Introduction to vaccines inspections
technical updates:
GMP inspections of Vaccines

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Talking points

- WHO Prequalification GMP Inspection Process
  - Objectives of Inspections
  - Key Documents
  - Inspection triggers and timelines
  - Inspection Team
  - Compliance status and inspection outcome

- Vaccines Inspection statistics
- Worrying and promising trends
- Responses to inspections
- Areas for improvement
- Concluding remarks
GMP Inspection Process: Objective of Vaccines Inspection

➢ To assess whether:

✓ The vaccine complies with WHO recommendations for production and quality control,
✓ The vaccine is produced in compliance with WHO-recommended GMP,
✓ The company has an adequate pharmaceutical quality system in place,
✓ 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:
  • Adequate labelling and packaging,
  • Post-marketing surveillance system,
  • Vaccine vial monitor (VVM) implementation when required, and,
  • Stability programme.
Product is produced in accordance to WHO GMP recommended requirements

- WHO GMP Technical report Series (TRS)

Key GMP Documents

Product meets the WHO recommended requirements for quality, safety and efficacy

WHO Product specific TRS

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
- Haemophilus influenzae (Hib)
- Hepatitis A
- Hepatitis B
- Human Papillomavirus (HPV)
- Influenza
- Japanese encephalitis (JE)
- Malaria
- Measles
- Meningocoecal meningitis

General topics and regulatory guidance

- Extended Controlled Temperature Conditions (ECTC)
- Biotechnology and related topics
- Cell substrates
- WHO reference cell banks (RCBs)
- Clinical evaluation of vaccines
- Good Manufacturing Practices (GMP)
- Lot Release of Vaccines
- Non-clinical evaluation of vaccines
- Human papillomavirus vaccines
- Shigella
- Tetanus
- Tuberculosis
- Typhoid fever
- Viral vector vaccines
- Varicella
- Yellow Fever

ESSENTIAL MEDICINES AND HEALTH PRODUCTS

- EMP home page
- Regulation
- Norms and standards

NEW PUBLICATIONS

Post ECBS 2016 documents

- Guidelines on evaluation of monovalent antibodies as similar biotherapeutic products (SBPs)
  pdf: 4526
- Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries
  pdf: 7714
- Labelling information of inactivated influenza vaccines for use in pregnant women: Addendum to Annex 3 of WHO Technical Report Series, No. 927
  pdf: 4018
- Guidelines on estimation of residual risk of HIV. HBV or HCV infections via cellular blood component and plasma
  pdf: 6488
- Guidelines on management of blood and blood components as essential

Reference: http://www.who.int/biologicals/vaccines/en/

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Key GMP Documents

Product meets the WHO recommended requirements for quality, safety and efficacy

- WHO Product specific TRS

Standardization of Biotherapeutic Products

The World Health Organization brings together international experts through its biological standardization programmes 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-adooption 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 as 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)

Reference: http://www.who.int/biologicals/biotherapeutics/en/

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GMP Inspection Coverage

- **Pharmaceutical quality system**
  - Annual product quality review
  - Quality risk management
  - Change control management
  - Deviation management
  - Corrective and preventive actions management
  - Management review
  - Lot release management

- **Good manufacturing practices**
  - Sanitation and hygiene
  - Qualification and validation
  - Complaints
  - Product recalls
  - Contract product, analysis and other activities

- **Self-inspection, quality audits and supplier s audit and approval**
- **Personnel, training and personal hygiene**
- **Premises**
- **Equipment**
- **Material**
- **Documentation**
- **Good practices in production**
- **Good practices in quality control**

Reference: WHO TRS 996, annex 4, appendix 1
You may wish to highlight that the revised GMP Guide for Biologics have replaced TRS 822, Annex 1
GMP Inspection Coverage for Biological Products Including Vaccines:

WHO TRS 996 annex 3, 2016

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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 summary file (PSF) and testing have been satisfactorily completed

- Post approval surveillance (routine)

- For special cause e.g. serious complaints or reports of serious adverse events following immunization (AEFIs) if a quality problem is suspected.
GMP Inspection Team

Has expertise in the areas of production, quality control, quality assurance, quality system and GMP,

✅ Usually includes one of the dossier (quality) reviewers,

✅ External expert(s) or co-inspector(s),
  ➢ Declaration of interest and confidentiality agreement.

