

# GMP and Market Control: Control of Manufacturing Industry perspective

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Improved Market Access for Authorised  
Veterinary Medicines – The Asian Perspective

Organising Committee:

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DIA DEVELOP  
INNOVATE  
ADVANCE



# Introduction

*The global animal health market has evolved substantially over the last 10 years in companion animals, dairy animals as well as livestock, etc. On the other hand Animal Health pharmaceuticals come with unique challenges related to cost, market size, diversity of animal species, etc.*

*Most important to cater to the needs of this dynamic and innovative sector we need to have robust GMP manufacturing and market control in place meeting all regulatory requirements for manufacturing of veterinary medicines, vaccines and other animal healthcare products.*



# Elements and requirements for GMP

- ❑ SITE MASTER FILE
- ❑ PERSONNEL
- ❑ GENERAL REQUIRMENTS –BUILDING AND PREMISES
- ❑ EQUIPMENTS
- ❑ UTILITIES
- ❑ DISPOSAL OF WASTE
- ❑ WAREHOUSE



# Elements and requirements for GMP

- ❑ PRODUCTION AREA
- ❑ MANUFACTURING OPERATION AND CONTROLS
- ❑ LABELLING AND PACKAGING
- ❑ QUALITY ASSURANCE AND QUALITY CONTROL
- ❑ PRODUCT CONTAINER AND CLOSURE
- ❑ GOOD DISTRIBUTION PRACTICE
- ❑ PRODUCT RECALLS
- ❑ COMPLAINTS AND ADVERSE REACTIONS
- ❑ ROLE OF QUALIFIED PERSON ( QP )



# Regulatory References

Regulatory Bodies	Good Manufacturing Practices (GMP) Guidelines
India	Schedule M (Good Manufacturing Practices and requirements of Premises, Plant and Equipment for Pharmaceutical Products)
PIC/S	Annex 4 (Manufacture of veterinary medicinal products other than immunologicals) Annex 5 (Manufacture of immunological veterinary medical products)
USFDA	Subchapter C—Drugs: General [Docket No. 75N-0339] Human and Veterinary Drugs
	CVM (Centre for Veterinary Medicine) GFI (Guidance For Industry) #42 Animal Drug Manufacturing Guidelines
European Communities	COMMISSION DIRECTIVE of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products
	EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, December 2010
Australia	Australian code of Good Manufacturing Practice for veterinary chemical products



# VICH Guidelines

VICH=International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VMPs)

Category		GL numbers <a href="http://www.vichsec.org">http://www.vichsec.org</a>
Pharmaceuticals	Quality	1, 2, 3, 4, 5, 8, 10, 11, 17, 18(R)*, 39, 40, 45, 51
	Efficacy	7, 12, 13, 14, 15, 16, 19, 20, 21
	Environmental Safety	6, 38
	Metabolism and Residue	46, 47, 48(R), 49(R)
	Toxicology	22, 23, 28, 31, 32, 33, 37
	Target Animal Safety	43
	Antimicrobial Safety	27, 36
Biologicals	Quality	34, 25, 26
	Target Animal Safety	41, 44, 50
General	GCP	9
	Pharmacovigilance	24, 29, 30, 35, 42



# **CHALLENGES/LEARNING INITIATIVES BENEFITS**



# Personnel

## Challenges/Learnings

- Human error
- Training
- Attrition

## Initiatives

- Trend analysis of the errors and appropriate CAPA
- Systems/Process Simplification
- Culture improvement
- On the job trainings
- Right peoples at right place

## Benefits

- Reduction in errors and re-work
- Compliance improvement
- Reduction in attrition



# Building and Premises

## Challenges/Learnings

- **Designs**
  - Suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations
- **Poor containment**
  - Adequate space for orderly placement of equipment and materials to prevent mix-ups and contamination
  - Design the adequate flow of materials & persons to prevent contamination

## Initiatives

- Facility, design and construction as per regulatory requirement
- Periodic building and facility maintenance
  - Part of PM program with adequate check list

## Benefits

- Improved containment
- Improved compliance



# EQUIPMENT

## Challenges/Learning

- Manual operation
- Stand alone equipment
- Frequent equipment breakdown
- Poor maintenance

## Initiatives

- Automation of equipment
- Integrated lines
- Risk based preventive maintenance

## Benefits

- Consistent quality of the product
- Improvement of product yield
- Reduction of product failure
- Reduced equipment downtime
- Improved operational efficiency



# UTILITIES – Water System

## Challenges/Learning

- **Biofilm Generation**
- **Microbial contamination**
- **TOC/Conductivity failure**
- **Too much of raw water consumption in generation of PW/WFI**

