Quality of Veterinary Medicinal Products

How to ensure the quality of Veterinary Medicinal Products

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INTRODUCTION

Ensuring the quality of Veterinary Medicinal products is an essential and basic requirement for the good governance of VMPs.

Three Pillars

QUALITY

MARKETING AUTHORISATION

INSPECTION

SURVEILLANCE

*VMP: Veterinary Medicinal Products
Marketing Authorisation dossier

• Part 1: Administrative Part
  summary of the dossier

• Part 2: Pharmaceutical quality Part
  Constituents, Manufacturing process, Control of starting materials, tests carried out at intermediate stages of the process, finished product ...

• Part 3: Safety and residues tests Part
  Toxicology tests (single dose toxicity, repeat dose, effects on reproduction), user safety, environmental risk assessment ...(chemical products), administration of one dose, overdose, repeated administration, effects on reproductive performance... (immunological products)

• Part 4: Efficacy tests
  Preclinical and clinical trials...
QUALITY PART

A - Qualitative and Quantitative Particulars of the Constituents
B - Description of the Manufacturing Method
C - Control of Starting Materials
D - Control Tests Carried out at intermediate stages of the Manufacturing Process
E - Tests on the Finished Product
F - Stability Test
G - Other Information
A - Qualitative and Quantitative Particulars of the Constituents

A1 - Composition

• Composition in terms of active and excipients
• Description of primary and secondary Packaging
• Formula used for clinical trials

• Objective: Describe precisely the product

A2- Development Pharmaceutics

Objective: Justify the formula, choice of containers, manufacturing process
B- Description of the Manufacturing Method

• Manufacturing formula

• Description of manufacturing process and in process controls

• Validation

• GMPs for all sites needed: manufacturing site, sterilisation, packaging, control and release sites

Objective: quality of finished product is reproducible
C. Control of starting materials

II.C.1. Control of active substance

II.C.2. Control of excipients

II.C.3. Container closure systems for active substance and finished product

Objective: Ensure that the product contains starting materials of good and controlled quality
E- Tests on the Finished Product

• E.1 – Specifications and routine tests

  examples of release specifications :
  – Appearance/description
  – General characteristics (pH, water content, viscosity, particle size, dissolution time, disintegration, reconstitution time, uniformity of dosage unit…)
  – Identification of active substances and preservatives
  – Assay of active substances (limits:95-105%) and preservatives
  – Determination of impurities
  – Determination of residual solvants
  – Sterility/Microbiological quality

• E.2 – Scientific data

  Validation of methods
  Certificates of analysis

Objectives:

Define precisely the specifications of the products, define limits of acceptance

Important for the Quality control by the authorities.
F Stability Tests

F.1 Stability Test on the active substance

F.2 Stability Test on the Finished product

Objectives:
1. Propose a shelf-life as package for sale, and storage conditions if necessary
2. Propose a shelf-life after first opening of the immediate packaging
3. Propose a shelf-life after dilution or reconstitution
4. Propose a shelf-life after incorporation into meal or pelleted feed
VICH guidelines available

http://www.vichsec.org/guidelines/biologicals/bio-quality/stability.html

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

Inspection
An appropriate regulatory framework

Need of prior Authorization and periodic control for Veterinary Product companies

Manufacturer, Importer, Wholesaler...

• These activities should be governed by rules:
  – Good practices as
    • Good manufacturing practices (GMP)
    • Good distribution practices (GDP)
    • Good prescription practices …
GMP legislation

- The EU(EEA) Regulatory Framework
  - Areas for Veterinary Legislation:
    - Veterinary Medicinal Products: **GMP Directive 91/412/EEC** laying down the **principles and guidelines of good manufacturing practice for veterinary medicinal products**.
      - Quality management
      - Personnel
      - Premises and equipment
      - Documentation
      - Production
      - Quality control
      - Work contracted out
      - Complaints and product recall
      - Self inspection
GMP guidance

• The EU(EEA) Regulatory Framework
  – Areas for Veterinary Legislation:
    • Veterinary Medicinal Products: **GMP**

Volume 4 EUDRALEX: Good manufacturing practice (GMP) Guidelines. (near 200 pages)

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP.

