

Illegal veterinary drugs

How to ensure the quality and traceability of Veterinary Medicinal Products

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Anses/ANMV

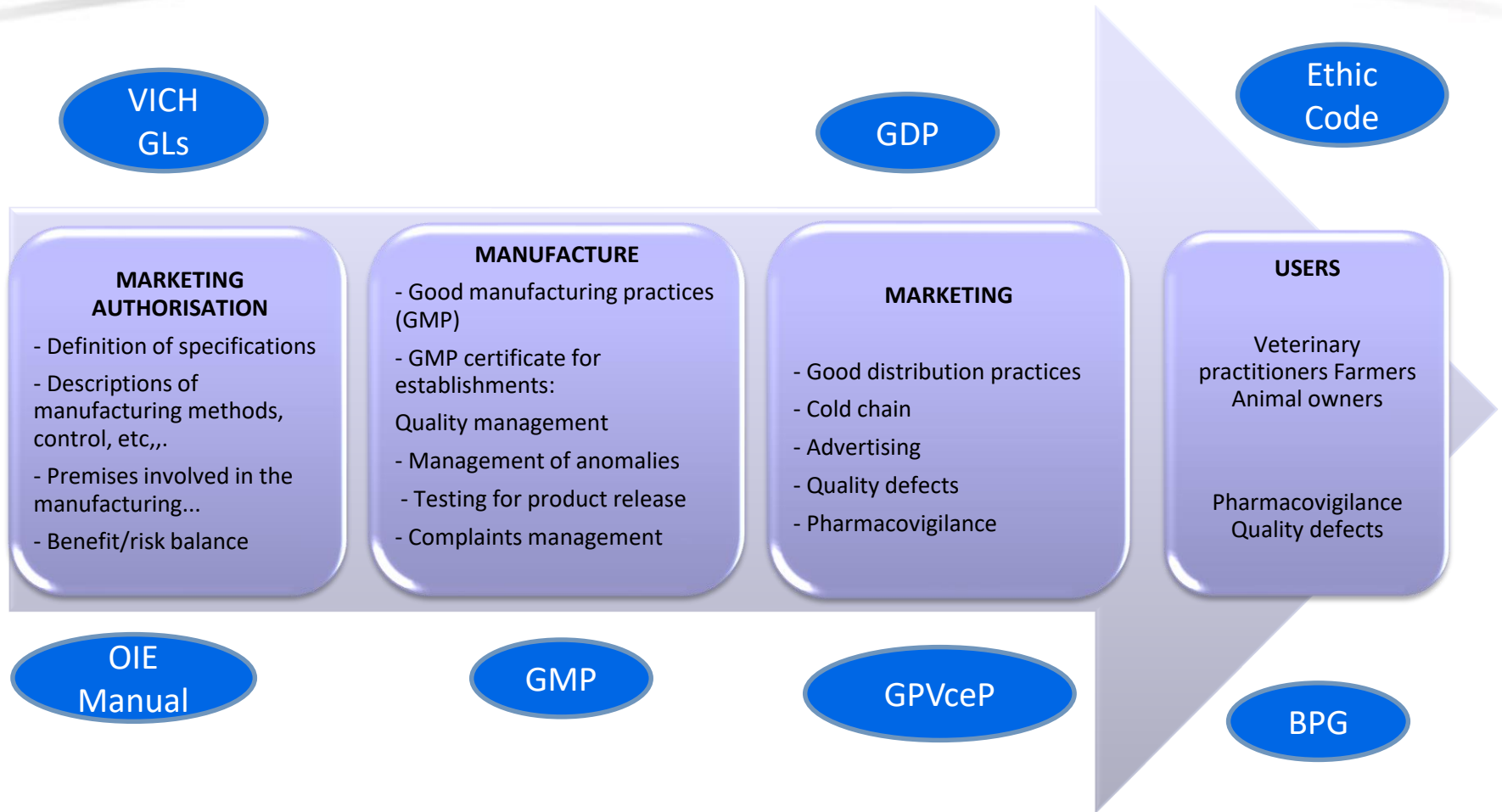
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Ensuring the Quality of Veterinary Medicinal Products (VMPs) is an essential and basic requirement for the good governance of VMPs

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

Quality at all steps of VMPs life



How to assure the good quality of VMPs ?