## Initiatives

- **Continuous circulation loop.**
- **Avoid dead legs and stagnancy of water.**
- **Periodic cleaning and sanitization with appropriate validated methods**
- **Online monitoring of TOC and Conductivity with auto draining system**
- **Source of raw water with appropriate monitoring of quality**
- **Risk assessment of water system**

## Benefits

- **Consistent water quality**
- **Reduction in consumption of water**
- **Reduce downtime**



# UTILITIES - HVAC

## Challenges/Learnings

- Differential pressure issue
- Environmental condition not achieved like temperature/humidity
- Excursion in particle count in classified area
- Excursion in viable particle count

## Initiatives

- Effective, cleaning and monitoring and qualifying the filters
- Effective and risk based PM of HVAC
- Continuous monitoring of HVAC like DP across filters/Chill water temperature in and out/noise level and motor RPM of water

## Benefits

- Prevention of cross contamination
- Reduce down time
- Reduce product impact due to environment



# Manufacturing and Operation function

## Challenges/Learnings

- Operator dependent processes
- Complex Process/Systems
- Product failures and investigations
- Delivery issues due to Quality

## Initiatives

- Operator independent processes as far as possible by automation
- Simplified processes – A focused approach
- Risk management of drug products
- Task force and SME for investigations
- Effective CAPA implementation

## Benefits

- Robust formulation
- Reduction of product failure and investigations
- Increase in operational efficiency
- Increased yield
- Increased productivity



# Quality function

## Challenges/Learning

- Laboratory errors
- Lack of ownership from user departments
- Issuance and retrieval of documents
- QA and QC is policing function
- Lack of analysis and evaluation of quality trends

## Initiatives

- Creation of cohesive team by notion of friend, philosopher and guide.
- Trend analysis of QMS documents
- Quality metrics implementation
- QMS softwares implementation
- Continuous on the job training to the analyst
- Usage of statistical tools in the analysis and evaluation of trends

## Benefits

- Ease of operation
- Reduction in generation of papers
- Reduction in lab errors
- Improved compliance in quality and service level



# Aseptic Manufacturing operation

## Challenges/Learning

- Sterility Assurance Level
- Environment monitoring excursions
- Poor aseptic practices
- Sterility failures

## Initiatives

- Risk management of Aseptic processes
- Improved Aseptic practices through trainings and workshops
- Automation and integrated line - reduce human interventions
- Online monitoring systems

## Benefits

- Improved Sterility Assurance Level
- Reduction in sterility failures



# Documentation

## Challenges/Learning

- Documents are not generated contemporaneously
- Obsolete documents are not retrieved timely
- Incomplete entries in GMP documents
- Hectic and complex GMP documentation

## Initiatives

- Training on Good Documentation practices and awareness on repercussions of offline documentation
- Software for issuance and retrieval of documents
- Documents simplified by reducing number of signatures, providing adequate spaces for entries and removing non-value adding information from documents

## Benefits

- Improved documentation
- Reduction in error
- Improved compliance and reduction of risk



# DISPOSAL OF WASTE



# Disposal of Waste

## Environmental Impact Assessment (EIA) for Veterinary Medicinal Products

- ❑ There should be **proper control and EIA on** release of 'hazardous' substances from manufacturing facilities that produce licensed pharmaceuticals or API.
- ❖ **EIA is based on the accepted principle that risk is a product of the exposure, fate and effects assessments of the veterinary medicinal products (VMP)** for the environmental compartments of concern.
- ❖ **EIA is based on a Risk Quotient (RQ )approach**, which is the ratio of the **predicted environmental concentration (PEC) and the predicted no effect concentration (PNEC) on non-target organisms**. The RQ (PEC/PNEC) is compared against a **value of one**, and a **value less than one indicates that no further testing is recommended**.
- ❑ The disposal of sewage and effluents (solid, liquid and gas) be **in conformity with** the requirements of **environment pollution control board**.



# Disposal of Waste

## Environmental Impact Assessment (EIA) for Veterinary Medicinal Products

- ❑ Global bodies/national governments and regulators should establish evidence-based, enforceable targets for maximum levels of antimicrobial active pharmaceutical ingredient (API) discharge associated with the manufacture of pharmaceutical products.
- ❑ Pharmaceutical companies should improve monitoring of API emissions from directly-operated manufacturing facilities as well as those of third party suppliers, and support the installation of proper waste processing facilities to reduce or eliminate API discharge. Such efforts should be based in voluntary, transparent and auditable commitments, with a globally-consistent 'quality mark' applied to end products produced on 'environmentally responsible' basis.



