Quality of Veterinary Medicinal Products

How to ensure the quality of Veterinary Medicinal Products

Jean-Pierre ORAND

Anses/ANMV

OIE Collaborating Centre on Veterinary medicinal products

Jean-pierre.orand@anses.fr

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

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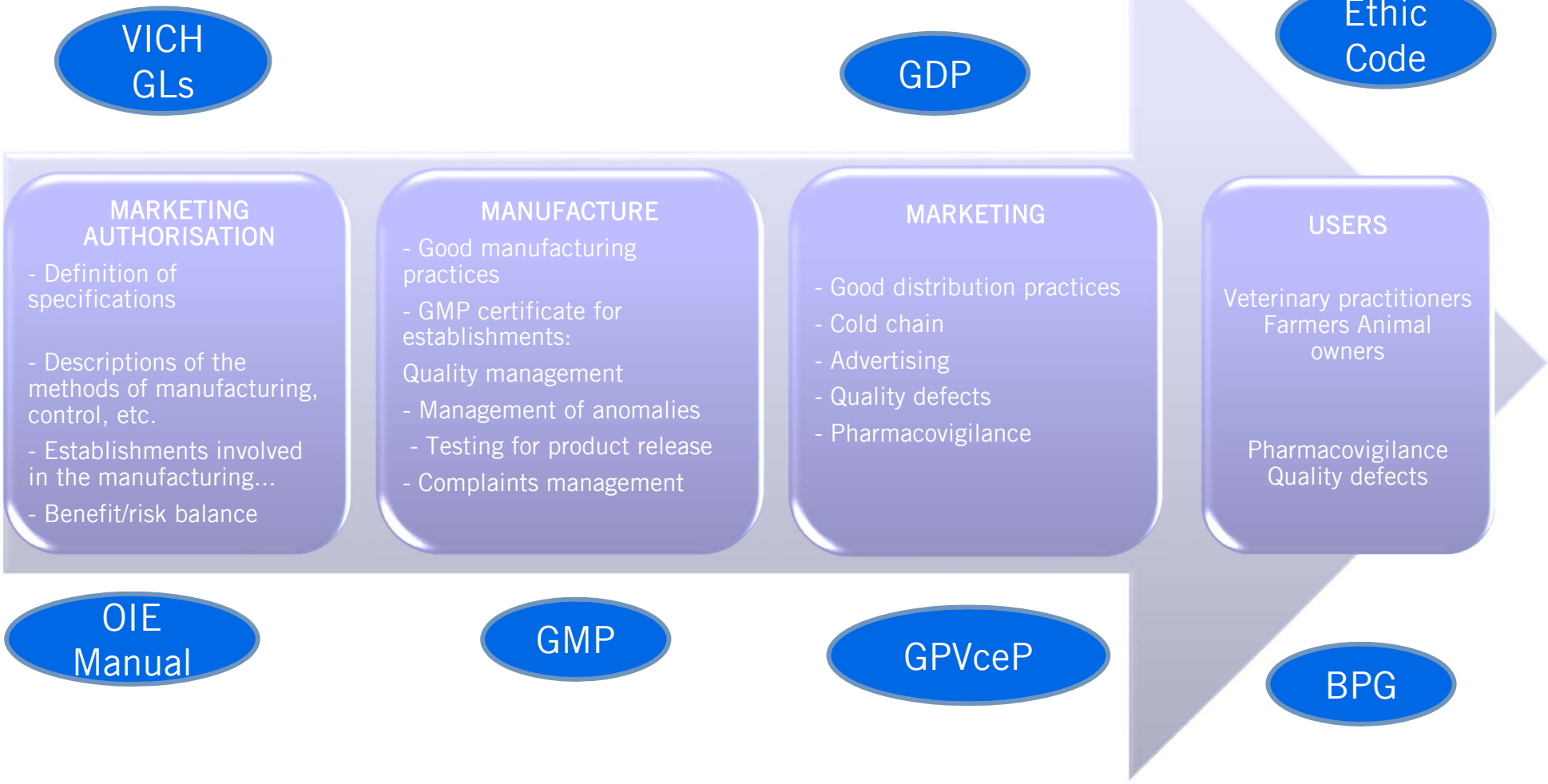
Quality at all steps of VMPs life



Good governance of quality

How to assure the good quality of VMPs ?