- ✓ Risk assessment and risk management at each step considering international standards
- ✓ Inspection and control at each step
- ✓ Deterrent penalties



Marketing Authorisation

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



- ✓ Qualitative and Quantitative Particulars of the constituents :
 - composition : describes precisely the product
- ✓ Description of the Manufacturing Method to assure that quality of finished product is reproducible :
 - description of the manufacturing process : **GMP for all sites needed**

Quality Part defines control to conduct



✓ Control of Starting Materials

- ▢ to ensure that the product contains starting materials of good and controlled quality

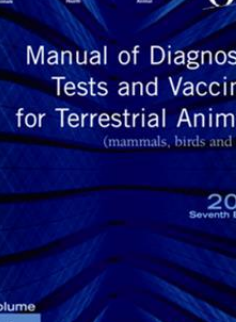
✓ Control Tests Carried out at intermediate stages of the Manufacturing Process

✓ Control on the Finished Product for batch release :

- ▢ define precisely the **specifications of the product** and the limits of acceptance
- ▢ Important for the Quality control performed by authorities

✓ Stability Test

- Proposal of a shelf-life and storage conditions if necessary
- Proposal of a shelf-life after first opening of the immediate packaging
- Proposal of a shelf-life after dilution or reconstitution
- Proposal of a shelf-life after incorporation into meal or pelleted feed



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**Manual of Diagnostic
Tests and Vaccines
for Terrestrial Animals**
(mammals, birds and bees)

2012
Seventh Edition

Volume
1

10



Manufacture and Marketing

An appropriate regulatory framework



- ⇒ **Need of prior authorisation and periodic control for veterinary medicinal product companies**
 - **Manufacturer, Importer, Wholesaler...**

- ⇒ These activities should be governed by rules of **Good practices as :**
 - Good manufacturing practices (GMP)
 - Good distribution practices (GDP)
 - Good prescription practices ...

- **The EU(EEA) Regulatory Framework**

- Veterinary Medicinal Products: **GMP**

Volume 4 EUDRALEX: Good manufacturing practice (GMP) Guidelines

<http://ec.europa.eu/health/documents/eudralex/vol-4/>

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



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 comprises around **50 Participating Authorities** coming from all over the world (Europe, Africa, America, Asia and Australasia)



LIST OF PIC/S PARTICIPATING AUTHORITIES



www.picscheme.org

PIC/S and Working group on VMPs



• 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”
- PIC/S Goal to be achieved by:
 - **Developing** and **promoting** harmonised GMP standards and guidance documents
 - **Training** competent authorities, in particular GMP inspectors
 - **Assessing** (and reassessing) GMP Inspectorates
 - Facilitating the **co-operation** and **networking** for competent authorities and international organisations



GMP at OIE LEVEL



Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2017



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)
- Chapter 1.1.10. [Vaccine banks](#) (NB: Version adopted in May 2016)

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*
 - *Premises for Medicated feeding stuff*
 - Herbal products
 - Homeopathic medicines
- And contract company providing
 - Transport, quality control...



GMP Requirements

Target/product

- Range of products
 - Sterile
 - Non sterile
 - Biologic
 - Chemical
 - Tablets, oral powder
 - ...



Not covered: medical device, reagents, biocides and veterinary food additives

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
- 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.