# ANTIBIOTICS



## Resistance to Antibiotics and Roadmap to Combat Antimicrobial Resistance

- ❑ Resistance to antibiotics is a worldwide concern both in human and veterinary medicine.
- ❑ The concern of the possible **emergence of superbugs able to decimate whole populations** has led to **proposals to restrict the non-therapeutic use of antibiotics in farm animals** and also to find alternatives that do not carry the risk of the induction of resistance. For instance, bacteriophages and their products have been evaluated for application in both human and veterinary medicine.
- ❑ Reduce the environmental impact from the production of antibiotics
- ❑ Establish a common framework for assessing and managing antibiotic discharge
- ❑ Help ensure antibiotics are used only by patients who need them
- ❑ Improve access to current and future antibiotics, vaccines and diagnostics



# INDIAN VETERINARY INDUSTRIES

5<sup>th</sup> Global Animal Health Conference and Workshop 2016



# Indian Veterinary Industry

- ❑ India with the largest animal population heads is a largely untapped market so in coming years going to be the largest hub for Animal Healthcare Industry.
- ❑ The penetration of animal health care products is less than 15% in India.
- ❑ Indian manufacturers are one of the lowest cost producers of drug in the world, drug manufacturing in India is up to 50% less than in other countries and well developed industry with strong manufacturing base.
- ❑ Animal healthcare companies promotional strategy is based on direct contacts with customers like dairy farms, poultry farmers and indirect selling through veterinarians.
- ❑ Animal drug competition is less susceptible to generic influence except some oral supplements as well as nutritional products.



## **Our strengths**

- Skilled and educated manpower.**
- Strong regulatory knowledge and GMP history.**
- State of art facilities.**
- Government support.**
- Strong research base.**
- Stable environment.**



## CONCLUSION

*The control of Veterinary Medicinal Products is not merely an exercise in red tape. It is there for very good reason – the protection of animals, businesses and individuals.*



Thank You

Questions?





# ANNEX

## Overview of GMP requirements



# Site Master File

- ❑ Site Master File shall contain specific and factual Good Manufacturing Practices about the production and/or control of pharmaceutical manufacturing preparations carried out at the licensed premises.
  
- ❑ It shall contain the following:
  - ❖ General information
  - ❖ Personnel
  - ❖ Premises
  - ❖ Equipment
  - ❖ Sanitation
  - ❖ Documentation
  - ❖ Production
  - ❖ Quality control
  - ❖ Loan licence manufacture and licensee
  - ❖ Distribution, complaints and product recall
  - ❖ Self-Inspection
  - ❖ Export of drugs



# Personnel

- ❑ **Number of personnel** employed shall be **adequate** and in direct proportion to the workload.
- ❑ **Training** appropriate to the duties and responsibilities
- ❑ Written **duties responsibilities of technical** and quality control personnel shall be laid and followed strictly.
- ❑ The manufacture shall be conducted under the direct supervision of **competent technical staff with prescribed qualifications** and practical experience in the relevant dosage/API.
- ❑ The head of the QC shall be independent of the manufacturing unit.



# General requirements Building and Premises

The premises shall be,

- ❑ Designed/constructed/maintained to prevent entry of insects, pests, birds, vermin's and rodents. **Effective pest control program** and need to be reviewed by Quality unit.
- ❑ **Drainage system-** of **adequate size**, designed to **prevent backflow**.
- ❑ **Walls and floors:**
  - ❖ Free from cracks, open joints, should be smooth, washable, covered and shall permit easy and effective cleaning and dis-infection.
  - ❖ Walls, floors and ceiling should be impervious, non-shedding, non-flaking and non-cracking.
- ❑ **Ceiling** shall be solid and joints shall be sealed. **Light-fittings and air-grills** shall flush with the walls and not hanging from the ceiling, so as to prevent contamination.
- ❑ **Doors** shall be made of **non-shedding material**. Doors shall open towards the higher-pressure area so that they close automatically due to air pressure.
- ❑ The furniture used shall be **smooth, washable and made of stainless steel** or any other appropriate material other than wood.
- ❑ There shall be **no sinks and drains in Grade A and Grade B areas**.



# Equipment

- ❑ Equipment shall be **located, designed, constructed, adapted and maintained to suit the operations** to be carried out.
- ❑ Equipment **log book shall be maintained.**
- ❑ **Production equipment that come in contact with the product shall not be reactive, additive or adsorptive** to an extent that would affect the quality of the drug product.
- ❑ Equipment **shall be calibrated and checked on a scheduled basis** in accordance to SOP and maintain records.
- ❑ Wherever possible, **non toxic/edible grade lubricants shall be used.**



# Sanitation in the Manufacturing Premises

- ❑ The manufacturing premises shall be cleaned and in an orderly manner. A **validated cleaning procedure** shall be maintained.
  