- ✓ **Risk assessment and risk management at all steps considering international standards**
- ✓ **Inspection and control at all steps**
- ✓ **Deterrent penalties**

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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 manufacturing process : GMPs for all sites needed

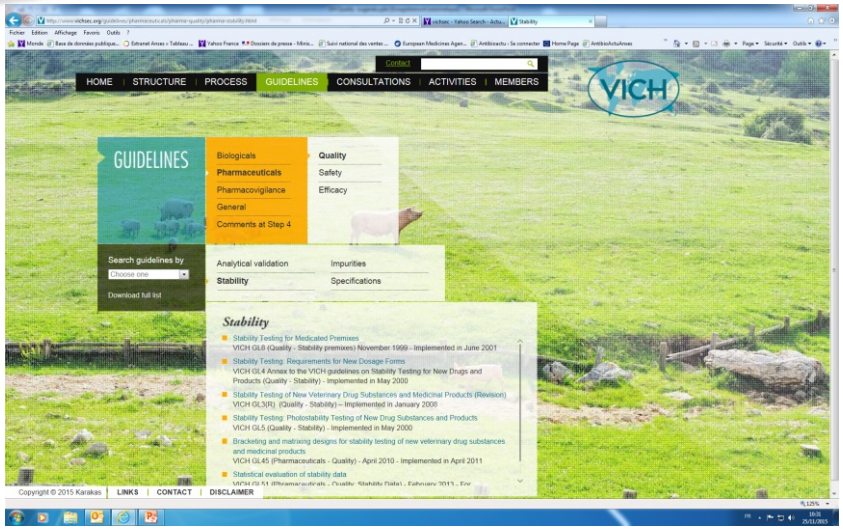
Quality Part defines control to conduct

- ✓ 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 products** and the limits of acceptance
  - Important for the Quality control by the authorities

Quality Part

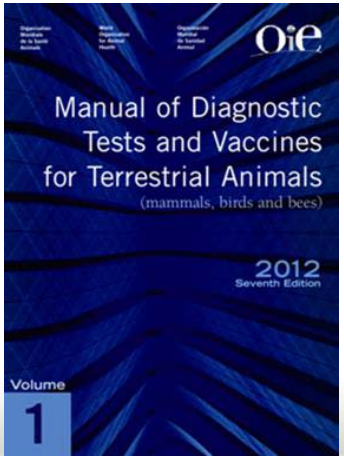
- ✓ Stability Test
  - Propose a shelf-life and storage conditions if necessary
  - Propose a shef-life after first opening of the immediate packaging
  - Propose a shelf-life after dilution or reconstitution
  - Propose a shelf-life after incorporation into meal or pelleted feed

VICH guidelines available



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

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals



http://www.oie.int/en/international-standard-setting/terrestrial-manual/

Manufacture and Marketing

An appropriate regulatory framework

- **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 …

GMP legislation

- The EU(EEA) Regulatory Framework
  - Veterinary Medicinal Products: **GMP**

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

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

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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).

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)

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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*
  - 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

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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.

