Manufacturing of veterinary medicinal products: some controls for industry and regulatory authorities

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Good Regulatory Practice for the Marketing Authorisation of Veterinary Products in an African Context

Organising Committee:
Session overview

Session content

- Some controls on manufacturers
  - Approval and inspection
- Some controls at manufacturers’ level
  - Quality control and product release
- Some controls for regulatory agencies
  - Inspection programmes and qualification, training and impartiality of inspectors

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Controls on VMP manufacture

- VMPs are usually subject to a number of controls:
  - Product related controls e.g. product authorisation
  - Manufacturing site controls
  - Other controls and surveillance
  - Often similar approaches as for human medicines

Frequently similar approaches are adopted for both human medicines and VMP manufacture.
Potential controls on VMP manufacturers

Some controls may include:

- “Desktop assessment” of site information
  - Blueprints, procedures, records, etc.
- Official testing of VMPs by regulatory authorities
- Inspection of VMP manufacturing sites

Inspections may be used in combination with other controls

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Some general expectations of manufacturers which may be verified during inspections

- A formal quality management system (QMS)
- Sufficient numbers of appropriately trained staff
- Suitable premises and equipment
- Adequate documentation in place
- Secure retention of accurate records

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Some general expectations of manufacturers which may be verified during inspections

- A formal quality management system (QMS):
  - Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice.

- Sufficient numbers of appropriately trained staff

- Suitable premises and equipment:
  - Appropriate size for the operations, clean and well maintained. The equipment is designed and maintained in a way to suit the operations to be carried out.

- Adequate documentation in place and secure retention of accurate records
Some general expectations of manufacturers which may be verified during inspections, continued

- Suitable, defined production processes
- Appropriate quality control testing throughout manufacture
- Formal product release mechanisms
- Systems to address complaints, quality defects and product recall

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Overall expectation

- All the systems in place ensure quality is built into a VMP as this cannot be tested into the product once manufactured.
Requirements or manufacturing standards applied should be:

- Formal / defined
- Based on good science
  - risks applying to a particular dosage form
- Transparent / published

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Requirements or manufacturing standards applied should be:

- Local requirements / standards
- International Good Manufacturing Practice (GMP) standards
  - e.g. EU GMP, PIC/S GMP, WHO GMP
Prior to being placed onto the market a VMP is usually quarantined until a number of controls have been applied:

- All QC testing has been completed with a satisfactory outcome
- Formal release of the VMP batch following independent review and approval, e.g. by a member of the Quality Assurance team or the Qualified Person (EU requirement)
Some information to be reviewed prior to product release:

- Batch production and packaging records
- In process and finished product quality control testing results,
- Associated documentation,
  - e.g. deviation / investigation reports, complaints, adverse event data, environmental monitoring data, trend reports

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Formal review prior to product release should confirm:

- The VMP batch complies with its product licence / authorisation
- All QC testing results are within specification
- Appropriate requirements / standards (e.g. GMP) were applied during manufacture
Industry controls on VMP manufacture – some questions for discussion

In your territory:

- How is a VMP manufacturer defined / which activities (e.g. active substance, intermediate, finished product manufacture) are within scope?
- Are VMP manufacturers subject to formal approval / regulation?
- If so, what requirements are in place for holding an approval?

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Industry controls on VMP manufacture – some questions for discussion, continued

In your territory:

► What measures are in place to ensure that manufacturing requirements are met?
► If an inspection system is in place is compliance against formal standards checked?
► If so which standards are applied, e.g. local, EU GMP, PIC/S GMP, WHO GMP?

PIC/S: Pharmaceutical Inspection Cooperation Scheme

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Industry controls on VMP manufacture – some questions for discussion, continued

In your territory:

- Is greater emphasis placed on quality assurance throughout the manufacturing process or QC testing at the end?
- How is it ensured that any QC samples are representative of the VMP batch as a whole?
Industry controls on VMP manufacture – some questions for discussion, continued

In your territory:

► Is it expected that manufactures’ have a formal VMP batch release system?
► If so what requirements are in place?
► Are designated personnel responsible for batch release at the manufacturer?
► If so, what arrangements are in place to avoid conflicts of interest and is their role formally defined?

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Industry controls on VMP manufacture – some **questions** for discussion, continued

In your territory:

- Is there a requirement for official (i.e. state/governmental) batch release?
- If so are all VMPs within scope or a limited range?
- If a limited range, what criteria are used to select products?
- What mechanism is applied for official release (e.g. laboratory testing, protocol review)?