- ❑ The manufacturing areas shall not be used for other operations.
  
- ❑ A **routine sanitation program** shall be drawn up which shall be properly recorded and which indicate;
  - ❖ Specific area to be cleaned at define cleaning intervals.
  
  - ❖ **Different sanitizing agent** shall be used in rotation
  
  - ❖ **Cleaning procedure** to be followed.
  
  - ❖ Personnel assigned to and responsible for the cleaning operation.
  
  - ❖ Adequate working and **in-process storage space – mix up and cross contamination.**



# Documentation and Records

- ❑ Good Documentation Practices (GDP) is key to ensuring data integrity, and a fundamental part of a well designed QMS system.
- ❑ Documents and records need to be **designed, prepared, reviewed and controlled considering ALCOA(Attributable, Legible, Contemporaneous Original, Accurate ++=complete, consistent, enduring, available** concept.
- ❑ Documents shall specify;
  - ❖ The title, nature and purpose
  - ❖ Laid out in an orderly fashion
  - ❖ Kept up to date
- ❑ Documents and records (both paper and electronic) life cycle which starts with **Creation, processing, retention and disposal** shall be controlled.



# Air Handling System

## Oral Solid Product

- ❑ The processing of **dry materials and products creates problems of dust control and cross-contamination.**
- ❑ **Dust control manufacturing systems shall be employed.**
- ❑ **Air dust extraction system** shall be employed.
- ❑ AHU configurations by Re-circulation system/ Full fresh air systems/ Additional system components
- ❑ **6 to 20 minimum air changes/Hr rate** standards for oral dosage facilities.
- ❑ **Process core area shall be negative pressure** against adjacent area.

## Sterile Product

- ❑ AHU for sterile product manufacturing areas shall be **different from those for other areas.**
- ❑ Critical areas, such as the aseptic filling area, sterilized components unloading area and change room conforming to Grades B, C and D respectively **shall have separate air handling units.**
- ❑ The minimum air changes for Grade B and Grade C **areas shall not be less than 20 air changes per hour** in a room with good air flow pattern and appropriate HEPA filters.
- ❑ **Process core shall be positive pressure** against adjacent area.



# Water System

## Solid Oral Product

- **Potable Water**
  - ❑ Potable water =NMT 500 cfu/ml.
  - ❑ Final rinse of product containers and machine parts shall be done with purified water.
- **Purified Water**
  - ❑ Purified NMT 100 cfu per ml.
  - ❑ Purified water shall be used for all operations except washing and cleaning operations.

## Sterile Product

- **Purified Water**
  - ❑ Purified NMT100 cfu per mL.
  - ❑ Purified water shall be used for hand washing in change rooms. Containers, closures and machine parts may be washed with purified water.
- **Water for Injection (WFI)**
  - ❑ WFI NMT 10 cfu per 100 ml.
  - ❑ Bulk solutions of liquid parenteral shall be made in WFI. Final rinse of product containers and machine parts shall be done with WFI. Disinfectant solutions for use in aseptic areas shall be prepared in 0.2  $\mu$  filtered WFI.
  - ❑ Endotoxin NMT 0.25 EU/ mL.
  - ❑ WFI has been kept NLT 70°C in circulation loop.



# Air Handling System

## Oral Solid Product

Grade	Types of operations
D	Dispensing
D	Sifting, Blending
D	Milling
D	Encapsulation & compression
D	Coating
D	Primary Packing
CNC	Secondary Packing

## Sterile Product

Grade	Types of operations for Aseptic preparations
A	Aseptic preparation and filling
B	Background room conditions for activities requiring Grade A
C	Preparation of solution to be filtered
D	Handling of components after washing

Grade	Types of operations to be carried out in the various grades for terminally sterilized products
A	Filling of products which are usually at risk
C	Placement of filling and sealing machines, preparation of solutions when usually at risk. Filling of products when unusually at risk.
D	Moulding, blowing (pre-forming) operations of plastic containers, preparation of solutions and components for subsequent filling.



