RESIDUES OF VETERINARY DRUGS IN FOOD, HEALTH ASPECTS AND MAXIMUM RESIDUE LIMITS

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Content

Summary

Veterinary drugs administered to animals contain pharmacologically active substances intended to treat animal diseases. Any active substance has an intrinsic activity but also an intrinsic toxicity. The drug and/or its metabolites will remain in the animal until it is eliminated by urine and/or feces. During this time, any food product derived from the animal treated may contain residues that may be toxic for the consumer.

Methodologies have been put in place at the international level to determine the maximum residue limit (MRL) that is without concern for human health. This value is established for each drug, food commodity and animal species. These MRLs will be the basis to determine when products derived from the animal will be safe for the consumer

and will enable to establish a "withdrawal period" after the treatment of animals for the products of animal origin, before any product can be consumed.

The MRL is also the basis for the control of residues that is performed by the competent authorities.

This paper will describe the role of international organizations in the establishment of MRLs and will give a general outline of the methodology used for setting MRLs and withdrawal periods. It will also review the main problems linked with the establishment of MRLs and will address the residue control plans.

1. Introduction

Veterinary Medicinal products are used for the prevention or treatment of animal diseases. Once administered to the animals the active ingredient or metabolites will diffuse and remain in the body according to the pharmacokinetic properties of the drug, the route of administration, the dose, the duration of treatment, the medicinal product formulation.

Therefore, products from animal origin (meat, milk, eggs and honey) may be contaminated with residues of veterinary drugs that may have adverse effect on human health.

In order to avoid any risk for the consumer, two assessment processes are implemented. At the active ingredient level, Maximum Residue Limits (MRLs) are defined according to risk analysis principles.

At the Veterinary product level, an appropriate withdrawal period is established in order to ensure that food from animal origin may be consumed without risk.

In order to ensure the efficiency of the system, a control of residues is performed by the competent authorities. If residues represent an important issue for human health, they may also be of concern with regard to international trade.

This paper will describe the role of international organizations in the establishment of MRLs and will give a general outline of the methodology used for setting MRLs and withdrawal periods. It will also review the main problems linked with the establishment of MRLs and will address the residue control plans.

2. Marketing Authorization Process and Maximum Residue Limits

As a general rule, a veterinary medicinal product needs to be authorized by the responsible competent authority before it can be marketed and used. The application submitted by the future Marketing Authorization Holder should be accompanied by a comprehensive set of data ensuring the quality, the safety and the efficacy of the veterinary medicinal products.

For Veterinary medicinal products intended to be used in food producing animals, studies should be performed in order to determine when the animal products will be safe for the consumer following the end of the treatment. This period of time is defined as the withdrawal period.

Definitions (CAC- 1993)

Withdrawal Time, Withdrawal period:
"This is the period of time between the last administration of a drug and the collection of edible tissue or products from a treated animal that ensures the contents of residues in food comply with the maximum residue limit for this veterinary drug."

The withdrawal period is based on established Maximum residues limits. In a number of countries, Maximum residue limits should be established before any Marketing Authorization dossier can be submitted to the authorities.

Maximum residue limits of veterinary drugs may be defined at the national/regional or international level. In that case, it is established by the Codex Alimentarius

Maximum Residue Limit for Veterinary Drugs (extract):
"It is the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food."

Residues of Veterinary Drugs: Include the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the veterinary drug concerned

3. Maximum residue limits

3.1. International Standard Setting Bodies

3.1.1. Codex Alimentarius

The Codex Alimentarius Commission was created in 1963 by the Food and Agriculture Organisation (FAO) and the World Health Organisation (WHO) to develop food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme. The main purposes of this Programme are to protect health of the consumers, to ensure fair trade practices in the food trade, and to promote coordination of all food standards work undertaken by international governmental and non-governmental organizations.

The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) is the Codex committee in charge of the establishment of Maximum residue limits.

According to CCRVDF terms of reference, its mandate is:
(a) to determine priorities for the consideration of residues of veterinary drugs in foods;
(b) to recommend maximum levels of such substances;

(c) to develop codes of practice as may be required; and,
(d) to consider methods of sampling and analysis for the determination of veterinary drug residues in foods.

The World Trade Organisation through the Sanitary and Phytosanitary Agreement (SPS agreement) recognizes the standards, guidelines and recommendations of the Codex Alimentarius. Therefore MRLs established by the Codex Alimentarius will serve as reference for any trade problems regarding food safety.

