Technical updates on GMP inspections of vaccines

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Session outline

General background
Guidelines for inspections
Process of inspections
Worrying trends
GMP area for improvement
Concluding remark
Complexity of 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
- ...
The opportunities for contamination and cross contamination

Microbial growth
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

Personnel

Starting/processing materials:
Serum, peptones, growth factors, enzymes, … etc), Reusable resins and filters, Cell substrates, …

Processes and procedures :
(Open versus Closed, Hold times. …)

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

Facility:
Dedicated versus shared, …

Utilities: Air, Water, Process gases, …
Regulatory prospective

Good Manufacturing Practices (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.

Quality can not be assessed, tested or inspected into the product, BUT it has to be built into it!
WHO Guidelines

Product is produced in accordance to WHO GMP recommended requirements

• WHO GMP Technical report Series (TRS)

GMP Main Principles: WHO TRS 986 annex 2

Sterile products: WHO TRS 986 annex 6

Under review

Biological Products: WHO TRS 999 annex 2

Implemented since end 2016

GMP for API: WHO TRS 957 annex 2

HVAC: WHO TRS 1010 annex 8

Validation: WHO TRS 937 annex 4

QRM: WHO TRS 981 annex 2

.....
Vaccine Standardization

The World Health Organization brings together international experts in specific fields through its biological standardization programme to develop and revise specific recommendations for the production and quality control of vaccines of major international public health importance. Authoritative, harmonized guidelines and recommendations, for use by manufacturers and regulatory authorities, are published in the reports of ECBS meetings in the WHO Technical Report Series.

These include recommendations for individual vaccines, and also more general guidelines on technical or regulatory topics such as cell substrates, nonclinical evaluation, or clinical evaluation. This programme also establishes and distributes the WHO Biological Reference Materials required for the standardization of assays to laboratories around the world such as manufacturers and National Control Laboratories (NCLs) who are involved in the quality control of vaccines. This activity is critical to ensure the quality of essential vaccines in a global market.

Vaccine-specific standardization

- BCG (Tuberculosis)
- Cholera
- Combined DT-Based Vaccines
- Dengue
- Diphtheria
- DNA vaccines
- Mumps
- Pertussis
- Plant-derived vaccines
- Pneumococcus
- Poliomyelitis
- Rabies
Standardization of Biotherapeutic Products

The World Health Organization brings together international experts through its biological standardization programme to develop and revise guidance on biotherapeutic products. The norms and standards programme for biotherapeutics is responsible for developing and establishing both international biological reference preparations and written standards (Recommendations and Guidelines) for these products. The promotion of WHO biological standards is undertaken in a variety of ways including rapid publication on the WHO website, as well as by the organization of post-adoptive workshops to facilitate the implementation of highly complex or topical guidelines/recommendations into regulatory and manufacturers’ practice. Such workshops have proved extremely valuable not only in promoting the WHO recommendations/guidelines in question, but also as a means of obtaining information from countries about their use of WHO guidance documents and their ability to follow WHO guidance, as well on interpreting difficult aspects of the guidance given in the documents.

Biotherapeutic-specific standardization
- Biotherapeutic product
- Similar biotherapeutic product

General topics and regulatory guidance
- Cell Substrates
- WHO reference cell banks (RCBs)
- Good Manufacturing Practices (GMP)
- Sterility testing
- Transmissible Spongiform Encephalopathies (TSE)

Essential Medicines and Health Products
- EMP home page
- Regulation
- Norms and standards

New Publications
Post ECBS 2016 documents
- Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs).pdf, 452kb
- Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries.pdf, 771kb
- Guidelines on estimation of residual risk of HIV, HBV or HCV infections via cellular blood component and plasma.pdf, 349kb
- Guidelines on management of blood and blood components as essential medicines.pdf, 500kb
- Manual for the preparation of secondary reference materials for in vitro diagnostic assays designed for infectious disease nucleic acid or antigen detection: Calibration to WHO International Standards.pdf, 3.58Mb
- WHO Guidelines for the production, control and regulation of Snake Antivenom Immunoglobulins.pdf, 2.10Mb