# Warehousing Area

- ❑ **Adequate areas** to allow orderly warehousing of various categories of materials. Good storage conditions.
- ❑ **Receiving and dispatch bays** shall **protect materials and products from adverse weather conditions.**
- ❑ **Quarantine materials:** Separate earmarked area giving assurance of segregation.
- ❑ **Sampling Area :** There shall be a separate sampling area in the warehousing area for active raw materials and excipients.
- ❑ **Segregation** shall be provided for the storage of rejected, recalled or returned materials or products.
- ❑ **Hazardous, toxic substances and flammable materials** shall be stored in suitably designed and segregated enclosed areas.
- ❑ **Primary packaging materials** shall be stored in **safe, separate and secure areas.**



# Production Area

- ❑ **Production areas – Preferably designed in uni-flow** with logical sequence of operations.
- ❑ **Separate dedicated and self-contained facilities** shall be made available for the production of sensitive pharmaceutical products like Penicillin or biological preparations with live micro-organisms.
- ❑ Orderly and **logical positioning of equipment, materials and movement of personnel and to minimize risk** of omission or wrong application of any manufacturing and control measures.
- ❑ **Services lines** shall preferably be **identified by colours and the nature of the supply and direction of the flow shall be marked/indicated.**



## Dedicated area for premixes

- ❑ **Premixes:** a pre-mix for **medicated feeding stuffs** is any **veterinary medicinal product prepared in advance** with a view to the subsequent manufacture of medicated feeding stuffs.
  
- ❖ Manufacture of premixes in **dedicated areas** which, if at all possible, do not form part of a main manufacturing plant. Such dedicated areas should be **surrounded by a buffer zone in order to minimize the risk of contamination** of other manufacturing areas.
  
- ❑ **Sealed transport system and dust extraction :**
  
- ❖ As large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to **avoid cross contamination and facilitate cleaning** .
  
- ❖ There shall be installation of **sealed transport systems and dust extraction**, whenever possible.



# Manufacturing Operations and Controls

- ❑ All manufacturing operations shall be carried out under the supervision of technical staff approved by the licensing authority.
- ❑ All the vessels and containers shall be conspicuously labelled.
- ❑ **Precautions against mix-up and cross-contaminations.**
  - ❖ By proper air handling system, **pressure differential, segregation of area, status labelling and cleaning.**
  - ❖ **Proper labelling** of materials and equipments.
  - ❖ Packaging lines shall be **independent and adequately segregated.**
  - ❖ All **printing and overprinting shall be authorized** in writing.
  - ❖ **Authorised persons** shall ensure **change-over into specific uniforms** before undertaking any manufacturing operations including packaging.
  - ❖ **Segregated secured** areas for **recalled or rejected material** and for such materials which are to be re-processed or recovered.

