How to ensure the quality of VMPs

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Ensuring the Quality of Veterinary Medicinal Products (VMPs) is an essential and basic requirement for the good governance of VMPs.

Use of non good quality VMPs presents risks:

- **For animal health**: inefficient medicines
- **For human health**: 
  - Risk of residues in food
  - Inefficient vaccines could have impact on zoonosis outbreak
- **For environment**: pollution
Definition

Marketing authorisation:
- Composition: API, dosage
- Specification

Analysis

Compliance with MA
Good Quality

Non compliance

Substandard:
- Pb of manufacturing
- Pb of dosage...

Falsification:
- No API
- False API...
Quality at all steps of VMPs life

**MARKETING AUTHORIZATION**
- Definition of specifications
- Descriptions of the methods of manufacturing, control, etc.
- Establishments involved in the manufacturing...
- Benefit/risk balance

**MANUFACTURE**
- Good manufacturing practices
- GMP certificate for establishments:
  - Quality management
  - Management of anomalies
  - Testing for product release
  - Complaints management

**MARKETING**
- Good distribution practices
- Cold chain
- Advertising
- Quality defects
- Pharmacovigilance

**USERS**
- Veterinary practitioners
- Farmers
- Animal owners
- Pharmacovigilance
- Quality defects

**VICH GLs**
- OIE Manual

**GMP**
- GDP

**GPVceP**
- Ethic Code

**BPG**
Quality during manufacturing, storage, distribution and use

**VMPs Importers**

**VMPs Manufacturer**

**Wholesaler**

**Retailer veterinarians Pharmacist others**

**Farm**

**GDP**

**GMP**

Transparency:
- Official list of the registered VMP
- Official list of the authorised premises
- Website

Good practices:
- Conditions of manufacturing
- Traceability
- Conditions of Storage
- Conditions of deliverance

Notifications:
- Substandards, Quality defects
- Adverse effects: Pharmacovigilance
Inspection and control

- **Farm**
  - **Retailer veterinarians**
  - Pharmacist
  - others

- **Wholesaler**

- **VMPs Importers**

- **VMPs Manufacturer**

- **Sampling**

- **Quality Control**

- **GDP**

- **GMP**

**Control of:**
- List of VMPs (only VMPs authorised)
- Conditions of manufacturing
- Traceability
- Conditions of Storage
- Conditions of Retail
Need of prior authorisation 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 …
Manufacturer, impoter
And wholesaler
Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2017

Summary

Part 1  General Standards
Section 1.1.  Introductory chapters
Chapter 1.1.1.  Management of veterinary diagnostic laboratories (NB: Version adopted in May 2015)
Chapter 1.1.2.  Collection, submission and storage of diagnostic specimens (NB: Version adopted in May 2013)
Chapter 1.1.3.  Transport of specimens of animal origin (NB: Version adopted in May 2013)
Chapter 1.1.5.  Quality management in veterinary testing laboratories (NB: Version adopted in May 2017)
Chapter 1.1.6.  Principles and methods of validation of diagnostic assays for infectious diseases (NB: Version adopted in May 2013)
Chapter 1.1.7.  Standards for high throughput sequencing, bioinformatics and computational genomics (NB: Version adopted in May 2016)
Chapter 1.1.9.  Tests for sterility and freedom from contamination of biological materials intended for veterinary use (NB: Version adopted in May 2017)

Section 3.7  Recommendations for the manufacture of vaccines
Chapter 3.7.1.  Minimum requirements for the organisation and management of a vaccine manufacturing facility (NB: Version adopted in May 2016)
Chapter 3.7.2.  Minimum requirements for the production and quality control of vaccines (NB: Version adopted in May 2016)
Chapter 3.7.3.  Minimum requirements for aseptic production in vaccine manufacture (NB: Version adopted in May 2016)
GMP Requirements

Target/activity

• Manufacturing sites for
  – Pharmaceutical products
  – Medicinal products for clinical trials

• Also, manufacturing sites for
  – Actives ingredients
  – Autogenous-vaccines ….
  – Premixes for Medicated feeding stuff…

• Range of products
  – Sterile, Non sterile
  – Biologic, Chemical
  – Tablets, oral powder
GMP Requirements

Target/process

• **Quality management system**
  – manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation

• **Documentation**

• **Premises and equipment**

• **Production**

• **Quality control :**
  – sampling, specifications and testing as well as the organisation, documentation and release procedures

• **Self-inspection**

• **Complaints and product recall :**
  – system and appropriate procedures to record, assess, investigate and review complaints including potential quality defects
  – Quality Risk Management principles applied for investigation, assessment of quality defects and decision to product recalls, corrective and preventative actions and other risk-reducing actions.
**PIC/S and Working group on VMPs**

- **What is PIC/S?**
  - PIC/S is a *non-binding co-operative arrangement* between Regulatory Authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use.