Copenhagen, Denmark 24 – 27 September 2018
GMP inspection coverage and report

Essential GMP elements:
1. Pharmaceutical quality system
2. Good manufacturing practices
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract product, analysis and other activities
8. Self-inspection, quality audits and supplier's audit and approval
9. Personnel, training and personal hygiene
10. Premises
11. Training
12. Personnel hygiene
13. Equipment
14. Material
15. Documentation
16. Good practices in production
17. Good practices in quality control

Six systems:
1. Pharmaceutical quality system
2. Production system
3. Facility and equipment system
4. Laboratory control system
5. Material system
6. Packaging and Labelling system

Reference: WHO TRS 996, annex 4, appendix 1
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Copenhagen, Denmark | 18-21 September 2018
Annex 1 updated
- Draft published 20\textsuperscript{th} December 2017
- Published by EMA/WHO and PIC/S
- Consultation period closes 20\textsuperscript{th} March 2018
- Review and \textit{redraft being discussed at present}

Key changes in summary:
- Introduction and emphasis of QRM,
- Need to have a documented \textit{contamination control strategy},
- Based on QRM, \textit{design is paramount to risk reduction},
- Need to \textit{use current technologies} (e.g. RABS, Isolators and even robotics),
- Old 70s technologies such as \textit{open “grade A” or curtains will not be acceptable going forward},
- Needs to be designed to keep \textit{operators outside of the Grade A},
- ...
GMP inspection triggers

Manufactures are inspected by WHO-PQT on a routine basis using a risk based approach,

As part of pre-approval activity

- When the review of the product dossier and testing have been satisfactorily completed

Post approval surveillance (routine)

- Due date: risk-based, 1 – 3 years from date of previous inspection

For special cause e.g. serious complaints or reports of serious adverse events following immunization (AEFIs) if a quality problem is suspected.
Team of experienced inspectors:
In the areas of production, quality control, quality assurance, quality system and GMP,
- GMP inspector(s),
- Co-inspector(s)
- Product expert,
- National inspector(s),
- Technical staff from a relevant UN procurement agency,
- Observer from recipient/other countries.

Scope:
- Compliance with WHO GMP,
- Compliance with product specific TRS (Production and Quality Control),
- to have an adequate Pharmaceutical Quality System
- The “vaccine” meets the United Nations’ specifications for tender (which reflect the needs of the immunization programmes at country level),
- Other aspects are in place:
  - Post-marketing surveillance system,
  - Vaccine vial monitor (VVM) implementation.
Pre inspections

- Verify the objective of inspection to be carried out
- Review the previous inspection reports and CAPAs
- Review the quality assessment reports and PSFs
- Review the site master file
- Review the annual vaccine quality reviews
- Review the complaints register and the list of variations
- Determine the scope to be covered (products, areas, sites, activities, …)
- Preparation of tentative inspection plan
- Share the inspection plan and the list of experts/co-inspectors with the manufacturers
Onsite Inspection

- Opening meeting, daily discussions, full transparency

- Assessment of robustness of Pharmaceutical Quality System and GMP compliance, what the company is good at and where there are gaps and weaknesses
  - Tour of the site to review facility, equipment, manufacturing processes, quality control activities, warehousing and shipment
  - Assessment of the data and accuracy of the submitted dossier

- Closing meeting to discuss the deficiencies and the initial outcome

- A draft report with list of findings is left onsite for the manufacturer to begin CAPA preparation
Post Inspection

- Issuance of inspection within 30 days
- Approval and release of the report by the group lead of inspection services (peer review)
- Review and assessment of the CAPA
- Statement of the GMP compliance and recommended inspection re-interval
- Publication of WHOPIR on the WHO Web Site
Outcome of the inspection – risk based approach

Deficiencies are descriptions of non-compliance with GMP requirements.

✓ Critical: potential risk/harm to the user,
✓ Major: major deviation from GMP,
✓ Other: departure from GMP.

1. When there are "other" deficiencies only ➔ Acceptable level of compliance with WHO GMP.

2. When there are "other" and a few "major" deficiencies ➔ Compliance made after the CAPAs have been positively assessed.