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Controls for regulatory agencies

Aspects to be considered

- Inspection programmes
- Inspector qualification, training and impartiality
Inspection programmes

The inspection system / programme should ensure:

- Adequate surveillance of all VMP manufacturers
- Adequate standards are in place and maintained at the regulatory agency / inspectorate
Manufacturers would normally be subject to:

- Initial inspection (new sites), followed by
- Periodic inspections

- Periodic inspections may be repeated on
  - a fixed (e.g. two yearly) basis,
  - a risk based approach (e.g. PIC/S and EU)
Criteria for risk based inspection frequency may include:

- Compliance observed at previous inspections
- Complexity of the manufacturing operations
- Size of the operations
- Triggers such as complaints, quality defects, recalls, pharmacovigilance issues
- Intelligence from other regulatory agencies or sources
The inspection programme may cover:

- Inspections within national boundaries

- Third country inspections
  - These may be alone or in conjunction with the local regulatory agency or another agency

- Inspections may be general, process or product focussed
Inspection programmes, continued

Inspection programmes normally use formal systems to ensure:

- Full impartial application equally to all manufacturers
- Appropriate record control, e.g. reports and correspondence kept and confidentiality maintained
- Non-compliance is addressed in a consistent way

Quality management systems (QMS) are expected at regulatory agencies as well as manufacturers!

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Inspection programmes, continued

Inspection programmes would normally be subject to formal systems to ensure:

- Full impartial application of the programme to all manufacturers
- Appropriate record control, e.g. reports and correspondence kept and confidentiality maintained
- Non-compliance is addressed in a consistent and appropriate manner

Quality management systems (QMS) are expected at regulatory agencies as well as manufacturers! For example, this is a requirement for PIC/S member authorities.
Regulatory agency controls: Inspectors

Adequate measures should be in place to ensure that inspectors are:

- Appropriately qualified
- Suitably trained
- Impartial
An inspector recruitment exercise would normally focus on:

- Appropriate educational qualifications
- Demonstration of key competencies
- Suitable experience
New inspector training programmes would normally include:

- Induction training
- Documentation training
- On the job training
- External courses as required

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New inspector training programmes would normally include the following aspects:

- Induction training
- Documentation training (legislation, agency procedures, manufacturing standard guidance, etc.)
- On the job training (observing, participating through to leading inspections)
- External courses as required
Regulatory agency controls: Inspectors, continued

For qualified inspectors:

- Training requirements / expectations should be defined
- Training requirements should be reviewed on a periodic basis and matched to inspectors’ needs
- Training records should be kept
Regulatory agency controls: Inspectors, continued

Systems to ensure impartiality of inspectors include:

- Sign up to a code of conduct
- A requirement to declare any interests
- A gifts and hospitality policy
- A formal period of time before an inspector can inspect a company for which they have worked
- Periodic change over of responsibility of sites

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Regulatory agency controls: Inspectors, continued

- Normally systems will be in place to ensure impartiality of inspectors such as:
  - Sign up to a code of conduct
  - A requirement to declare any interests
  - A gifts and hospitality policy
  - A formal period of time before an inspector can inspect a company for which they have worked
  - Periodic change over of responsibility of sites (e.g. after 2 or three inspection cycles)
Regulatory agency controls – some questions for discussion

In your territory:

► Is inspection of VMP manufacturers required before approval?
► Once approved are VMP manufacturers subject to periodic re-inspection?
► If so are all manufacturers captured in a formal inspection programme?
► If so how frequently are manufactures re-inspected – is the period set or varied on a risk basis?
► If inspection programme is risk based, which risk criteria are applied?

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Regulatory agency controls – some questions for discussion

In your territory:

► Are inspections and their outcomes documented and records kept?
► If non-compliance is identified, what options are available to deal with this?
► Are inspection programmes coordinated / performed in conjunction with other countries in your region?
► Does your authority recognise the findings of any other inspectorate in your region or elsewhere?
► If so, what is the basis for this recognition?
Regulatory agency controls – some questions for discussion

In your territory:

- If a VMP inspection programme is in place, who performs the inspections (governmental agency staff, non-governmental consultants / contractors)?
- What systems are in place to ensure impartiality of inspectors?

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Regulatory agency controls – some questions for discussion

In your territory:

▸ What systems are in place to ensure that inspectors possess the appropriate qualifications, experience and competencies?
▸ What systems are in place to ensure that inspectors’ knowledge and experience remains current?
▸ Are there regional training opportunities to allow interaction between inspectors in different territories?

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Thank you for your attention

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