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Good Distribution practices (GDP)

Target/activity

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

Use

Veterinarians / Pharmacists

– 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

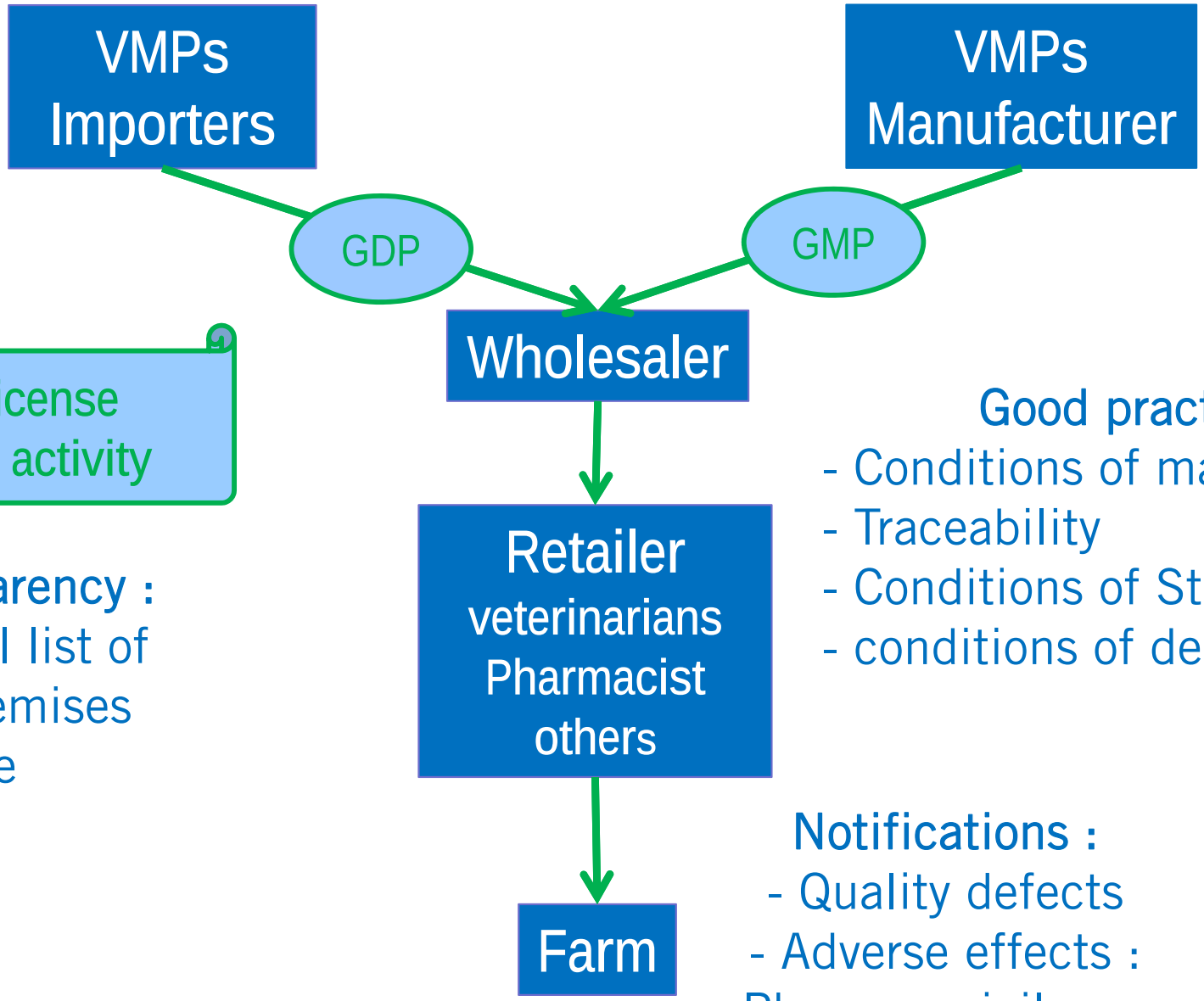
- Farmers shall use only good quality products :
  - absence of counterfeits or unauthorised products
  - Respect the conditions of storage defined in the MA
  - Keep record
  - Respect the conditions defined in the prescription (dose, withdrawal period…)

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.

