Regulatory Inspection for GMP Compliance, Major Inspection Findings

APV Training Course

GMP Requirements

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risk based approach for planning of inspections

Type of company	Compliance	Time factor
- Sterile production - Vaccines/ biotech - non sterile production - packaging - storage/ distribution - wholesaler	- criminal offences - public offences - critical GMP deficiencies - major GMP-findings - others	- Last inspection when? - Plant size

Risk based measures for surveillance

F1: critical GMP deficiencies

M1: measures: immediately, suspension of production

F2: severe GMP- findings

M2: formal acts; e.g. public offences, re-inspection

F3: other deficiencies: neither F1 nor F2

M3: company is responsible for corrective actions

Critical Observations Premises

- No or inadequate ventilation system to eliminate airborne contaminants generated during fabrication with evidence of cross-contamination
- Inadequate segregation of manufacturing or testing areas for high risk products from other manufacturing areas

Critical Observations Equipment

- Critical equipment does not operate within its specifications
- Severe lack of qualification detected for equipment used for critical manufacturing operations

Critical Observations Personnel

- Individuals in charge of QC or production for a manufacturer of critical products are not qualified by education, training and experience

Critical Observations Sanitation

- Sanitation programme not followed combined with dirty premises and equipment (evidence of accumulation of residues)
- Gross infestation

Critical Observations
Raw material testing

- Falsification or misrepresentation of analytical results
- Raw materials not tested to ensure compliance with their specifications

Critical Observations Manufacturing control

- No written master formulae or
- Prepared and /or verified by unqualified personnel and showing gross deviations or calculations errors
- Falsification or misrepresentation of manufacturing and packaging orders (including combination of batches without proper documentation

Critical Observations Manufacturing control (2)

- Insufficient process validation when public health is affected
- Recalls:

  - absence of recall procedure combined with distribution practices that would not permit to adequately recall a product (distribution records unavailable or not kept)

  - Improper quarantine and disposal practices that would allow recalled/rejected units to be returned for sale

Critical Observations
Quality control department

- No QC department available on site
- QC department not an independent unit, lacking real decisional power, with evidence that QC decisions are overruled by production department or management

Critical Observations Finished product testing

- Products not tested before release for sale
- Falsification or misrepresentation of testing results
- forgery of Certificate of analysis

Critical Observations Records

- Absence for records for product(s)
- Falsification or misrepresentation of records

Critical Observations Stability

- No data available to establish the shelf-life of products
- Falsification or misrepresentation of stability data
- Forgery of Certificate of analysis

Critical Observations
Sterile products

- Critical sterilisation cycles not validated
- PW and WFI systems not validated with evidence of problems such as high microbial/endotoxin counts
- No or insufficient media fill performed to demonstrate the validity of aseptic filling operations

Critical Observations Sterile products (2)

- Aseptic filling operations maintained following unsatisfactory results obtained from media fills
- Batches failing initial sterility test release for sale on the basis on a second test without proper investigation (“testing into compliance”)

Major Observations Premises

- Malfunction of the ventilation system resulting in possible migration of materials between manufacturing areas ↑
- Accessory supplies (steam, air, nitrogen, dust collection, etc…) not qualified
- HVAC and purified water system not qualified; Temp. and humidity not controlled or monitored where required

Major Observations Premises (2)

- Damages (holes, cracks or peeling paint) to walls/ceilings immediately adjacent or above manufacturing areas or equipment where the product is exposed
- Un-cleanable surfaces created by pipes, fixtures or ducks directly above products or manufacturing equipment
- Surfaces finish (floor, walls and ceilings) that do not permit effective cleaning

Major Observations Premises (3)

- Unsealed porous finish in manufacturing areas with evidence of contamination (mildew, powder from previous production, etc…)
- Insufficient manufacturing space that could lead to mix-ups
- Physical and electronic quarantine accessible to unauthorized personnel
- Physical quarantine not well defined
- No separate area/insufficient precautions for raw material sampling

Major Observations Equipment

- Lack of maintenance resulting in equipment that does not operate within its specifications
- CIP equipment not validated ↑
- Tanks for manufacturing of liquids and ointments not equipped with sanitary clamps
- Stored equipment not protected from contamination ↑
- Inappropriate equipment for production: surface porous and not cleanable; material to shed particles ↑

Major Observations Equipment (2)