✅ May include technical staff from a relevant UN procurement agency,

✅ Lead inspector from the Inspection Service Group in PQT.

The NRA of the manufacturing country, or the NRA with regulatory oversight of the product, is invited to join the WHO team as observers or to participate in the mission.
Type and Target Inspection Timelines

✓ First inspection: 6 months from dossier acceptance for assessment or from site confirms it is ready.

✓ Surveillance/Routine monitoring inspection:
  ✓ due date: risk-based, 1 – 3 years from date of previous inspection
  ✓ Actual date: ± 3 months from due date.

✓ For Cause/Notification:
  ✓ Announced: 1 – 2 months before inspection.
  ✓ Unannounced/short announced: 0 – 7 days before inspection
Target Inspection Timelines

✓ **Onsite days:** 3 – 5 days.

✓ **Report:** 30 days from last date of inspection.

✓ **CAPAs:** 30 days from receipt of report (max 2 rounds, comprehensive, on CDs and not hard copies)

✓ **Closing of inspection:** 6 months from inspection.

✓ **Follow-up inspection:** 6 months from inspection
Inspection Planning

➢ Before the inspection the inspectors are required to:
  ✓ Verify the objective of inspection to be carried out;
  ✓ Review the previous inspection reports and CAPAs;
  ✓ Review the quality assessment reports and the PSF;
  ✓ 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,
The onsite Inspection

- Opening meeting, daily discussions, full transparency

- Systemic and risk based emphasis
  - Sampling process

- Assessment of robustness of Pharmaceutical Quality System and GMP compliance, what the company is good at and where there are gaps and weaknesses
  - Inspection and tour of the site to review the 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
Definition and classification of deficiencies

Deficiencies are descriptions of non-compliance with GMP requirements. Deficiencies are based on:

- Requirement/Recommendation
- Evidence/Fact
- Deficiency

A distinction is made between deficiencies as a result of:

- a defective system or,
- failure to comply with the system.

Deficiencies may be classified as:

- Critical: potential risk/harm to the user,
- Major: major deviation from GMP,
- Other: departure from GMP.
The colour of the header is too light in my opinion, will check during dry run.
Compliance Status and Inspection Outcome

- When there are "other" deficiencies only:
  - ✓ considered to be operating at an **acceptable level of compliance** with WHO GMP,
  - ✓ The manufacturer is expected to provide CAPAs,
  - ✓ CAPAs are evaluated and followed up during the next routine inspection.

- When there are "other" and a few "major" deficiencies:
  - ✓ **compliance** with WHO GMP is **made after** the **CAPAs have been assessed**,
  - ✓ CAPAs for majors to include documented evidence of completion,
  - ✓ CAPAs evaluated ± an on-site **follow up** inspection.
Compliance Status and Inspection Outcome

- When there are "critical" or several "major" deficiencies:
  - considered to be operating at an **unacceptable** level of compliance with WHO GMP guidelines,
  - **Another inspection** will be required.

- When there are serious non-compliances:
  - **Notice of Concern**,  
  - **Notice of Suspension**,  
  - **De-listing** from the list of prequalified vaccines
Post Inspection

- A report is to be issued within 30 days of the site inspection
- Approval and release of the report by the group lead inspection services
- Send the inspection report to the company
- Review of the company CAPA, and
- Final compliance decision and recommended inspection re-interval
- WHOPIR excluding confidential and proprietary information are published on the WHO Web Site
Vaccines Inspection Statistics

Number of inspections

Number of vaccines covered

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This slide should provide number of inspections performed in each year (no labels)

SACHDEVA, Vimal, 16/09/2017
Vaccines Inspection Statistics

- Break up of vaccines inspections:

![Chart showing the break up of vaccines inspections between 2016 and 2017.](chart.png)
Provide number of inspections in 2016 and 2017

SACHDEVA, Vimal, 16/09/2017
Vaccines Inspection Statistics

Initial outcome 2016

- Immediate compliance, 0
- Ongoing, 1
- Requires follow up inspection, 2
- After First CAPA, 1
- After second or more round, 10

