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Quality of Veterinary Medicinal Products

How to ensure the quality of Veterinary Medicinal Products

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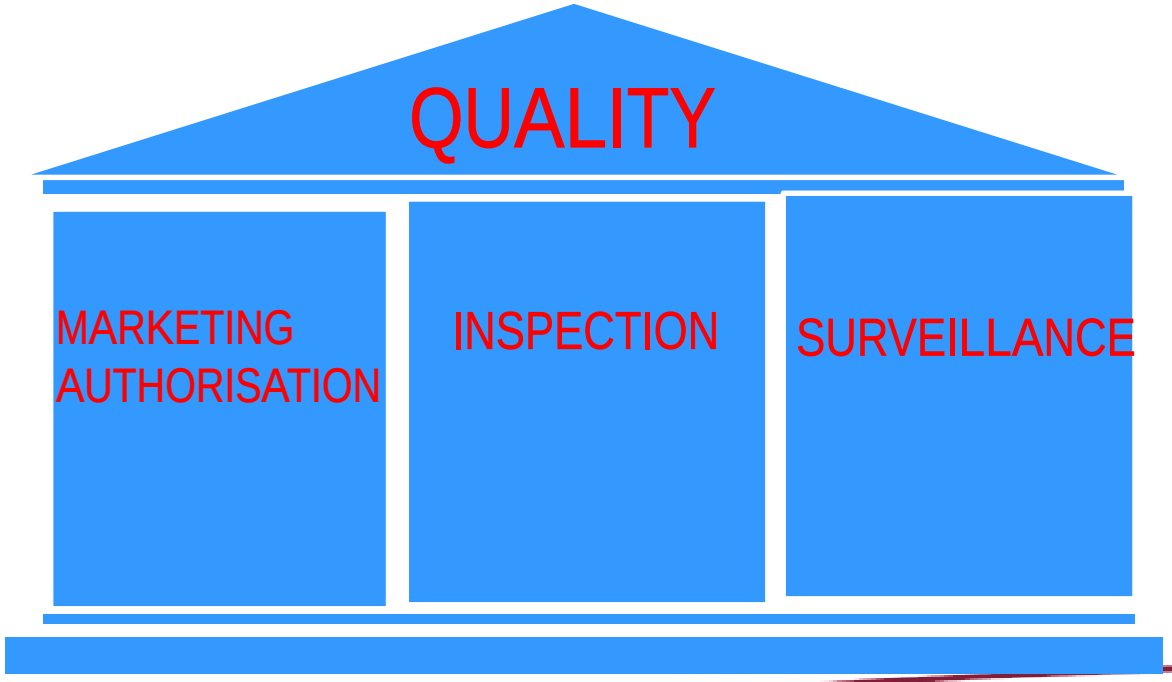
INTRODUCTION

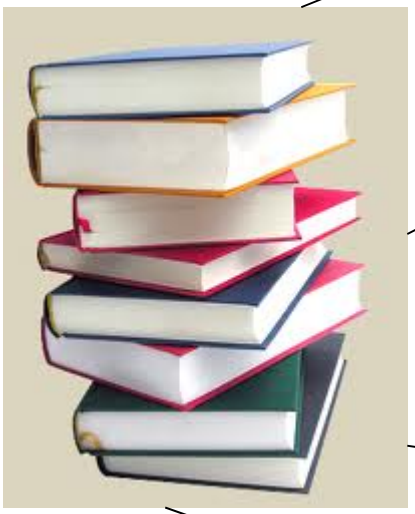
Ensuring the quality of Veterinary Medicinal products is an essential and basic requirement for the good governance of VMPs.