3. When there are "critical" and/or several "major" deficiencies ➔ Unacceptable level of compliance with WHO GMP guidelines.

Serious non-compliances can lead to:

✓ Notice of Concern,
✓ Notice of Suspension and or de-listing.
Worrying trends

Few critical deficiencies,
- Mainly data integrity issues.
- Snake anti-venoms (neglected area)

High number of raised deficiencies,
- Majors and Others.

Knee Jerk for responses to inspection observations,

Many « Awaits CAPAs » on inspection,
- Poor investigations into root cause.

Work hard to pass first inspection and forget the compliance is an ongoing process.
Hidden non compliances: the ICEBERG

No effective Training of operators and poor upper management involvement

Risk Management

- Poor GMP / reactive / immature
- Poor QMS implementation
- Poor QRM implementation
- Poor Product Quality Reviews
- Poor design and maintenance
- Facility and equipment
- Poor manufacturing validation
- Product development/Tech transfer
- Poor Self inspection
Product Quality Review (PQR):

PQR often found barely implemented for compliance standpoint. Sparsely gathering data and information.

... and not with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

Opportunity to gain knowledge and demonstrate compliance and compliance sustainability.
Quality Risk Management (QRM):

Poor and immature implementation of the QRM principles.
Limited expertise within some companies for performing comprehensive and detailed risk assessments and risk mitigation and control measures.

QRM principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimize variability and to reduce the opportunity for contamination and cross-contamination.

Opportunities to better control the process and the product and make best use of available resources.
The good data and record management practices:

... 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

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.
Example 1 of critical deficiency raised during PQT inspections:

The company failed to record and report reliable and accurate data for the environmental monitoring test results. The critical data integrity issues in form of fraudulent data were witnessed during the inspection:

- False results were recorded on the QC records and reports. It was witnessed that the plates recorded and reported as negative by QC personnel were in fact positive for contaminations.
- Contaminations (cfu counts) in grade A were recorded and reported as nil but in fact were positive. Contaminations of grade B were recorded and reported as nil or as within the specification of established alert limit but in fact they were positive and above the specified limit. Contaminations (cfu counts) for operators gown in grade B were reported as nil but in fact they were positive.

GMP non compliance
Example 2 of critical deficiency raised during inspections:

The company representative reported that no failure of integrity test of sterilising filters was recorded. Indeed, in the logbook of the integrity tester, no failure of the integrity test was recorded. However, when the inspectors switched on the integrity tester and had access to the soft history file, several failures were recorded.

No deviation raised …,

No investigation conducted …,

GMP non compliance
GMP areas for improvement

Facility and equipment:

– Inadequate design of filling lines
  • Extensive manual operations within grade A
  • Open doors

– Inadequate design of equipment
  • Lyophilisers
  • Fermentors/bioreactors
  • vessels

– Use of disposable without appropriate qualification and validation
  • Leachable, extractibles, integrity, …
Facility and equipment:

- Inadequate design for containment versus cross-contamination
  (Shared HVAC systems, inappropriate pressure cascade)

- Inadequate segregation (pre- and post-inactivation)
  - Use of shared equipment for pre- and post-live organisms inactivation steps

- Inadequate decontamination for campaign production

- Inadequate cleaning and disinfection of aseptic rooms
GMP area for improvement

Manufacturing processes and procedures:

- **Sterile filtration**
  - Not in place for filterable product
  - Not validated
  - No bioburden

- **Lyophilisation process**

- **Inactivation processes**

- **Holding storage periods of intermediates, media and buffers**
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
- Control for detection of the presence of specific micro-organisms used for production
**Seed lots:**

- GMP history and preparation of banks
- Adequate sealing, labelling and temperature monitoring
- Minimize the risks of contamination or alteration
- Storage in two controlled separate, based on a contingency plan
GMP areas for improvement

**Biological starting materials:**

- Adequate information on source, origin, suitability
  - Qualification of the supplier

- Microbiological quality

- Freedom from adventitious agents
Concluding remark

Quality is not an act but a habit.

“Aristotle”.

Copenhagen, Denmark  24 – 27 September 2018
Thank you