- Evidence of contamination of products by foreign materials such as grease, oil, rust and particles from the equipment ↑
- No covers for tanks, hoppers or similar manufacturing equipment
- No/inadequate precautions taken when equipment such as oven or autoclave contains more than one product ↑

Major Observations Equipment (3)

- Equipment location does not prevent cross-contamination for operations performed in common area
- PW system not maintained or operated to provide water of adequate quality
- Leaking gaskets
- No calibration program for automatic, mechanical, electronic or measuring equipment / no records maintained
- No equipment usage logs

Major Observations Personnel

- Individuals in charge of QC/Production for a manufacturer are not qualified by education, training and experience
- Delegations of duties for QC and manufacturing director to insufficiently qualified persons
- Although academically qualified, insufficient practical experience for QC and manufacturing director

Major Observations Personnel (2)

- Personnel in insufficient number for manufacturing and QC operations resulting in a high probability of error; for critical products ↑
- No/insufficient initial and continuing training program for personnel involved in manufacturing with evidence of insufficient knowledge of the processes, no evaluation of training, no record kept, no periodic review for critical products ↑

Major Observations Personnel (3)

- Insufficient training and /or experience for individuals responsible for packaging operations
- Inadequate number of personnel with the necessary qualifications

Major Observations Sanitation

- Sanitation program not in writing or incomplete but premises in acceptable state of cleanliness
- No SOP for microbial/environmental monitoring, no action limits for areas where susceptible products are manufactured ↑
- cleaning procedure for production equipment not validated (including analytical methods)
- No or incomplete health and hygiene program

Major Observations
Raw material testing

- Reduce testing program in place without any data to certify the vendors/suppliers
- Incomplete SOP or data to certify vendors/suppliers, to address NC results and re-certify the vendors
- Incomplete testing of RM
- Incomplete specifications of RM

Major Observations
Raw material testing (2)

- Production personnel do not respect the quarantine status of raw materials
- Specifications not approved by QC
- Test methods not validated
- No stability consideration; no retesting after two years
- No consideration for multiple receptions for the same lot; multiple lots comprising one reception

Major Observations
Raw material testing (3)

- No SOP for conditions of transportation an storage
- No ID done after receipt; testing for identity not done on each containers after manipulation or repackaging by third party
- No system for notification of changes in specifications and process by the vendor
- Certification of brokers or wholesalers allowed

Major Observations Manufacturing controls

- Absence of or incomplete SOPs for handling of materials and products
- Incomplete validation studies/reports for critical processes (lack of evaluation/approval)
- Unapproved/undocumented major changes compared to master production documents ↑
- Deviations from instructions not documented or no final approval from QC
- Discrepancies in yield or reconciliation following manufacturing and packaging not investigated ↑

Major Observations Manufacturing controls (2)

- Absence of or non-validated changeover procedures for manufacturing of medicinal/non-medicinal products
- Purging between manufacturing/packaging of different products not covered by SOP or not documented
- No regular checks for measuring devices; no records existing
- Lack of proper identification of in-process materials and production rooms resulting in a high probability of mix-ups ↑

Major Observations Manufacturing controls (3)

- Inadequate labelling, storage of rejected materials and products
- Bulk and in-process drugs, RM and PM not held in quarantine till release by QC
- Inadequate checks for incoming material; no investigation from QC on damaged containers
- Inadequate, inaccurate labelling of bulk or in-process drugs, RM, PM

Major Observations Manufacturing controls (4)

- RM dispensing not done by designated persons, according to an SOP
- Master formulae incomplete or showing inaccuracies in the processing operations
- Changes in batch size not prepared/verified by qualified personnel
- Inaccurate, incomplete information in manufacturing /packaging work orders

Major Observations Manufacturing controls (5)

- Combination of batches without QC approval; not covered by SOP
- Packaging operations not covered by written procedures or incomplete proc.
- Non-standard occurrences during packaging not investigated by authorized personnel
- Inadequate control of coded and non-coded printed packaging material (including storage, dispensing, printing, disposal)

Major Observations Manufacturing controls (6)

- Incomplete recall procedure
- No or inadequate self inspection program; program does not address all applicable sections of GMP; records incomplete or not maintained
- No or incomplete System to ensure GMP compliance of contractors and vendors

Major Observations Quality control department

- Inadequate facilities, personnel and testing equipment; lack of power to enter production areas
- No SOPs approved and available for sampling, inspection and testing of materials
- Products made available for sale without approval of QC department
- RM, PM used in production without prior approval of QC

