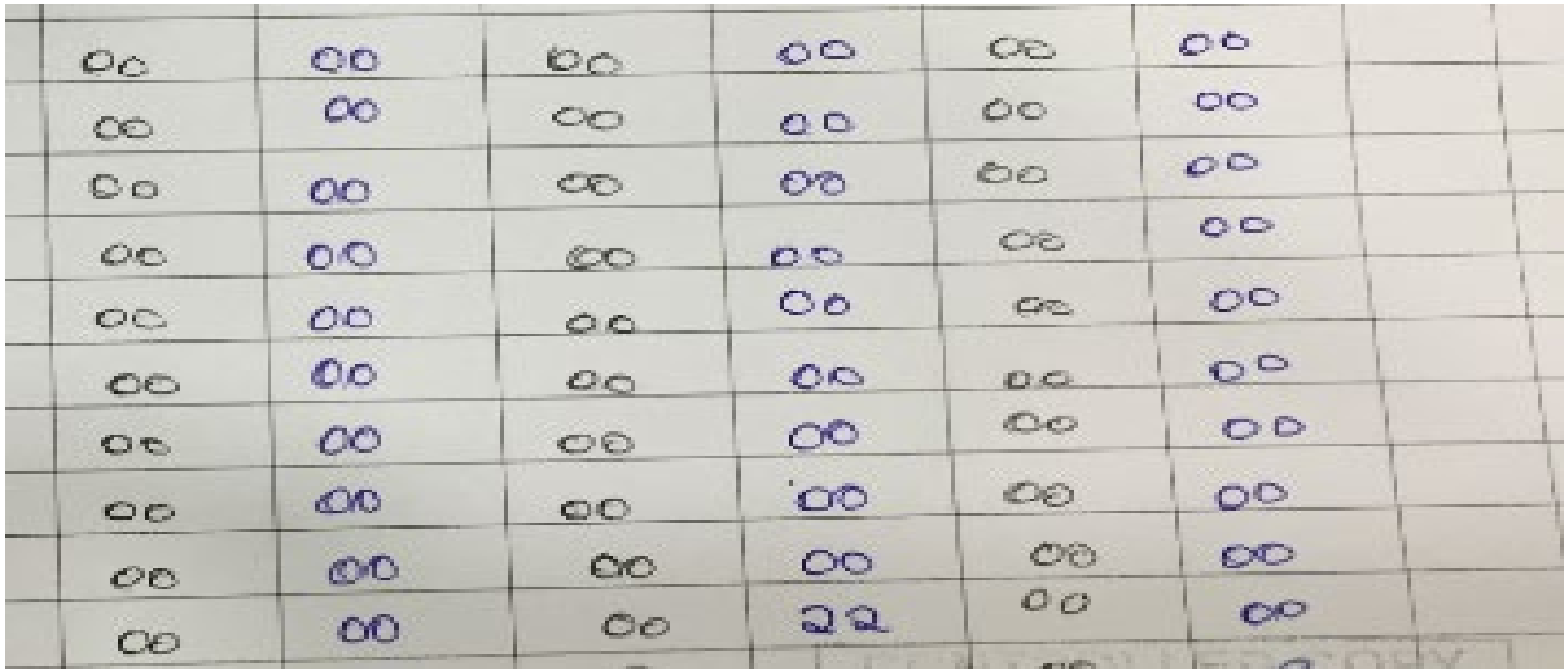
Hygiene, gowning and aseptic behavior are all of paramount importance for aseptic processes.

What might be expected



Nil recorded excursion or count in cfu in classified areas (aseptic room) with poor aseptic practices is a red flag.

What might be unexpected



False reporting of critical environmental monitoring test results (records not matching with actual cfu counts)

Poor root cause investigation

Poor root cause investigation

No deviation was raised

Contaminations were found by the inspectors in different media plates, from different sampling locations, incubated in different shelves and in different incubation rooms.

Several sampling locations were critical to the aseptic filling !!

Results recorded as nil cfu not matching cfu counts found in incubation rooms

Data integrity issues are corrosive to science and trust, once lost, trust cannot be overnight restored as there are no CAPAs to fix the trust.