Three Pilars



*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

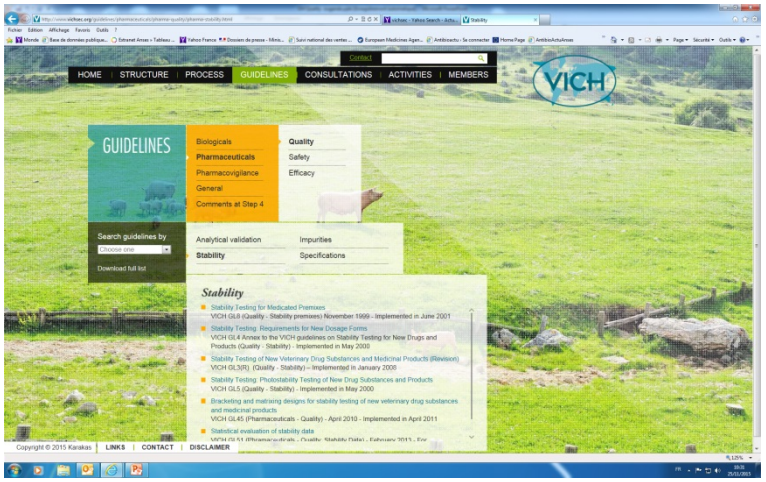
F.1 Stability Test on the active substance

F.2 Stability Test on the Finished product

Objectives:

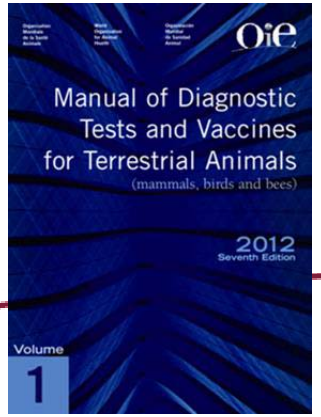
1. Propose a shelf-life as package for sale, and storage conditions if necessary
2. Propose a shef-life after first opening of the immediate packaging
3. Propose a shelf-life after dilution or reconstitution
4. Proposed a shelf-life after incorporation into meal or pelleted feed

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/

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 …

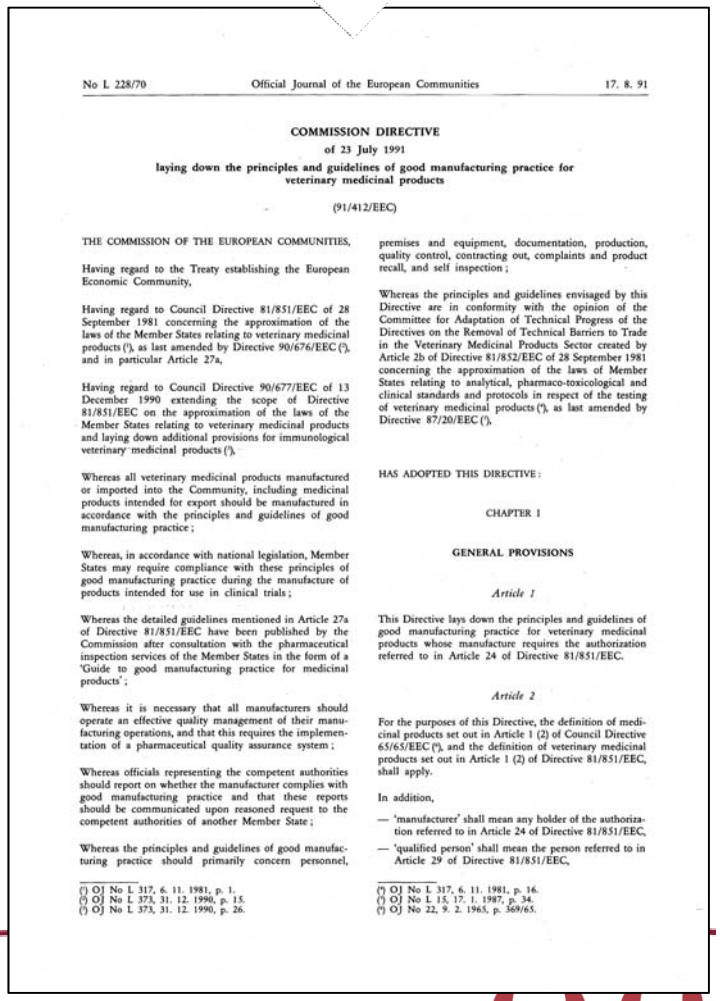
GMP legislation

- 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**.