Final outcome 2016

- Compliant, 11
- Non-compliant, 0
- Require Follow up, 3

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Vaccines Inspection Statistics

Initial outcome 2017

- Immediate compliance, 0
- Requires follow-up inspection, 1
- After First CAPA, 0
- After second or more round, 2
- Ongoing, 4

Final outcome 2017

- Non Compliant, 1
- Compliant, 2
- Ongoing, 5
- (ongoing), 5
Common worrying and promising trends

- Few to several major deficiencies and several other deficiencies
- 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
Responses to Inspection observations (1)

Inspection is based on sampling exercise, not all aspects of the manufacturing process may be inspected.

- The manufacturer should take the information provided in the inspection report as examples and to consider **vertical and horizontal analysis** of the issues.

- Deficiencies described in the report that are designated to be of lesser degree of severity, **may increase in severity if not satisfactorily addressed in a timely manner**.
The manufacturer is required to submit an action plan in response to the observations and all nonconformities noted in the final inspection report within **30 days after receipt of the report**.

**It is recommended that the action plan incorporates:**
- Root cause analysis *(how/why did this happen)*,
- Analysis regarding related areas *(is this same issue impacting/occurring elsewhere)*,
- Correction *(fix now)* with completion dates,
- Preventive action *(to prevent recurrence)* with completion dates and,
- The plan for demonstration of effectiveness of the actions taken.
Common deficiencies for vaccines inspections

- Risk of contamination (viable and non viable)
- Risk of cross contamination
- Facility and Equipment design and maintenance
- Qualification of critical equipment and validation of processes
- Supplier and Contractor selection/monitoring/audit
- Personnel Training, Hygiene and Clothing
- Computerized Systems – data integrity
- Product Quality Review
- Investigation and Root cause analysis of deviations, OOS and complaints
- Quality Risk Management
Areas for improvement: biological starting materials

- Qualification and control of biological starting material should include at least:
  - Source, Origin, Suitability
  - Method of manufacture and controls
    - (i.e. viral inactivation / sterilization by gamma irradiation)
  - Microbiological quality
  - Free from adventitious agents
Areas for improvement: risk of contamination and cross contamination through facility and equipment

- Privilege closed versus open equipment,
- CIP/SIP systems,
- Single use systems
  ✓ Qualification of suitability, extractable, leachable and integrity
- Air handling units (AHU) for air quality and segregation
  ✓ Separate AHU, or single pass air
    - To segregate post-inactivation/detoxification areas from pre-inactivation/pre-detoxification areas
    - To segregate live cell areas from cell free areas
    - To minimize mixing of air between different areas
- Adequate area classification
- Adequate pressure cascade and air flow pattern
Areas for improvement: risk of contamination and cross contamination

➢ Dedicated facility

➢ Multi-product facilities
  ✓ Design of the facility for possible need of fumigation
  ✓ Validated effective containment and decontamination
    o Live microorganism and viruses
  ✓ Documented QRM for introduction of new product
    o Containment requirements
    o Cross-contamination

➢ Campaign changeover:
  ✓ Decontamination, sterilisation and cleaning of all equipment and accessories as well as the facility itself
    o Bio-waste management
    o Transfer of material through validated procedures
    o Quality unit approval
Areas for improvement: risk of contamination and cross contamination

- Appropriate environmental monitoring program
  -Performed during setting up of the filling machine,
  -Risk assessment to include all critical locations,
  -EM devices of adequate design,
  -Media containing appropriate neutralizers,
  -Detection of the presence of specific microorganisms used for production (e.g. recombinant yeast and toxin and polysaccharide producing bacterium).
  -Detection of produced organisms and adventitious agents of production organisms, especially when campaign manufacture is applied on the basis of QRM principles.
Concluding remarks

- Strong commitment from senior management to always seek for compliance,
- Detailed knowledge of the requirements and the regulatory expectations,
- Detailed knowledge of the products and all the manufacturing processes and the control stages,
- Mistake should be perceived as an opportunity for improvement and not a room for data integrity issues,
- Have good quality metrics and monitoring processes to be predictive of unwanted or unanticipated factors.
Thank you