Challenges for Sars-Cov 2 candidate vaccines for EUL during the Covid 19 Pandemic

Established manufacturers

Need for extended production Capacity at short notice

- Lack of sufficiently experienced personnel (production and QC)
  - Relocate/reallocate staff from existing operations into new Covid19 vaccines
  - Recruit and train huge numbers of new employees
  - Long hours being worked with limited or no rest days.
  - Errors made not robustly and fully investigated. Emphasis on quick rather than on long term fixes

- Wide use of external support and vendors for installation and validation with in-house staff sometimes not having all necessary training and knowledge of the new equipment

Need to construct new facilities and install many new fill fines for extra capacity

- Issues of obtaining the equipment and vendor technical support
- Risks of opting for available sub-optimally lines and not what can be optimum due to time constraints
- Rushed URS, DS, DQ leading to equipment and system integration design errors
  - Often had to be retrospectively corrected
  - In some cases, only after inspection

Need for Repurposing of lines at short notice

- Risk of sub-optimal adaptation
- Insufficient time to remove redundant equipment

Travel and quarantine restrictions hamper communications and joined up working:

- Travel restrictions and availability meaning distant management of audit and qualification of new vendors

- Travel restrictions and availability meaning distant management of contractors for bulk or fill/finish adds to stress and complexity

Much added complexity

- Huge numbers of components and raw materials being required
  - Multi sourcing of materials add complexity to validation and variation in production.
  - Extensive stability studies being necessary, often in concurrent studies.
    - E.g. several sources of vials and several sources of stoppers

- Multi sourcing of filters necessary adding to validation complexity and back logs with validations outsourced to the filter vendors

Much added complexity

- Shortages, long and complex supply chains for many components and starting materials.
- Long lead times on any changes needed to SUS or PUPSIT rigs
- Widespread use of remote storage of raw materials and components outside of the normal pharma supply chain

Challenges for New Developers/Manufacturers

- Limited experience in Vaccines
- Limited or no experience at commercial scale
- Difficulty in recruiting experienced staff
- Poor understanding of regulatory requirements
- High reliance on contracted out services in most if not all parts of their operations
- Investor expectations and pressures
  - Rush to market

Key Achievements During Pandemic Covid-19

Going extra mile…

- WHO Prequalification Programme ensured EUL and PQ vaccines comply with WHO GMP
- Several Candidate Vaccines for EUL passed WHO Inspections
- Several Candidate Vaccines were Emergency Use Listed by WHO
- Millions of lives saved and EFFORTS WILL CONTINUE TILL WE ALL ARE SAFE

COVID-19 vaccines WHO EUL issued

Vaccine	WHO EUL Holder	NRA of record	Recommendation issued
COMIRNATY® COVD-19 mRNA Vaccine (nucleoside modified)	BioNTech Manufacturing GmbH	European Medicines Agency	31 December 2020
		Food and Drug Administration	16 July 2021
VAXZEVRIA COVID-19 Vaccine (ChAdOx1-S [recombinant])	AstraZeneca AB / SK Bioscience Co. Ltd	Ministry of Food and Drug Safety (MFDS)	15 February 2021
	AstraZeneca AB	European Medicines Agency	15 April 2021
		Ministry of Health, Labour and Welfare	09 July 2021
		Therapeutic Goods Administration	09 July 2021
		Health Canada	21 August 2021
		COFEPRIS (DP)	23 December 2021
		ANMAT (DS)	
COVISHIELD™ COVID-19 Vaccine (ChAdOx1-S [recombinant])	Serum Institute of India Pvt. Ltd	Central Drugs Standard Control Organization	15 February 2021
COVID-19 Vaccine (Ad26.COV2-S [recombinant])	Janssen–Cilag International NV	European Medicines Agency	12 March 2021
SPIKEVAX COVID-19 mRNA Vaccine (nucleoside modified)	Moderna Biotech	European Medicines Agency	30 April 2021
		Ministry of Food and Drug Safety (MFDS)	23 December 2021
	ModernaTX, Inc	Food and Drug Administration	06 August 2021
Inactivated COVID-19 Vaccine (Vero Cell)	Beijing Institute of Biological Products Co., Ltd. (BIBP)	National Medicinal Products Association	07 May 2021
CoronaVac COVID-19 Vaccine (Vero Cell), Inactivated	Sinovac Life Sciences Co., Ltd	National Medical Products Administration	01 June 2021
COVAXIN® Covid-19 vaccine (Whole Virion Inactivated Corona Virus vaccine)	Bharat Biotech International Ltd	Central Drugs Standard Control Organization	03 November 2021
COVOVAX™ COVID-19 vaccine (SARS-CoV-2 rS Protein Nanoparticle [Recombinant])	Serum Institute of India Pvt. Ltd	Central Drugs Standard Control Organization	17 December 2021
NUVAXOVID™ COVID-19 vaccine (SARS-CoV-2 rS [Recombinant, adjuvanted])	Novavax CZ a.s.	European Medicines Agency	20 December 2021