Major Observations
Quality control department (2)

- Products released for sale by QC without proper verification of manufacturing and packaging documentation (evaluation and borderline conformances not properly investigated and documented)
- Rejected batches reprocessed without approval of QC department
- No system for complaint handling, returned goods or transportation conditions

Major Observations
Quality control department (3)

- SOPs covering operations that can affect the quality of a product such as transportation, storage, etc…not approved by QC department
- QC decisions not attested by signature and/or not dated
- No change control system
- No system to ensure that the tests are performed by a competent laboratory

Major Observations Packaging material testing

- Reduce testing program in place without any data to certify the vendors/suppliers
- Incomplete SOP or data to certify vendors/suppliers, to address NC results, to re-certify the vendors
- Incomplete testing of PM; incomplete specifications
- Production personnel do not respect the quarantine status of PM

Major Observations
Packaging material testing (2)

- Specifications not approved by QC
- No consideration for multiple lots comprising one reception
- No ID done after receipt
- Certification of brokers and wholesalers allowed

Major Observations
Finished product testing

- Non-compliant products made available for sale without proper justification 
- Incomplete, inadequate specifications
- Incomplete testing
- Test methods not validated
- Reduce testing program in place without data to certify vendors

Major Observations
Finished product testing (2)

- Incomplete SOP or data to certify vendors/suppliers, to address NC results, to re-certify the vendors
- No SOP for conditions of transportation and storage
- Use of unique identifier principles not meeting the acceptable options described in the interpretive document ↑

Major Observations Records

- Incomplete records, documentation for a product
- Unavailability of documentation from suppliers in a timely manner

Major Observations Stability

- Insufficient number of lots; insufficient data (room temp. or accelerated) to establish shelf life
- No action taken following data showing that the products do not meet their specifications prior to the expiry date
- No cotinuing stability program; no stability data available
- No stability studies prior changes in manufacturing (formulation) or packaging materials
- Testing method not validated

Major Observations Sterile Products

- Aqueous-based products not subject to terminal steam sterilisation without proper justification
- Inadequate room classification for process/filling operations
- Aseptic manufacturing suites under negative pressure compared to clean (C-D) areas; clean (C-D) areas under negative pressure to unclassified areas ↑

Major Observations Sterile Products (2)

- Insufficient number of samples for room classification; inadequate sampling methods
- No environmental controls; no monitoring for viable micro-organisms during filling
- Premises and equipment not designed or maintained to minimize contamination/generation of particles
- Inadequate maintenance of PW and WFI systems; inadequate re-validation after maintenance, up-grading, out-of-spec trends

Major Observations Sterile Products (3)

- Inadequate formation, training of personnel/clothing requirements
- Sanitation/desinfection program incomplete
- Inadequate SOP; practices; precautions to minimize contamination or prevent mix-ups
- Non-validated time interval between cleaning, sterilization, use of components, containers and equipment

Major Observations Sterile Products (4)

- No consideration given to initial bioburden prior sterilization and no validated time limit between start of manufacturing and sterilization or filtration
- No SOPs for media-fills; insufficient number of units filled during media-fills
- Inadequate inspection for particles and defects; no leak test for ampoules
- Samples for sterility not representative of the entire production; insufficient number of units

Other Observations
Premises

- Doors giving access to exterior from manufacturing and packaging areas used by personnel
- Un-screened/Un-trapped floor drains
- Outlets for liquids and gases not identified
- Damages to surfaces not directly adjacent or above exposed products

Other Observations
Premises (2)

- Insufficient lightning
- Non-production activities performed in production areas
- Inadequate rest, change, wash-up and toilet facilities

Other Observations Equipment

- Insufficient distance between equipments and walls to permit cleaning
- Base of immovable equipment not adequately sealed at points of contact
- Fixed pipework not labelled to indicate contents and flow
- Use of temporary devices for repair
- Defective /unused equipment not removed/not labelled

Other Observations Personnel

- No provision for consultants/outside contractors
- No organization charts

Other Observations Sanitation

- Incomplete records on the application of the sanitation program
- Personnel responsible for the application
- Of the cleaning procedures not identified
- Sporadic dust/powder/residue noticed on some manufacturing areas/equipment
- Health and hygiene programs not properly implemented or followed by employees

Other Observations
Raw material testing

- Lots identified for confirmatory testing used in production prior QC approval