In 2011, MRLs have been established for 60 drugs by the CCRVDF and adopted by the commission of the Codex Alimentarius (CAC).
The responsibility of CCRVDF is to provide advice on risk management concerning residues of veterinary drugs while the responsibility for risk assessment lies primarily with the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

3.1.2. JECFA

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).
JECFA serves as an independent scientific committee which performs risk assessments and provides advice to FAO, WHO and the member countries of both organizations. The requests for scientific advice are for the main part channeled through the Codex Alimentarius Commission in their work to develop international food standards and guidelines under the Joint FAO/WHO Food Standards Programme.

The methodology for the establishment of MRLs is described in a guideline developed under the International Programme on Chemical Safety (IPCS): Principles for the Safety Assessment of Food Additives and Contaminants in Food (EHC 70). While this monograph remains valid, FAO and WHO initiated a project to update, harmonize and consolidate principles and methods used by JECFA and Joint FAO/WHO Meetings on Pesticide Residues (JMPR) for the risk assessment of food additives, food contaminants, natural toxicants and residues of pesticides and veterinary drugs. The monograph EHC 240: Principles and methods for risk assessment of chemicals in food is the outcome of that project. This monograph addresses the key issues considered by JECFA and JMPR in their food chemical risk assessments.

3.2. Methodology for the Establishment of Maximum Residue Limits

As part of the Codex definition of MRLs, the principles of the methodology used in establishing MRLs is defined:
“The MRL is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.

When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available."

The first step for establishing MRLs is the establishment of the Acceptable Daily Intake.

In order to establish the reference point for the hazard characterization and then the ADI, a set of toxicological studies should be available.

3.2.1. Data Needed

International guidelines are available for describing the toxicological studies needed. The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) establishes and implements harmonized technical requirements for veterinary medicinal products in the VICH regions (EU-Japan-USA). Safety guidelines are available for the evaluation of the safety evaluation of veterinary drug residues in human food. VICH guidelines refer and take into account Organisation for Economic Co-operation and Developement (OECD) Guidelines for testing of Chemicals.

These studies may be in vitro studies (using cultured organisms or cells or tissue preparations) or in vivo studies in laboratory animals or humans. Short-term and long-term tests for general systemic toxicity are usually conducted. The extent of toxicological testing required depends on the nature and use of the substance under consideration. Not all tests will necessarily need to be conducted in order to reach a conclusion on the risk assessment for a particular substance.

All these tests should be conducted in a manner that best relates to human exposure scenarios. Dose selection should take into account the anticipated human exposure, the frequency and the duration of exposure. For substances present in foods, administration of the substance in repeated-dose animal studies is usually by diet, gavage or drinking-water. Ideally, the dose levels selected are such that toxic effects, but not death or severe suffering, are produced at the highest dose level, with lower dose levels producing graded responses and no adverse effects at the lowest dose level.

Usually the basic classical toxicological studies are provided:

- Single dose toxicity

Single dose toxicity studies to assess acute toxicity are not required as only chronic toxicity is relevant for the assessment of consumer safety, but studies available may be provided.

- Repeated dose toxicity

Usually, repeated dose toxicity is assessed trough 90 days studies and Chronic toxicity studies

Repeated-dose toxicity testing is performed to define toxic effects based on repeated and/or cumulative exposures to the compound and/or its metabolites, the incidence and

severity of the effect in relation to dose and/or duration of exposure, the doses associated with toxic and biological responses. The length of the period of exposure shall be critically reviewed considering possible exposure to residues of human consumers.

Repeated dose (90-days) studies should be conducted in a rodent and a non-rodent species with the aim to identify target organs and toxicological endpoints and provide information to determine dose levels for chronic studies but also to identify the most appropriate species for chronic studies, and, identify a No-observed-effect level (NOEL). Further information is given in VICH Guideline 31: Safety Studies for Veterinary Drug Residues in Human Food: Repeat Dose (90-days) Toxicity Testing. Studies should be conducted in accordance with OECD Guidelines 408 (rodent) and 409 (non-rodent).

Chronic toxicity testing is conducted on a period of normally 12 months and should be conducted, in at least one species. This should be the most appropriate species chosen on the basis of all available scientific data, including the results of the 90-days studies. The default species is the rat. Further information is given in VICH Guideline 37, Safety: Repeat-Dose (Chronic) Toxicity Testing. The study should be conducted in accordance with OECD Guideline 452 (Chronic Toxicity Studies). Gross necropsy and histopathological examinations should be performed in accordance with details in the OECD 90-day toxicity study guidelines 408 (rodents) and 409 (non-rodents).