Quality during manufacturing, storage, distribution and use



Transparency :

- Official list of the premises
- website

Good practices :

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

Notifications :

- Quality defects
- Adverse effects : Pharmacovigilance

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 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

VMPs Importers

VMPs Manufacturer

GDP

GMP

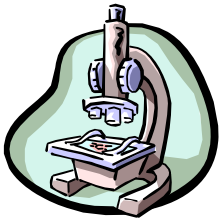
Wholesaler

Retailer
veterinarians
Pharmacist
others

Farm

Sampling

Quality Control



Inspection

Control of :

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

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)

Counterfeit products

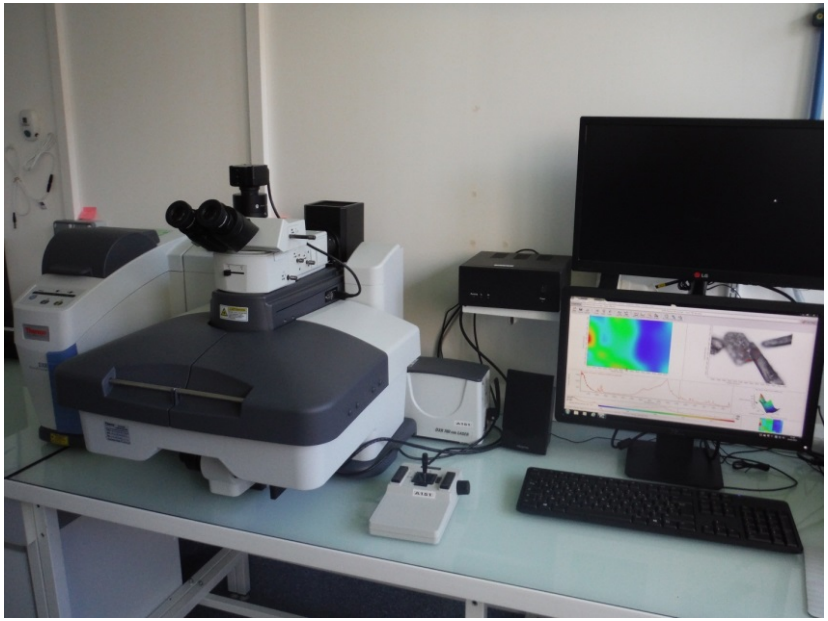
- Copy of authorised products
  - Modification of qualitative or quantitative active ingredients
  - Differencies in the labelling
- Need for national, regional and international cooperation
- Internet sales (a concern)