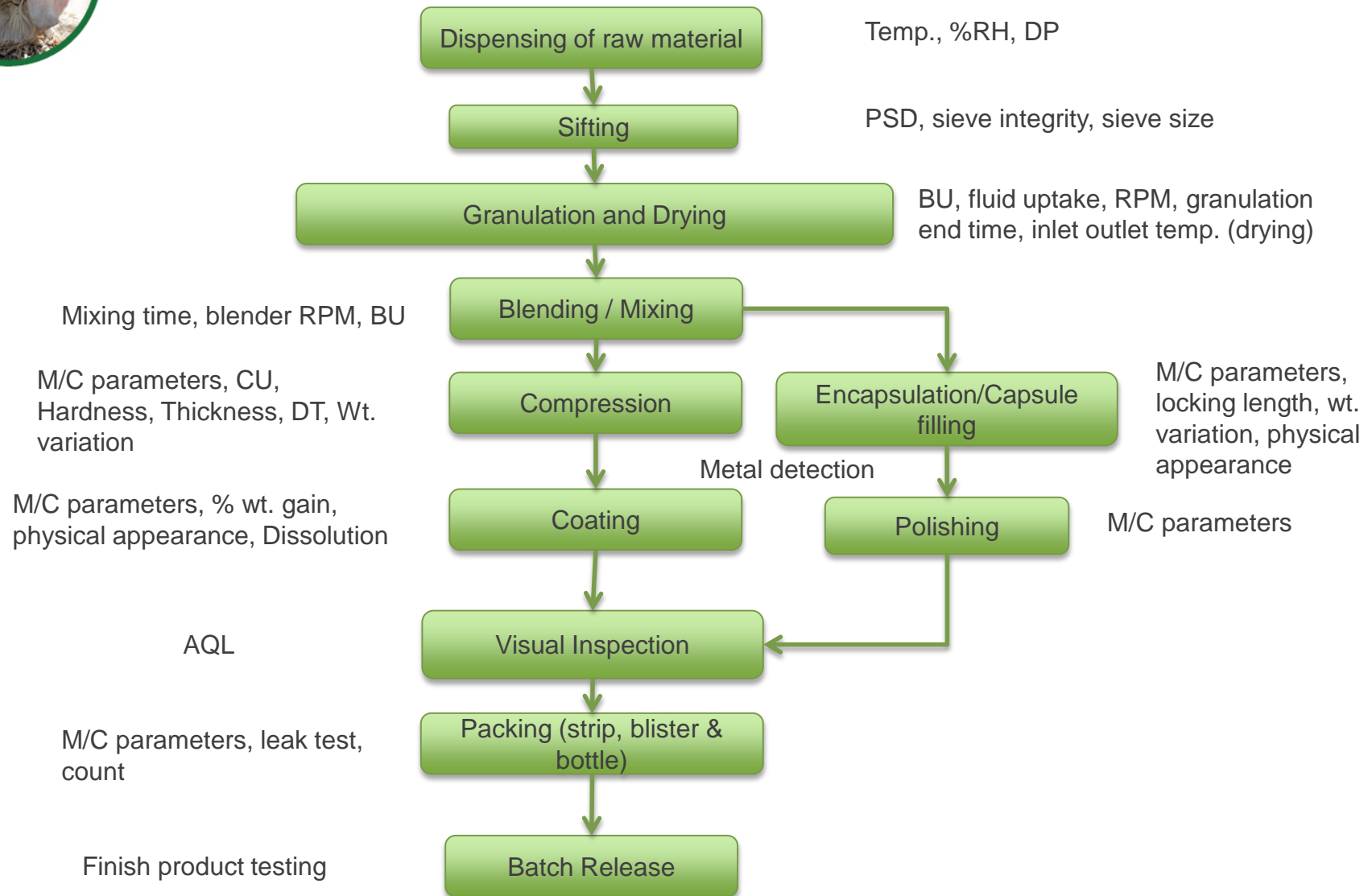


# Manufacturing Process control measures

- ❑ Critical steps in manufacturing :-All **critical steps in the manufacturing process** of veterinary products, and any changes to these steps, should be documented.
- ❑ Manufacturing processes review: should **be reviewed at defined regular intervals** and the outcome of that **review documented and acted upon**.
- ❑ **In-process controls** that are crucial to product quality, but which cannot be carried out on the finished product, **should be performed at an appropriate stage of production**.
- ❑ Parts of the **process likely to have a significant adverse influence** on the stability of the active ingredients (e.g. use of steam in pellet manufacture), **should be controlled to ensure batch-to-batch consistency**.
- ❑ Special attention needs to be paid to the prevention of **microbial contamination during manufacture or storage of susceptible liquid formulations**.