- **PIC/s Goal**
  - “To lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products”

- **Exchange of letters with OIE**

  [www.picscheme.org](http://www.picscheme.org)
GMP Inspection System

Inspection steps:

- Programming
- Planning
- Preparation for inspection
- Carrying out the inspection
- Writing and sending initial report
- Assessment of QP responses and conclusion
- Compliance status of VPC et decision

Preliminary stage

Inspection stage
Good Distribution practices (GDP)

Target/activity

• MAH and distributors
  – Quality management system including product review
  – Premises and Equipment: Storage condition, cold chain for vaccines
  – documentation
  – Traceability
  – Recall and complaints
Control of retailer and Control at farm
– Sell only authorised VMPs
  • Capacity to check on a public accessible list
– Respect of condition of storage
– Role in the detection of quality defects
  • Visual aspects (colour, consistency, particle…)
  • Defect in the label …
– Pharmacovigilance
  • VICH GL24: “Pharmacovigilance of veterinary medicinal products (VMPs) can be defined as the detection and investigation of the effects of the use of these products, mainly aimed at the safety and efficacy in animals and safety in people exposed to the products.”
At farm level

– Farmers shall use only good quality products:

• absence of counterfeits, falsified or unauthorised products
• Respect the conditions of storage defined in the MA
• Keep record
• Respect the conditions defined in the prescription (dose, withdrawal period...)

[Images of cows and farmers]
A specific issue: retail at village market level

- Access to medication is not enough in entire regions
- Little or no money for assistance to farmers
- Farmers resignation or no awareness of the importance of quality
- The size of some packaging remains a problem for many breeders
- Imports sometimes heavy and slow procedures.
Increasing problem in Europe

Concerns:

- May be a way of sales for falsified or counterfeit VMPs
- *unfair competition* in the field of VMP
- source of *illegal import* without any authorization
- source of *illegal retail*: VMPs on prescription sold without control and prescription

Should be controlled, regulated
Quality Control of VMPs
Control of the Market

• Objectives:
  – Detection of substandard and falsified VMPs
  – Surveillance of the Legal Market
  – Surveillance of illegal market

• How?
  – Need a competent authority, a legal basis for sampling…
  – Need an official accredited laboratory
  – Need a programme of surveillance

• Programme of surveillance with a risk analysis
Sampling

• Done by inspectorates (in wholesalers but also anywhere on the market: village market, internet at farm...)

Control

• Based on marketing authorisation
• Control of label and leaflet
• Qualitative and quantitative analysis: active ingredient
• Efficacy of vaccines
Counterfeit products

Copy of authorised products : Differences in the labelling
Counterfeit products
Quality control analysis

Control of veterinary medicinal products on legal market: programme of surveillance

• Risk based approach
  • Identification of priorities on the list of registered products based on defined criteria

By examples:
✓ Products used for food producing animals
✓ Focus on antibiotics and antiparasitics
✓ Products that present a risk for the users (vet, farmers, etc.)
✓ Biologicals involved in the control of zoonosis

• Campaign of products:
  – Same category of VMPs: AB, AP
  – Same API...
Quality control analysis

- **The sampling:**
  - ✓ by a mandated person: inspector
  - ✓ at wholesaler level, at market level, on internet....
  - ✓ Traceability of samples: record

- **Registration of the samples at the laboratory**

- **Request to the MAH (if the VMP came from legal market = is authorized)**
  - ✓ Reference standard of the active substance with documentation
  - ✓ Certificate of the batch control analysis realized for the batch release
Quality control analysis

Control of veterinary medicinal products

main analysis depending on the capacity of the laboratory

- Active ingredient concentration/identification by HPLC-UV
- Density
- pH
- Uniformity of mass of unidose preparations
- Loss on drying
- Water content (karl fisher)
- Raman Spectroscopy
- ....
Quality control analysis

Network of laboratories: the GEON of EDQM

• the GEON is the general european network of OMCLs (Official medicine control laboratory) coordonated by EDQM (European directorate for the quality of medicines and healthcare) in the European Council.

• Worksharing and multiplication of analysis: VMP marketed in all EU are controlled by an OMCL of the GEON in a general programme of surveillance, share information, share results

• Participation in Proficiency test studies (inter lab of the network assay) for improvement of the laboratories

• Compliance with OMCL guidelines

• System of audit: Joint Mutual Audit
Follow up

• **Conformity:**
  – Letter to inform the MAH

• **Non-compliance:**
  ▪ Action on the MAH or the VMPs owner, wholesaler, retailer where the VMPs has been sampled:
    • Letter asking the MAH to comment
    • May Lead to variations in some cases
    • If falsification or counterfeit → prosecution, legal action
  ▪ Action on the products: risk analysis of the quality defect
Assessment of a Substandard

• Falsification products
  → batch recall and destruction

• Substandard → Risk assessment
  ➢ Assessment standardisation: same kind of defects leads to the same decision of batch recall
  ➢ Criteria of assessment shared with Industry (transparency)
  ➢ Risk assessment taking into account:
    ➢ Impact on human health
    ➢ Impact on animal health
    ➢ Incident already observed or not
    ➢ Substandard observed on one batch or several batch…
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)
  – Transparency and communication
  – 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**