Counterfeit products

Counterfeit products

Quality Control Laboratory

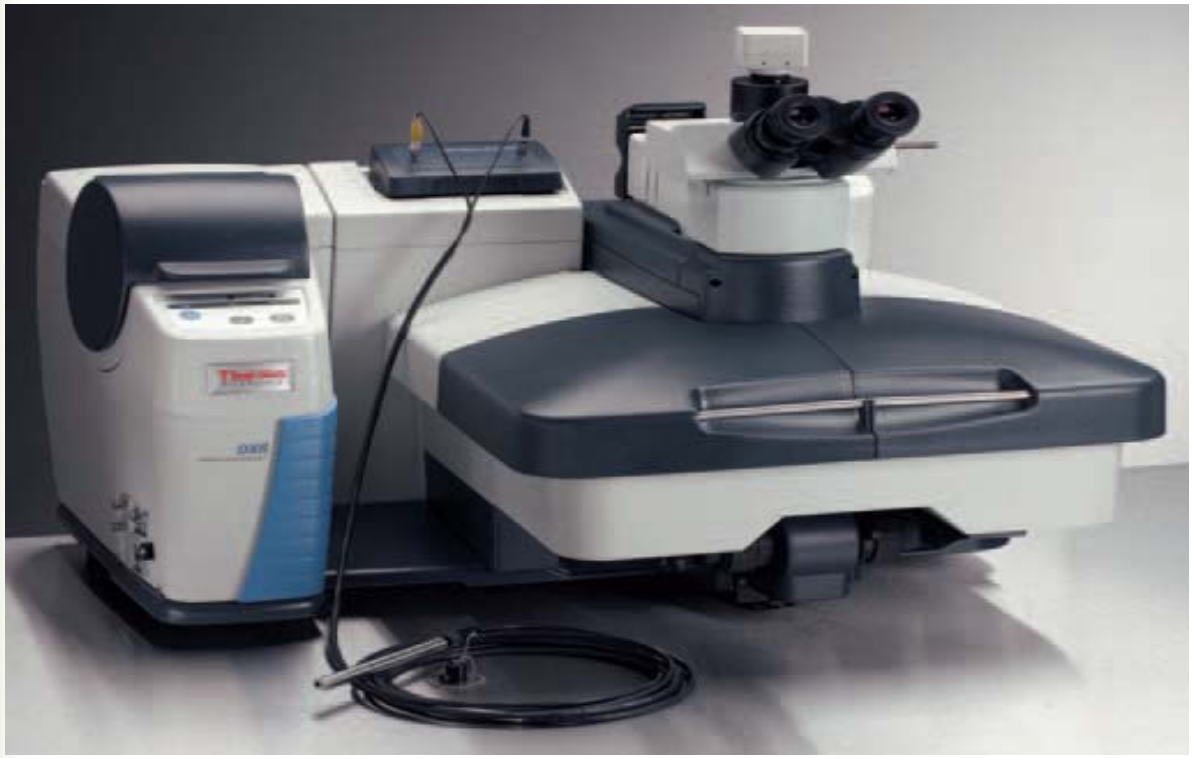
- Need for laboratory capacities to identify, analyse counterfeit products
- French work to develop counterfeit analysis :