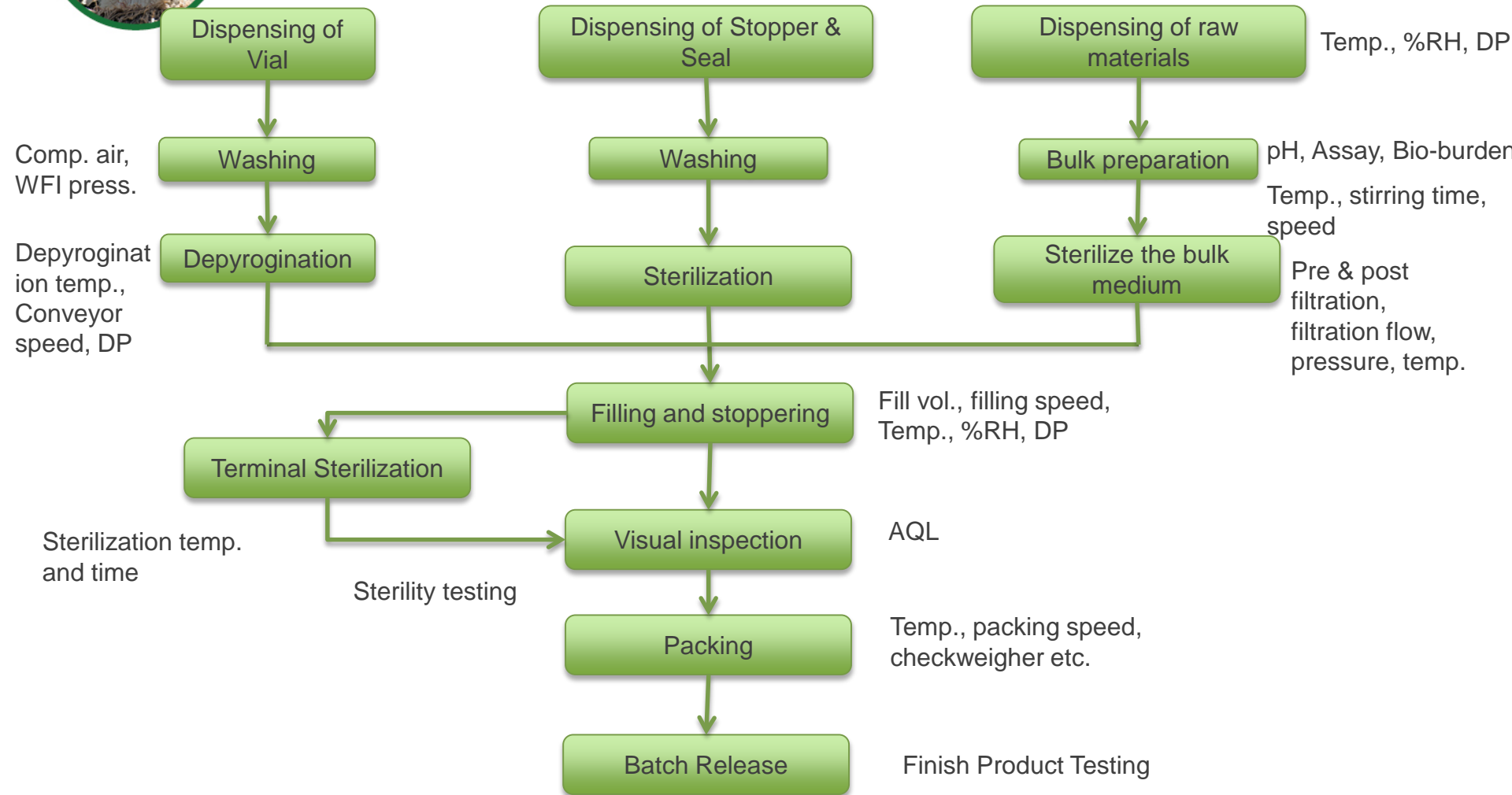


# Tablet/Capsule Product Process Flow





# Sterile Product Process Flow





# Completion/finalisation of sterile products

- ❑ All unit operations and processes in the manufacture of a batch **shall have a minimum time specified and the shortest validated time** shall be used from the start of a batch to its ultimate release for distribution.
- ❑ Containers **shall be closed by appropriately validated methods**. Containers closed by fusion e.g. glass or plastic ampoules shall be subjected to 100% integrity testing.
- ❑ Filled containers parenteral products **shall be inspected individually for extraneous contamination or other defects**.
- ❑ **Visual inspector doing the inspection** shall pass **regular eye-sight checks** with spectacles, if worn, and be allowed frequent rest from inspection.
- ❑ Bulk shall be released for further process based on AQL. Other methods of inspection are used, the process shall be validated.



# Quality Assurance

- ❑ QA shall ensure that;
  - ❖ The pharmaceutical **products are designed and developed in a way that takes account of the requirement of GMP, GLP and GCP.**
  - ❖ **Adequate arrangements** are made for manufacture, supply and use of the correct starting and packaging materials.
  - ❖ **Adequate controls** on starting materials, intermediate products and other in-process controls.
  - ❖ **Calibration and validations** are carried out.
  - ❖ Finished **product is correctly processed and checked in accordance with established procedures.**
  - ❖ The pharmaceutical products **are not released for sale or supplied before authorized persons have certified.**



# Quality Assurance

- ❑ QA shall ensure that
  - ❖ Training of all employee
  - ❖ Supplier qualification
  - ❖ Self inspection
  - ❖ To maintain quality governance structure
  - ❖ To strive for continuous improvement
  - ❖ To escalate cGMP action items to management



# Quality Control Area and System

- ❑ QC laboratories **shall be independent of the production areas.**
- ❑ QC laboratory may be divided into Chemical, Instrumentation, Microbiological and Biological testing.
- ❑ Shall be of **suitable design with sufficient space to avoid mix-ups and cross-contamination.**
- ❑ The microbiology section shall have **arrangements such as airlocks and laminar airflow work station**, wherever considered necessary.
- ❑ Quality control shall be concerned with **sampling, specifications, testing, documentation, release produces**. Materials are not released for use, nor products released for sale or supply until their quality has been judged to be satisfactory.
- ❑ QC shall have **qualified and experienced** staff.
- ❑ Adequate area to **store the reference standards.**



# Quality Control System

- ❑ SOPs :- Sampling, inspecting and testing of raw materials, intermediate bulk finished products and packing materials.
- ❑ Specifications: - Authorised and dated specifications for all materials, products, reagents and solvents including test of SISPQ.
- ❑ Retained samples :- Twice the quantity of the drug required to conduct all the tests except sterility and pyrogen/BET. The retained product shall be kept in its final pack or simulated pack for a period of three months after the date of expiry.
- ❑ The QC department shall conduct stability studies of the products to ensure and assign their shelf life. All records of such studies shall be maintained.
- ❑ All instruments shall be calibrated and validated before adopted for routine testing.
- ❑ Pharmacopoeia, reference standards, working standards, references spectra, other reference materials and technical books shall be available in the QC laboratory.



