anses
French agency for food, environmental and occupational health safety
Investigate, evaluate, protect

How to ensure the quality of VMPs

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Introduction

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

NO → **Unlicensed VMP**

YES : authorised VMP

Analysis

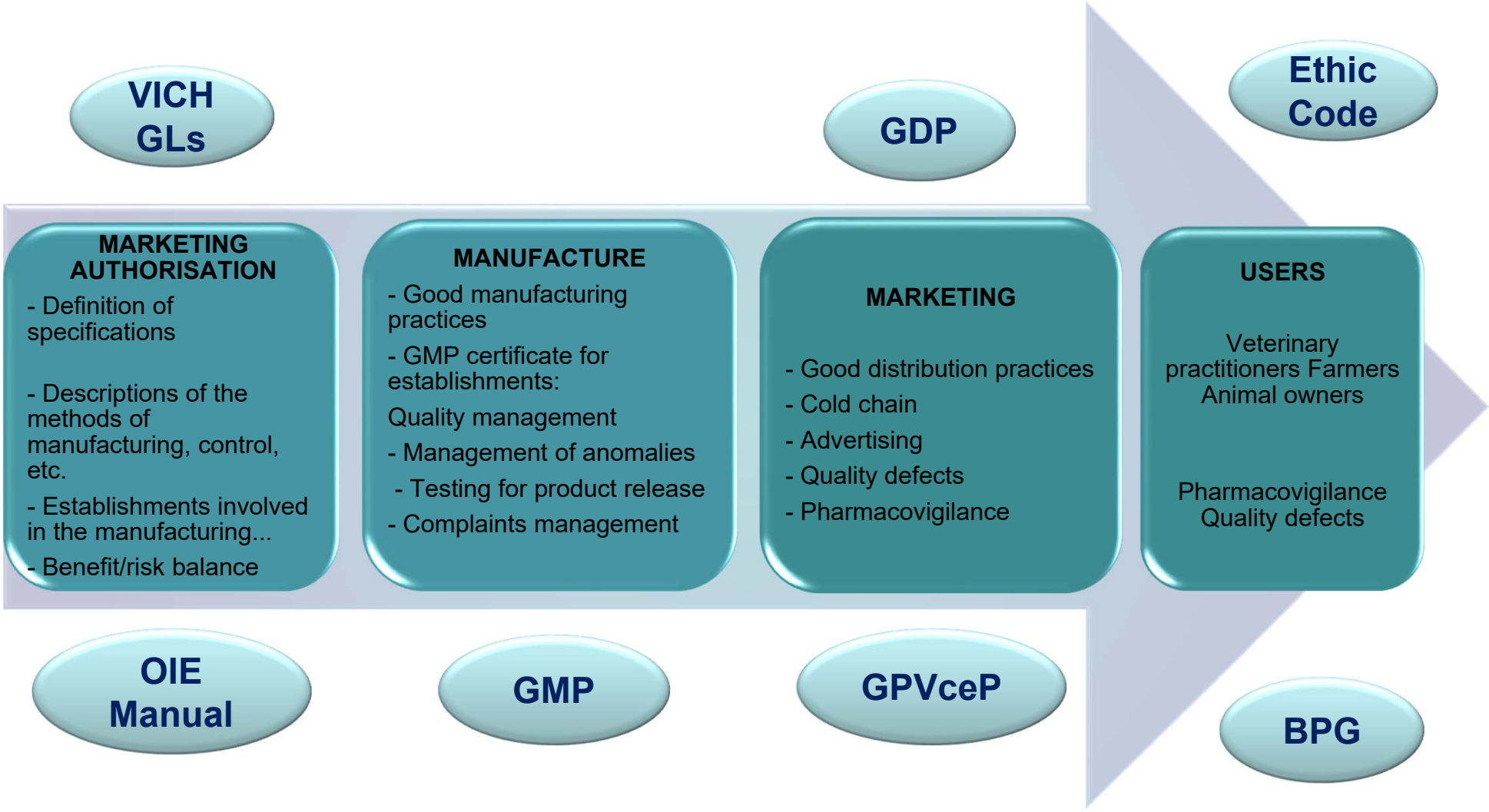
Compliance with MA
Good Quality

Non compliance

Quality defects :
- Pb of manufacturing
- Pb of dosage…

Falsification:
- No API
- False API…

Quality at all steps of VMPs life



Quality during manufacturing, storage, distribution and use

VMPs Importers

VMPs Manufacturer

GDP

GMP

Wholesaler

Retailer
veterinarians
Pharmacist
others

Farm

Transparency :

- Official list of the authorised VMP
- Official list of the authorised premises
- website

Good practices :

- Conditions of manufacturing
- Traceability
- Conditions of Storage
- conditions of deliverance

Notifications :

- Quality defects
- Adverse effects : Pharmacovigilance

Inspection and control

VMPs Importers

VMPs Manufacturer

GDP

GMP

Wholesaler

Inspection

Sampling

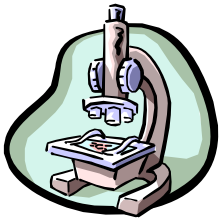
Retailer
veterinarians
Pharmacist
others

Farm

Control of :

- List of VMPs (only VMPs authorised)
- Conditions of manufacturing
- Traceability
- Conditions of Storage
- Conditions of deliverance

Quality Control



Manufacturing, wholesaling and retailing

⇨ **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

GMP at OIE LEVEL

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 1.1.4.	Biosafety and biosecurity: Standard for managing biological risk in the veterinary laboratory and animal facilities (NB: Version adopted in May 2015)
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 1.1.8.	Principles of veterinary vaccine production (NB: Version adopted in May 2015)
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

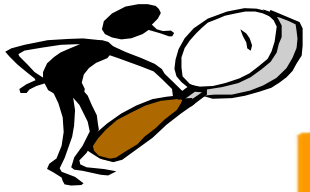
GMP Inspection System

Inspection steps:

- Programming
- Planning

Preliminary stage

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



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

Veterinarians / Pharmacists

- 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…)

A specific issue: retail at village market level

(photos : Dr. Albert Douffissa. Présentation " What is Needed to Improve Availability to Good Quality Veterinary Drugs and Vaccines.")

- 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.

A specific issue: internet sales

- 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, falsified and counterfeited 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 : Differencies 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 authorised 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 Quality Defect

- Falsification and counterfeit products

  → **batch recall and destruction**

- Quality defect : (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*
    - *Incidentalready observed or not*
    - *Quality defect 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