General provisions

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



No L 228/70 Official Journal of the European Communities 17. 8. 91

COMMISSION DIRECTIVE

of 23 July 1991

laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products

(91/412/EEC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to Council Directive 81/851/EEC of 28 September 1981 concerning the approximation of the laws of the Member States relating to veterinary medicinal products (1), as last amended by Directive 90/676/EEC (2), and in particular Article 27a,

Having regard to Council Directive 90/677/EEC of 13 December 1990 extending the scope of Directive 81/851/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products and laying down additional provisions for immunological veterinary medicinal products (3),

Whereas all veterinary medicinal products manufactured or imported into the Community, including medicinal products intended for export should be manufactured in accordance with the principles and guidelines of good manufacturing practice;

Whereas, in accordance with national legislation, Member States may require compliance with these principles of good manufacturing practice during the manufacture of products intended for use in clinical trials;

Whereas the detailed guidelines mentioned in Article 27a of Directive 81/851/EEC have been published by the Commission after consultation with the pharmaceutical inspection services of the Member States in the form of a 'Guide to good manufacturing practice for medicinal products';

Whereas it is necessary that all manufacturers should operate an effective quality management of their manufacturing operations, and that this requires the implementation of a pharmaceutical quality assurance system;

Whereas officials representing the competent authorities should report on whether the manufacturer complies with good manufacturing practice and that these reports should be communicated upon reasoned request to the competent authorities of another Member State;

Whereas the principles and guidelines of good manufacturing practice should primarily concern personnel, premises and equipment, documentation, production, quality control, contracting out, complaints and product recall, and self inspection;

Whereas the principles and guidelines envisaged by this Directive are in conformity with the opinion of the Committee for Adaptation of Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Veterinary Medicinal Products Sector created by Article 2b of Directive 81/852/EEC of 28 September 1981 concerning the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products (4), as last amended by Directive 87/20/EEC (5),

HAS ADOPTED THIS DIRECTIVE:

CHAPTER I

GENERAL PROVISIONS

Article 1

This Directive lays down the principles and guidelines of good manufacturing practice for veterinary medicinal products whose manufacture requires the authorization referred to in Article 24 of Directive 81/851/EEC.

Article 2

For the purposes of this Directive, the definition of medicinal products set out in Article 1 (2) of Council Directive 65/65/EEC (6), and the definition of veterinary medicinal products set out in Article 1 (2) of Directive 81/851/EEC, shall apply.

In addition,

— 'manufacturer' shall mean any holder of the authorization referred to in Article 24 of Directive 81/851/EEC,

— 'qualified person' shall mean the person referred to in Article 29 of Directive 81/851/EEC,