[Image of PIC/S website]

46 Participating Authorities in PIC/S
# GMP What’s different?

## Differences between GMPs
- Minor differences

<table>
<thead>
<tr>
<th>PIC/S GMP Guide v11</th>
<th>EU GMP Guide (31st Jan’13)</th>
</tr>
</thead>
</table>
| Part I Basic Requirements for Med. Products  
Chapter 1: Quality Management  
Chapter 7: Contract Manufacture and analysis | Part I Basic Requirements for Med. Products  
Chapter 1: Pharmaceutical Quality System  
Chapter 7: Outsourced activities |
| Part II Basic Requirements for APIs | Part II Basic Requirements for Active Pharmaceuticals ingredients |
| No Part III | Part III  
Site Master File  
Q9 - Quality Risk Management  
Q10 - Pharmaceutical Quality Systems  
Batch Certificate |
| Annexes  
1 – 20 | Annexes  
1 – 19 (20 = Q9) |
GMP What’s different?

• On going work at the OIE level
GMP Requirements

Vet GMP:

Target/activity?

- Manufacturing sites for
  - Pharmaceutical products
  - Medicinal products for clinical trials
- Also, manufacturing sites for
  - Actives ingredients
  - Auto-vaccines
  - Premixes for Medicated feeding stuff
  - Herbal products
  - Homeopathic medicines
- And contract company providing
  - Transport, quality control...
GMP Requirements

Vet GMP:

**Target/activity?**

- MAH and distributors
  - Recall and complaints
  - Quality product review
  - Traceability

- Importer
  - Quality control for importation
  - Recall and complaints
  - Quality product review
  - Traceability
GMP Requirements

Vet GMP

Target/product?

- Range of products
  - Sterile
  - Non sterile
  - Biologic
  - Chemical
  - Premix
  - Ectoparasiticides
  - Homeopathic
  - Herbal products
  - Medicated feeding stuff
  - Auto-vaccines

*Not covered: medical device, reagents, biocides and veterinary food additives*
Good Distribution practices

- Inspectors should verify
  - Record keeping
  - Storage conditions
  - Maintaining the cold chain for vaccines
  - The quality of VMPs distributed and used
Surveillance

- Legal Market
- Counterfeit products
Legal Market

Surveillance of the Legal Market

Elaborate a programme of surveillance with a risk analysis and in cooperation with other services (assessment, pharmacovigilance, inspection)

Risk based programme

Examples:

• Products used for food producing animals
• Products that present a risk for the users (vet, farmers, etc.)
• Focus on antibiotics and antiparasitics
• Biologicals involved in the control of zoonosis
• Biologicals involved in the control of regulated diseases
• Live vaccines

...
Sampling

• Done by inspectorates (in wholesalers but also anywhere on the market)

Testing

Qualitative and quantitative analysis
Active ingredient content
most often by HPLC (High performance Liquid Chromatography)

Other controls

Official Batch Release: Control for vaccines of the batch release by the Authority.
At farm level

- Inspectors should verify
  - Record keeping
  - The conditions of storage
  - The respect of the prescription rules
  - The compliance with the prescription
  - Veterinary medicinal products administered to the animals, dates of administration and respect of withdrawal periods
  - The absence of counterfeits or unauthorised products
Counterfeit products

- Medicinal products without a Marketing authorization
- Copy of Authorised products

Need for National, regional and international cooperation

No case in France for Veterinary medicinal products of real counterfeit products

Internet sales (a concern)
• Need for laboratory capacities to identify, analyse counterfeit products

• RAMAN SPECTROMETER
Conclusion

- Ensuring quality of Veterinary medicinal products is essential.
- Appropriate legislation and Staff (trained inspectors, laboratory capacities) are needed.
  - Efficient systems of Authorisation (VMP and companies)
  - Efficient Inspectorate body with appropriate power.
  - The possibility to survey both the legal and illegal market are essential as well as:

The capacity of prosecution and recalling products.
Thank you for your attention

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de la santé animale

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for Animal Health

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de Sanidad Animal