Good Distribution practices (GDP)



Target/activity

- MAH and distributors
 - Recall and complaints
 - Quality product review
 - Storage condition : **cold chain for vaccines**
 - Traceability





Use

– 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

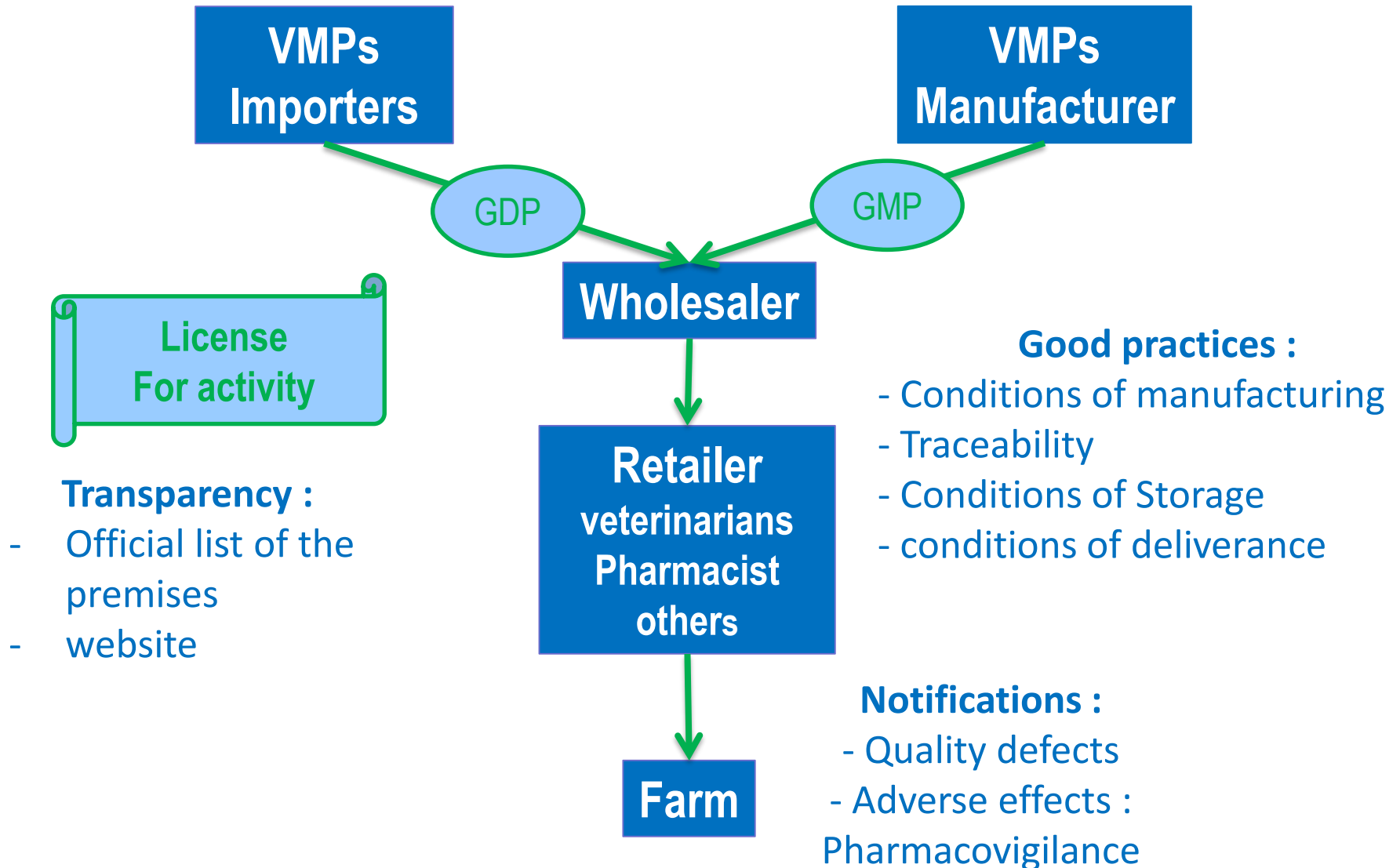
- Farmers shall use only good quality products :
 - absence of counterfeits or unauthorised products
 - Respect the conditions of storage defined in the MA
 - Keep record
 - Respect the conditions defined in the prescription (dose, withdrawal period...)