RAMAN SPECTROMETER

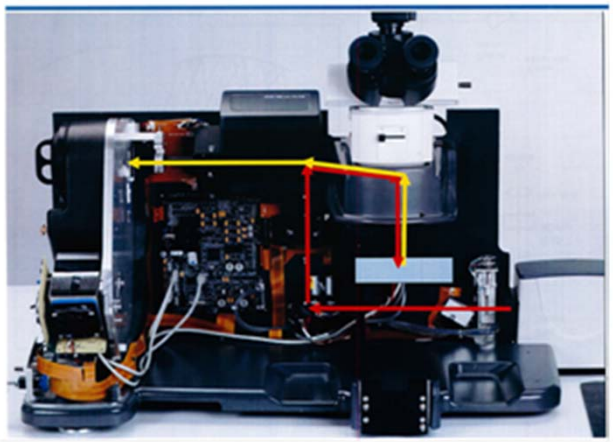
Applications at ANMV level

- 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

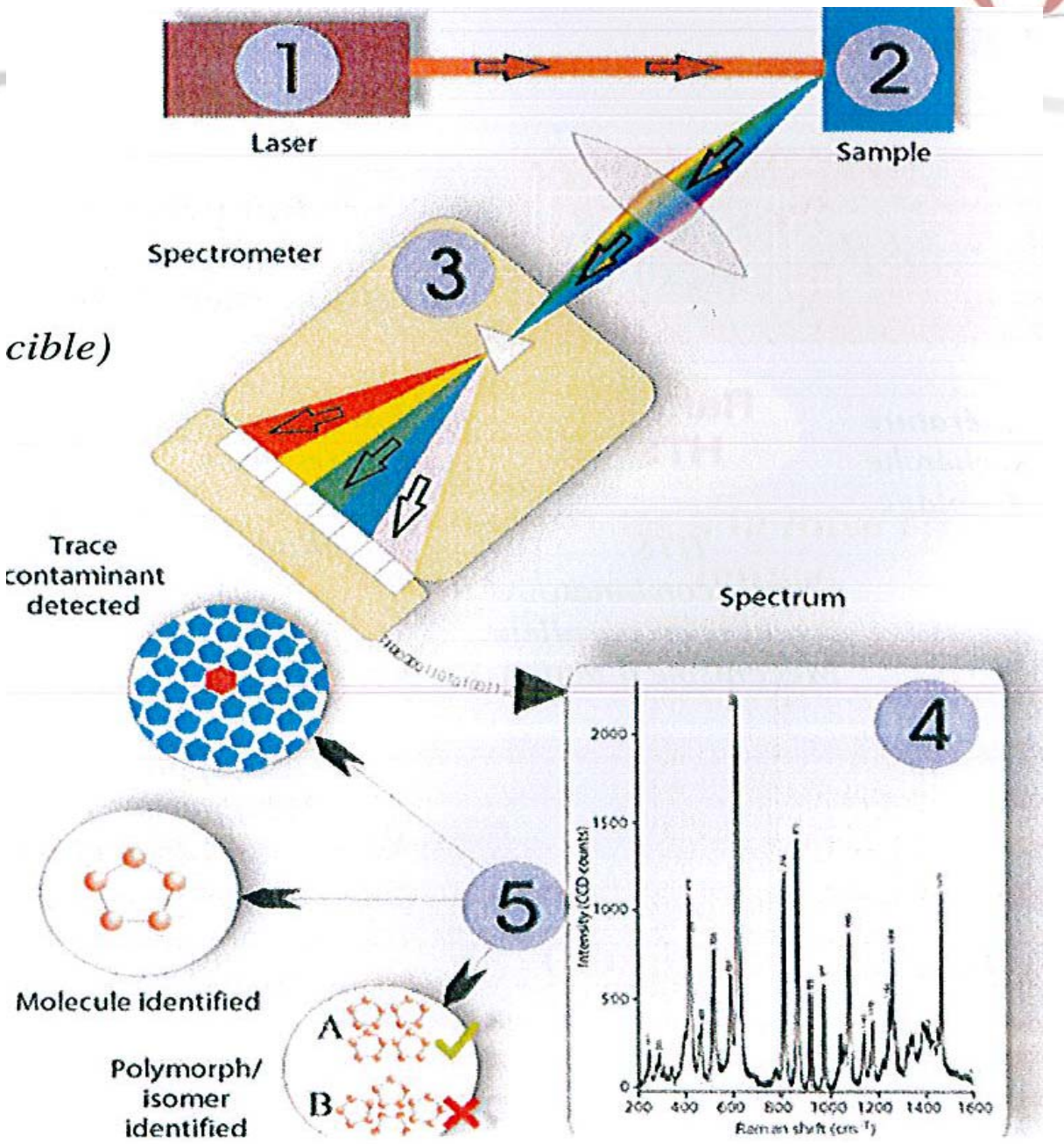
Mixture analysis

Mapping

- Quantitative analysis:

Dosage (assay)