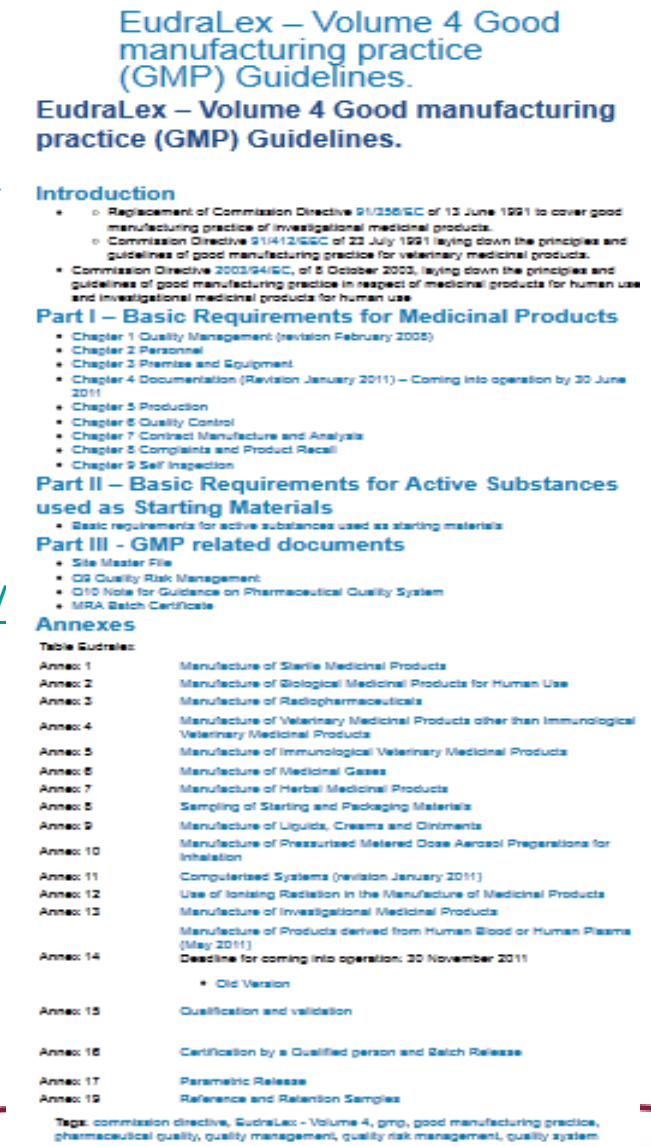
(1) OJ No L 317, 6. 11. 1981, p. 1.
(2) OJ No L 373, 31. 12. 1990, p. 15.
(3) OJ No L 373, 31. 12. 1990, p. 26.
(4) OJ No L 317, 6. 11. 1981, p. 16.
(5) OJ No L 15, 17. 1. 1987, p. 34.
(6) OJ No 22, 9. 2. 1965, p. 369/65.

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)

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



EudraLex – Volume 4 Good manufacturing practice (GMP) Guidelines.

EudraLex – Volume 4 Good manufacturing practice (GMP) Guidelines.

Introduction

- Replacement of Commission Directive 91/356/EC of 13 June 1991 to cover good manufacturing practice of investigational medicinal products.
- Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.
- Commission Directive 2003/94/EC, of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

Part I – Basic Requirements for Medicinal Products

- Chapter 1 Quality Management (revision February 2013)
- Chapter 2 Personnel
- Chapter 3 Premise and Equipment
- Chapter 4 Documentation (Revision January 2011) – Coming into operation by 30 June 2011
- Chapter 5 Production
- Chapter 6 Quality Control
- Chapter 7 Contract Manufacture and Analysis
- Chapter 8 Complaints and Product Recall
- Chapter 9 Self Inspection

Part II – Basic Requirements for Active Substances used as Starting Materials

- Basic requirements for active substances used as starting materials

Part III - GMP related documents

- Site Master File
- Q9 Quality Risk Management
- Q10 Note for Guidance on Pharmaceutical Quality System
- MRA Batch Certificate

Annexes

Table Eudralex:

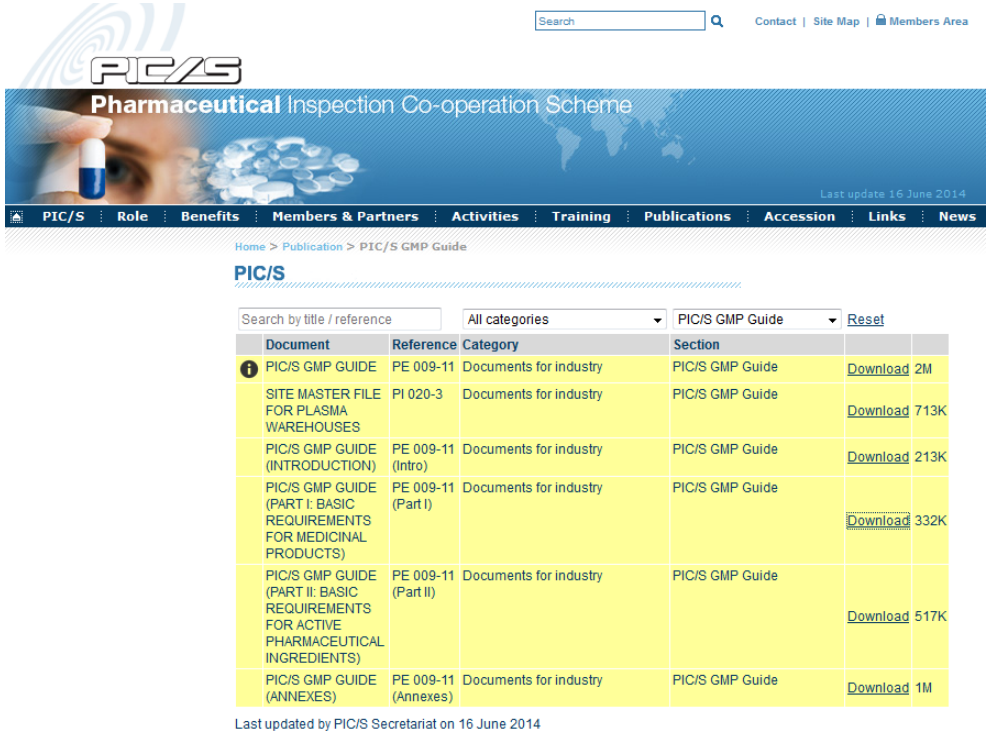
Annex 1	Manufacture of Sterile Medicinal Products
Annex 2	Manufacture of Biological Medicinal Products for Human Use
Annex 3	Manufacture of Radiopharmaceuticals
Annex 4	Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products
Annex 5	Manufacture of Immunological Veterinary Medicinal Products
Annex 6	Manufacture of Medicinal Gases
Annex 7	Manufacture of Herbal Medicinal Products
Annex 8	Sampling of Starting and Packaging Materials
Annex 9	Manufacture of Liquids, Creams and Ointments
Annex 10	Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation
Annex 11	Computerised Systems (revision January 2011)
Annex 12	Use of Ionising Radiation in the Manufacture of Medicinal Products
Annex 13	Manufacture of Investigational Medicinal Products
Annex 14	Manufacture of Products derived from Human Blood or Human Plasma (May 2011) Deadline for coming into operation: 30 November 2011 • Old Version
Annex 15	Qualification and validation
Annex 16	Certification by a Qualified person and Batch Release
Annex 17	Parametric Release
Annex 19	Reference and Retention Samples

Tags: commission directive, EudraLex - Volume 4, gmp, good manufacturing practice, pharmaceutical quality, quality management, quality risk management, quality system

PIC/S

- 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.

46 Participating Authorities in PIC/S



http://picscheme.org/

GMP What's different?

Differences between GMPs

- Minor differences

PIC/S GMP Guide v11	EU GMP Guide (31st Jan'13)
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

Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2015

Summary

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Volume 1

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

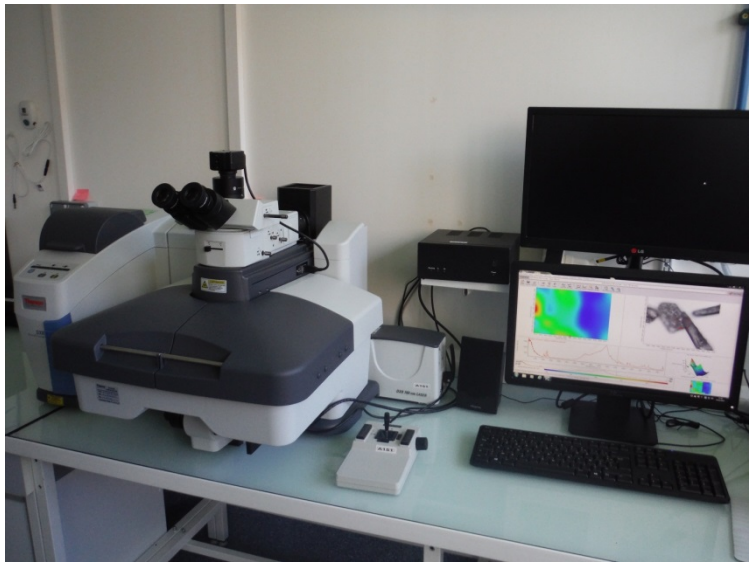
Need for National, regional and international cooperation

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

Internet sales (a concern)

Quality Control Laboratory

- 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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