Focus on traceability



Traceability at each step of the VMP chain



Traceability : what for?

- To guaranty the quality of VMP
- To ensure effective monitoring of VMP at any time
- to protect animal health and welfare and maintain public health
- to know the expiration date of the VMP
- to fight against counterfeiting
- to allow the recall of a VMP if necessary

Traceability : who is in charge



See the chapter of the Terrestrial Animal Health Code dedicated to vet legislation - art. 3.4.11 on Veterinary medicines and biologicals:

- At production, storage and wholesaling level
- At retailing and use level

Traceability

- At production, storage and wholesaling level
As a minimum : batch number, expiry date



- Part of GMP
 - ability to trace the history of manufacturing
- Part of GDP
 - ability to locate each batch following its distribution

*A traceability system should allow **to find and recall all defective product***

Expectations in relation to GDP requirements

- Recall
 - All customers to whom the batch was distributed should be informed
 - System of recording of deliveries and returned products
- Counterfeit VMP
 - Kept apart from other medicinal products to avoid any confusion
 - Records
 - Information to competent authorities and the holder of marketing authorisation of the original product
- Destruction
 - Destruction of defected, recalled and returned VMP
 - ✓ In accordance with the regulation in force
 - Record

Traceability : who is in charge



- At retailing level, registration by the vet or other:
 - Name, address of the animal owner
 - Name of the VMP
 - Dispensing date, quantity supplied
 - Manufacturer's batch number of the VMP
- At use level: the breeder should keep the prescriptions and/or have a register mentioning :
 - Name of the administered VMP (batch number)
 - Animals to which they are administered, route of administration and daily dose administered per animal (may be replaced by a reference to the prescription)
 - Starting date and ending date of treatment