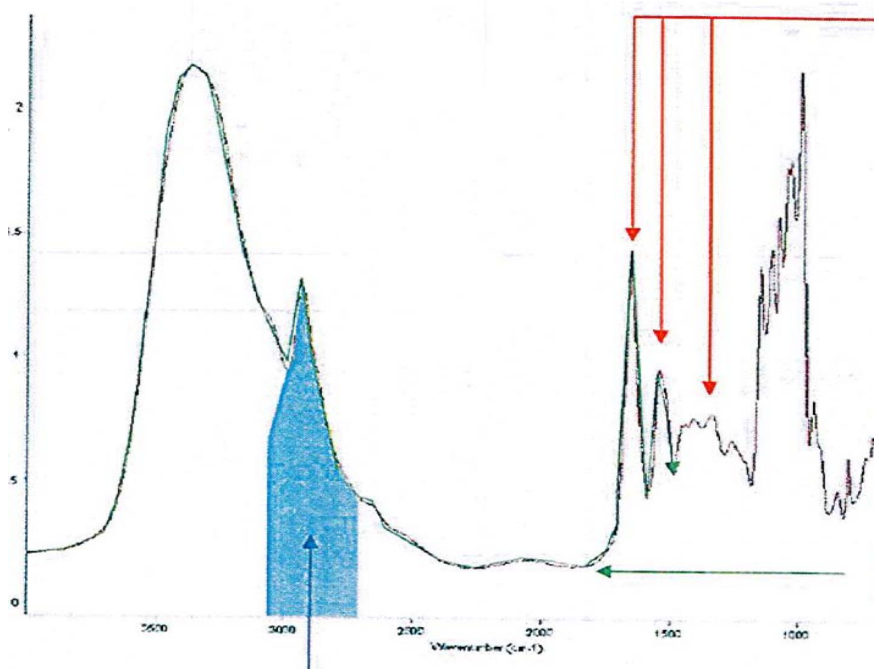
Quantitative imagery



Analytical applications

- Different approaches:

Structural: relative peak heights



Qualitatives:

spectral signature

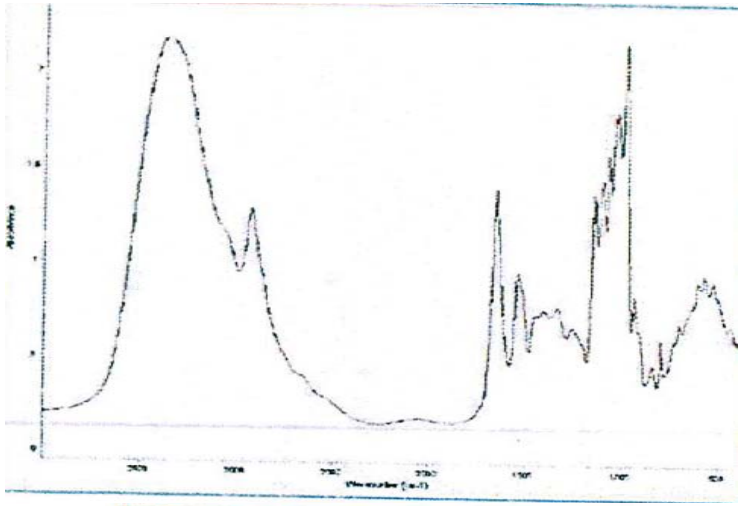
Quantitatives: identification

Quantitatives: area, dosage, detection

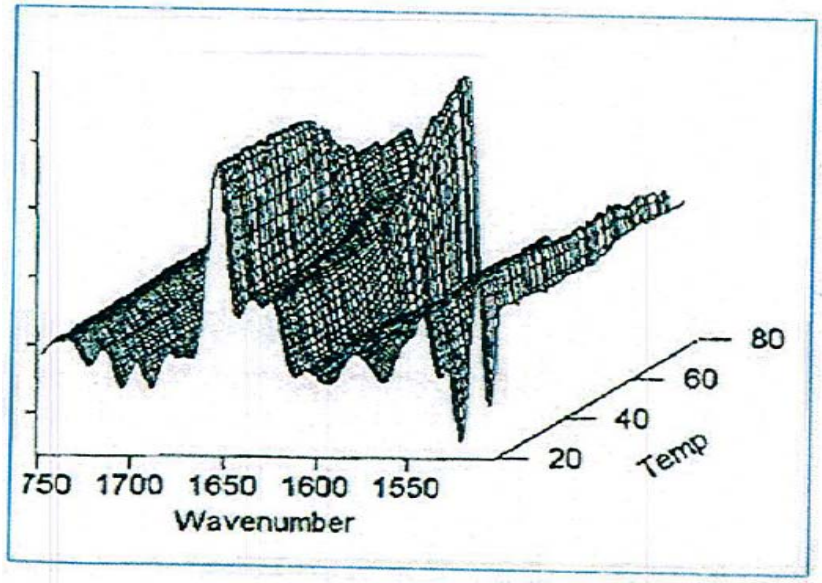
Analytical applications

- 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

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.

PANGEA

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

PANGEA

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

12 rue de Prony, 75017 Paris, France - www.oie.int – oie@oie.int