Veterinary Medicines Section

Presentation on the Essential Aspects of EU GMP

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Introduction

The presentation is divided in five parts:

1. What is GMP
2. Why is GMP important
3. Legal Basis of GMP
4. The 8 Essential Principles of GMP
5. Practical Principles of GMP

I. WHAT IS GMP

- Stands for Good Manufacturing Practice.
- Many GMP types. Important one is EU GMP (always will be assumed to be EU GMP)
- Certificate granted by a NCA of an EU MS. (first period: 3 years validity)
- Granted primarily to the Manufacturing Site but may be given to contracting labs/establishments.
- Can be renewed, amended or revoked in cases of non-compliance.
- An establishment may be granted other permits (depending on MS) but the main EU wide legal obligation is GMP.
- Different from MIL (Manufacturing Import Licence). This is basically a licence to Import and/or manufacture. GMP can exist without the other

2. WHY IS GMP IMPORTANT

- **Legal Aspect:** Without it a Manufacturing Site cannot trade its product in the EU. In fact it cannot manufacture any products even if not intended for the EU Market.

- **Practical Aspect**: Good guarantee that the products are consistently manufactured of *good quality*, and that the quality is consistently *controlled*.
  Is main aspect of Pharmaceutical Quality Assurance System.

- **Commercial Aspect:** By abiding with the same rules Member States can have confidence in each other. This facilitates trade in a single market. High standards.

3. Legal Aspects GMP

•Article 50 (f), 51, 55 and 80(2) of Directive 2001/82/EC on the Community code relating to VMPs.

• Directive 91/412/EEC (1991) laying down the principles and guidelines of good manufacturing practice for VMPs.

•EudraLex - Volume 4, GMP GL. Guidance for the interpretation of the principles of GMP for **BOTH** for human and vet medicines. Have legal standing. Use as a standard during GMP inspection.

•Member States enter the GMP certificate in database (Eudra GMP) managed by the EMA and publicly accessed by MS.

•Member States perform repeated Inspections to ensure compliance.

4. The 8 Essential Principles of GMP

- Personnel
- Premises and equipment
- Documentation
- Production
- Quality control
- Work contracted out
- Complaints and product recall
- Self-Inspection

Personnel

- Competent and appropriately qualified personnel.
- Duties defined in job descriptions and hierarchical charts.
- Given sufficient authority to perform responsibility correctly.
- Given initial and continuing training.
- Programmes on procedures relating to health, hygiene and clothing, e.g. hair tied up, watches/jewellery removed, no food/drinks at critical areas, biohazard measures followed, colour coded clothing, no dirty shoes.

Premises and Equipment

- Designed to suit intended operations.
- Designed to minimize the risk of errors.
- Designed to permit cleaning, maintenance, avoid contamination.
- Critical equipment subject to appropriate qualification/validation.
- Fit for purpose/intended use.

Documentation

- Specifications, formulae, processing instructions.
- SOPs, General and specific. One controlled version.
- Records of different operations.
- Documents clear, concise and up-to-date.
- Ease of traceability is extremely important.
- Kept for one year after exp of batch (after archived)
- Electronic documents acceptable but could be printed and system validated (back-ups important)

Production

- Carried out according to pre-established instructions.
- Resources available for in-process control.
- Measure to avoid cross contamination/mix-ups.
- New process or modification thereof validated.
- Critical phases regularly re-validated.

Quality Control

- An independent Dept under a qualified person.
- Dept at its disposal quality control lab/s.
- Tests on starting, packaging, intermediate materials.
- Contract labs possible but contract in line with provisions of directive.
- Final control includes both analytical tests/results and other information, e.g. results of in-process control, conformity with specifications.
- Samples retained for 1-2 years after expiry (less or more according to type as instructed by NCA)

Work Contracted Out

- Written contract between contract giver and contract acceptor.
- Define responsibilities of each party.
- GMP observance and certification of contract acceptor
- Sub-contracting by contract acceptor possible if authorized by contract giver.

Complaints and Product recalls

- System of recording and reviewing complaints.
- System of investigating.
- System of *prompt* recall.
- NCA may be informed of recalls.

Self Inspection

- Repeat self-Inspections to monitor implementation of GMP.
- Propose the necessary corrective measures.
- All documented, numbered, dated.

5. Practical Principles of GMP

PERSONNEL

•Senior Management appoint Key Management Personnel:

I. Head of Production
II. Head of Quality Control
III. Head of Quality Assurance

•Occupied by full-time personnel (ideally)

• Heads are independent from each other.

Premises and Equipment

Measures to prevent cross-contamination should be commensurate with the risks.
e.g. storage of microbe challenges tightly controlled.

Production line connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

Fittings, ventilation points designed and sited to avoid the creation of difficult to clean recesses.

Documentation

•Two primary types:

i. Instructions (directions, requirements)
ii. Records/reports

Instructions: Specifications, manufacturing formulae, processing, packaging and testing instructions, SOP, protocols

Records: certificate of analysis, reports (document the conduct of particular exercises, projects or investigations,
together with results, conclusions and recommendations)

- Laid out in an orderly fashion
- Written in an imperative mandatory style.
- Control measures for master documents.

Production

•Incoming materials checked to ensure that the consignment corresponds to the order.

•Containers cleaned where necessary and labelled.

•Damage to containers investigated, recorded and reported to the Quality Control Department .

•Any deviation from procedures approved in writing by a competent person.

•Risk of accidental cross-contamination from the uncontrolled release of dust, operators' clothing should be assessed.

•Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.

Quality Control

- Laboratory equipment should **not** be routinely moved between high risk areas.

- Attention given to the *quality* of lab reagents, solutions, glassware, reference standards and culture media.

- Laboratory reagents, reference standards, culture media etc should be marked with the preparation and opening date and the signature of the person who prepared them. (*easily forgotten*)

Contracting Out

- The Contract Giver is ultimately responsible to ensure processes are in place.

- Contract Acceptor should not make unauthorized changes, outside the terms of the contract.

- Outsourced activities by the contract acceptor, may be subject to inspection by the NCA.

Complaints, Quality Defects and Product Recalls

- Written procedures describing the actions to be taken upon receipt of a complaint.

- An investigation should address the extent, need to sample, assessment of risk, impact, identification of root cause.

- Finally the need for CAPA and after its effectiveness assessed.

Self Inspection

- Everything should be examined at intervals.
- Adverse events that effect *Quality* identified
- Conducted in an independent and detailed way by designated competent person.
- Reports with observations and actions taken.