Surveillance

- Legal Market
- Counterfeit products

Surveillance of the Legal Market

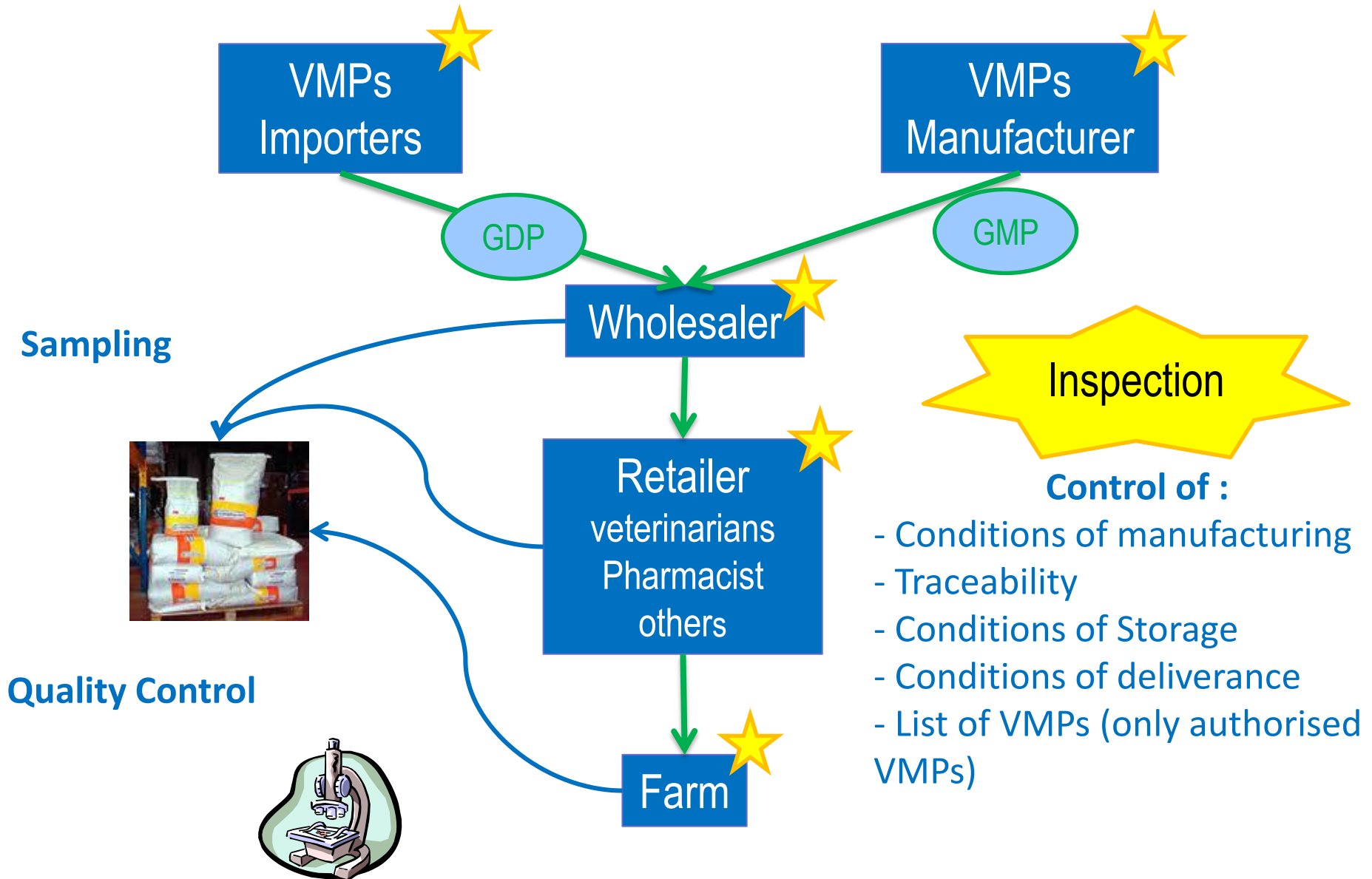
Elaborate a programme of surveillance with a risk analysis and in cooperation with all competent services

Risk based programme

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
- biologicals involved in the control of regulated diseases
- live vaccines...

Inspection and control



Sampling



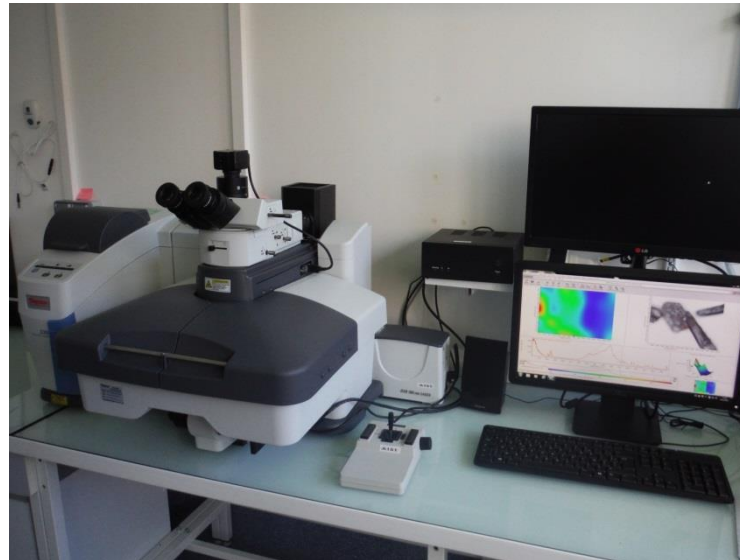
- Done by inspectorates (in wholesalers but also anywhere on the market)

Testing

- Qualitative and quantitative analysis : Active ingredient content
most often by HPLC (High performance Liquid Chromatography)
- Efficacy for vaccines
- Accredited laboratory or international recognition (OIE Ref. Lab)