# Product containers and closures

- ❑ All **containers and closures** intended for use shall comply with the **pharmacopoeial and other specified requirements**.
- ❑ Containers, closures and other component parts of **drug packages are suitable and are not reactive, additive, adsorptive or leachable or presents the risk of toxicity** to an extent that significantly affects the quality or purity of the drug.
- ❑ No second hand or used containers and closures shall be used.
- ❑ Plastic granules shall also comply with the pharmacopoeial requirements including physio-chemical and biological tests. All containers and closures shall be rinsed prior to sterilization with WFI according to written procedure.
- ❑ The **design of closures, containers and stoppers** shall be such as to make cleaning easy and also to make airtight seal when fitted to the bottles.
- ❑ Whenever glass bottles are used, the written schedule of cleaning and depyrogenation shall be laid down and followed.



# Good Distribution Practices

**Good Distribution Practices (GDP)** means that part of quality assurance which ensures that the quality of a pharmaceutical product is maintained through adequate control throughout the numerous activities which occur during the distribution process.

- **Transportation**

- ❖ During the supply of medicinal products, **the transport conditions** are such as

- To maintain the quality of the product, to protect **against breakage, adulteration and theft, and to ensure appropriate environmental conditions** are maintained during transport.

- Storage conditions** for medicinal products should be maintained.

- Deviation during transportation** should be reported.

- Vehicles shall be **equipped to prevent exposure of the products.**

- Calibrated equipment** used for **temperature monitoring during transport** within vehicles and/or containers.



# Good Distribution Practices

- ❑ Containers, packaging and labelling
  - ❖ Containers should bear labels providing sufficient information on handling and storage requirements
  
- ❑ Temperature Control during Transport
  - ❖ **Validated temperature-control systems** should be used to ensure correct transport conditions are maintained between the distributor and customer.
  
  - ❖ The process for **delivery of sensitive products and control of seasonal temperature variations** should be described in a written procedure.
  
  - ❖ If **cool-packs are used in insulated boxes then product does not come in direct contact with the cool-pack.**
  
  - ❖ Where transportation hubs are utilised in the supply chain, a **maximum time limit of normally 24 hours should be set** to await the next stage of the transportation route.



# Complaints and Adverse Reactions

- ❑ All complaints thereof **concerning product quality** shall be carefully **reviewed and recorded according to written procedures**.
- ❑ Each complaint shall be **investigated/evaluated by the designated personnel** of the company and records of investigation and remedial action taken thereof shall be maintained.
- ❑ Reports of **serious adverse drug reactions resulting from the use of a drug** shall **be forthwith reported to the concerned licensing authority**.
- ❑ There shall be **written procedure describing the action to be taken, recall to be made of the defective product**.



# Product recalls

- ❑ A **prompt and effective product recall system of defective products shall be devised** for timely information of all concerned stockists, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard.
  
- ❑ The effectiveness of the arrangements for recalls shall be **evaluated from time to time.**
  
- ❑ The distribution records shall be readily made available to the persons designated for recalls.
  
- ❑ The **recalled products shall be stored separately in a secured segregated area** pending final decision on them.



## Role of the Qualified Person (QP)

- ❑ QP shall ensure that
  - To certify batches
    - The QP role should not be an administrative one focused on batch release paperwork
  - Medicinal products manufactured within the European Union have been manufactured and checked within the boundaries of national law and the requirements of the Marketing Authorisation (MA).
  - Any pharmaceutical imported from a third country must have undergone, within the EU, a full qualitative analysis, a quantitative analysis of at least all the active ingredients and all other tests necessary to confirm compliance with the MA.
  - Finally, the QP is bound by law to certify in a register or equivalent document, that the above-mentioned provisions are satisfied before the batch is placed on the market.



## Role of the Qualified Person (QP)

- ❑ QP shall ensure that
  - Compliance with the MAA
  - Compliance with GMP
  - Manufacturing and testing processes validated
  - Deviations and changes approved and additional samples tested (if necessary)
  - Checks and tests performed
  - Documents completed and endorsed
  - Audits carried out
  - All relevant factors considered