- **Copy of authorised products**
 - Modification of qualitative or quantitative active ingredients
 - Differences in the labelling
- **Need for national, regional and international cooperation**
- **Internet sales (a concern)**

- Need for laboratory capacities to identify, analyse counterfeit products
- French work to develop counterfeit analysis :



RAMAN SPECTROMETER

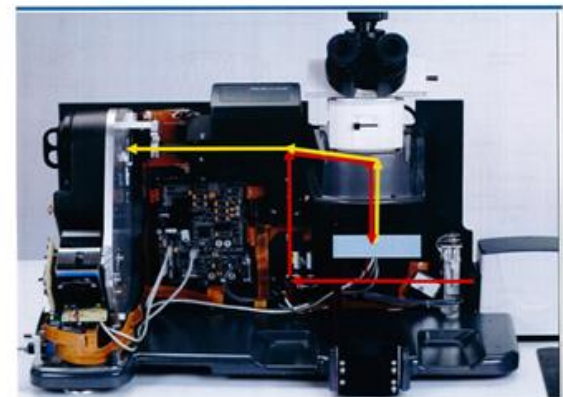
Applications at ANMV level

- Acquisition DXR MICROSCOPE RAMAN



DXR MICROSCOPE RAMAN

- Photo of the inside of our DXR Raman



Pharmaceutical applications with RAMAN SPECTROMETER

➤ Structural study:

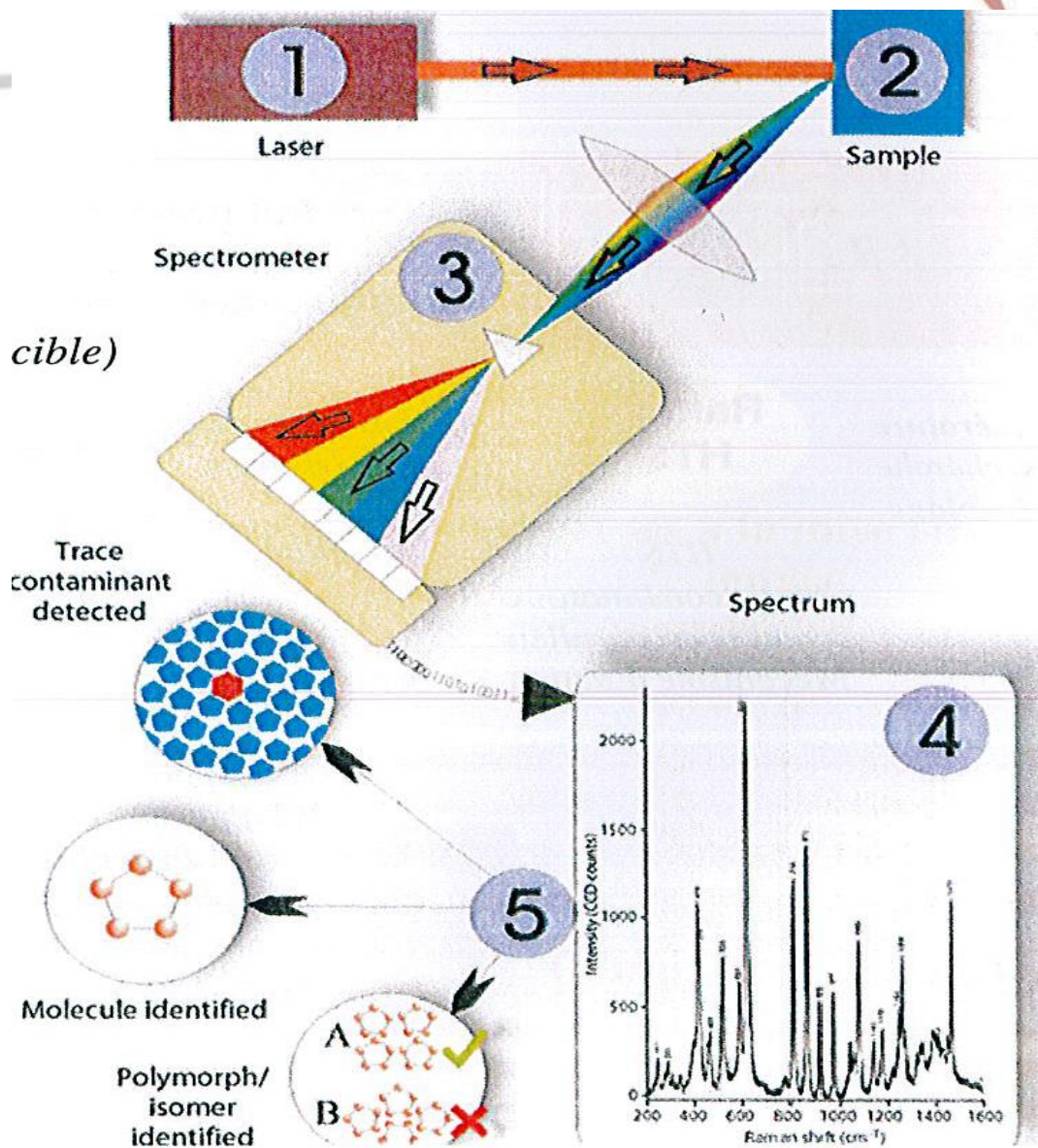
Conformation
Interactions

➤ Qualitative analysis:

Identification
Qualification
Mixture analysis
Mapping

➤ Quantitative analysis:

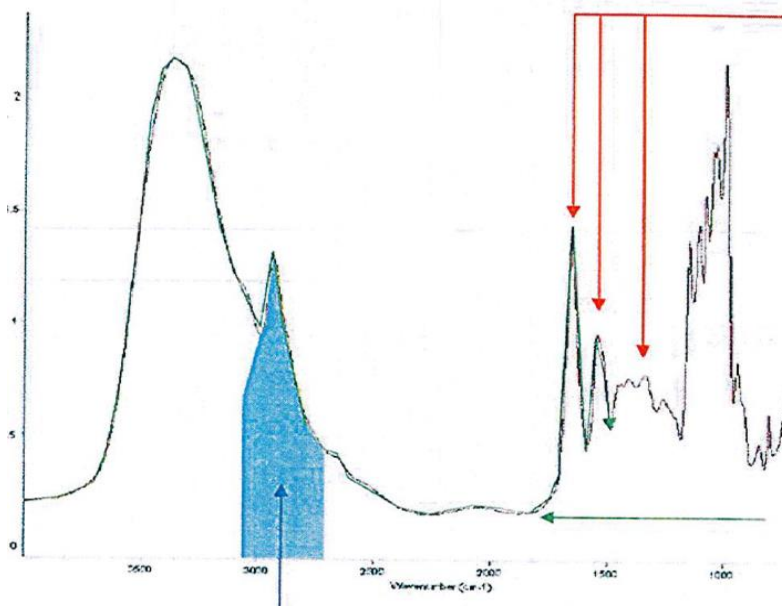
Dosage (assay)
Quantitative imagery



Analytical applications

- Different approaches:

Structural: relative peak heights



Qualitatives:
spectral signature

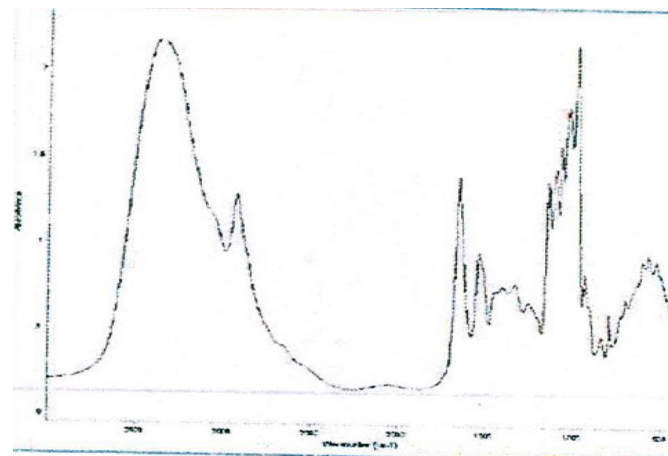
Quantitatives: identification

Quantitatives: area, dosage, detection

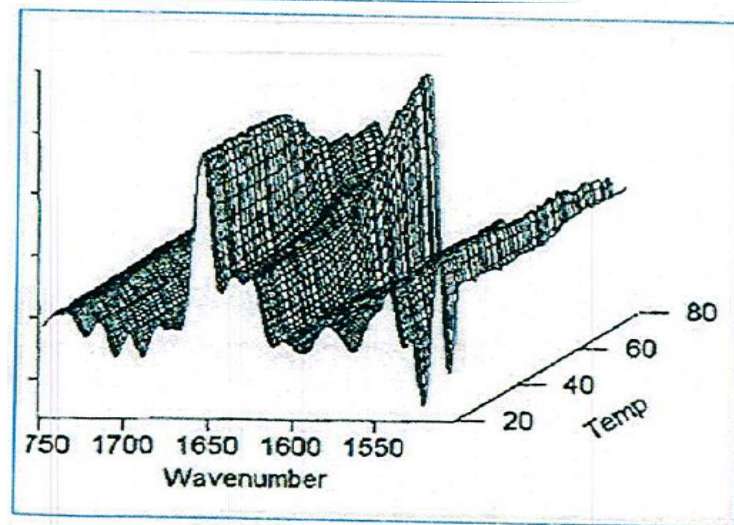
Analytical applications

- Object of interest = one spectrum or one collection

➤ One spectrum, direct analysis,
Spectral library



➤ Collection of spectrum, statistic
approach, chemometrics



Quality control applications



- Identification: analysis of active substances and finished products

Using reference library and spectra comparison algorithms

- Research – development and expert applications:

Specificity of spectra, in situ measurement capabilities, Raman image to characterize presence and distribution of different substances

- Counterfeit drugs:

Spectral comparison methods and multivariate statistical methods to obtain a rapid response

Pangea operation: Combating the sale of illegal medicines online

- Operation Pangea is an international week of action tackling the online sale of counterfeit and illicit medicines and highlighting the [dangers of buying medicines online](#).
- Coordinated by INTERPOL, the annual operation brings together customs, health regulators, national police and the private sector from countries around the world.
- Key international organizations have joined the effort as well, including Europol, the World Customs Organization and the Universal Postal Union.



Operation Pangea : OBJECTIVES

- Safeguard public health;
- Seize counterfeit and illegal products and remove them from the market;
- Identify the producers and distributors of counterfeit and illegal medical products and the criminal networks supporting them;
- Shut down fraudulent websites;
- Raise public awareness of the risks of buying medicines online;
- Enhance cooperation amongst agencies combating the illicit trade of counterfeit and illegal medical products.

Develop a collaborative approach to combat the illicit trade of counterfeit and illicit medical products worldwide



Operation Pangea IX in 2016 :

- involved 103 member countries and 193 police, customs and health regulatory agencies.
- Inspection of more than 335,660 packages, 167,917 of which were seized when found to contain counterfeit or illicit medical products.
- More than **12.5 million units of counterfeit and illicit medicines** with an estimated value of **USD 53.7 million were taken out of circulation**, some 5,000 websites selling illicit pharmaceuticals were suspended and nearly **400 people were arrested** worldwide.

What about a Vet PANGEA ?

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

Thank you for your attention



Organisation mondiale
de la santé animale

World Organisation
for Animal Health

Organización Mundial
de Sanidad Animal