- Reproductive toxicity including developmental toxicity

Pharmacologically active substances can adversely influence reproductive performance of exposed adults as well as the normal development of their progeny. Tests for effects on reproduction are carried out with the objective to discover potential effects on male and female reproductive performance, such as gonadal function, estrus cycle, mating behavior, conception, parturition, lactation, weaning and on the growth and development of the offspring. These studies may also provide information about adverse developmental effects such as teratogenesis and serve as a guide for subsequent tests.

- Study of the effects on reproduction

The aim of the study is to detect toxic effects on fertility in males and females and on other reproductive functions. Such data should usually be provided by a two-generation study in at least one species, usually a rodent. The oral route of administration should be used. The drug under study is administered to males and females for an appropriate time prior to mating. Males should be dosed during growth and for at least one spermatogenic cycle; females should be dosed for at least two oestrus cycles. Administration is continued until weaning of the second generation (F2-generation). Each test group should yield a sufficient number of pregnant females at or near term. Additional information is available in VICH Guideline 22; Safety Studies for Veterinary Drug Residues in Human Food: Reproduction Studies. Advice on the conduct of two-generation reproduction studies is available in OECD Test Guideline 416.

- Study of developmental toxicity including teratogenicity

The objective of this study is to detect any adverse effects on the pregnant female and the development of the embryo and fetus as a result of exposure from implantation through the entire gestation period. Such effects include enhanced toxicity in the pregnant females, embryo-fetal death, altered fetal growth and structural abnormalities and anomalies in the fetus. VICH Guideline 32 (Safety Studies for Veterinary Drug Residues in Human Food: Developmental Toxicity Testing) recommends a tiered approach. This starts with testing in the rat. If a negative or an equivocal result for teratogenicity is observed, another developmental toxicity study should be conducted in a second species, preferably the rabbit. If the rat study is positive for teratogenicity, a study in a second species is not necessary except where a review of all the core studies indicates that the ADI would be based on the rat teratogenicity. In this case a study in a second species would be required to determine the most sensitive species for this endpoint. Advice on the conduct of developmental toxicity studies is available in OECD Test Guideline 414.

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World Health Organization Environmental Health Criteria 240 Principles and Methods for the Risk Assessment of Chemicals in Food, WHO 2009 http://www.who.int/foodsafety/chem/principles/en/index.html (Accessed on 12/09/2011) [This document update, harmonize and consolidate principles and methods used by JECFA and JMPR for the risk assessment of food additives, food contaminants, natural toxicants and residues of pesticides and veterinary drugs.]

Biographical Sketches

MOULIN Gérard, Deputy Director of the National Agency for Veterinary Medicinal Products (since 2008) Head of Marketing authorization Department (2005-2008) Director Delegate to International Affairs (2003 – 2005 Head of Pharmaceutical Assessment Unit (1995 -2002), ANMV/Anses, Fougères, France

National level:

- Commission for Marketing Authorization of Veterinary Medicinal Products (CAMM)- 1984 - 2007
- Summary of Product Characteristics Working Party (CAMM) - 1991
- Quality Working Party (CAMM) - 1994
- Use of Antibiotics in Veterinary Medicinal Products and Public Health Working Party – INVS – 1999
- Antimicrobial therapy in Food Producing Animals Working Party (CAMM) – 2002
- Availability of Veterinary medicinal Products Working Party – 2001 -2005
- AFSSA Working Party on antimicrobial resistance: Antimicrobial Veterinary usage, antimicrobial resistance and human health consequences - 2004-2006
- Technical Veterinary Group (GTV) working party on Prudent use of Antimicrobials - 2008-2010

European level:

Legislation activities:

- Working Party of the Veterinary Pharmaceutical Committee on Recasting of the Veterinary Pharmaceutical Legislation - Brussels – Member 1995-1996
- Steering committee on implementation of the variation regulation – London – Member 2008 – 2011
- Task Force on the review of the legislation – HMA – Head of Medicinal Agencies – Rapporteur 2008 -2010
- CVMP Working Party on the review of Legislation – Member - London – 2009 - 2010

Assessment:

- Veterinary Mutual Recognition Facilitation Group (VMRF) – London - Member 1997- 2000 (**Chairman** during the French presidency 2nd semester 2000)
- Committee for Veterinary Medicinal Products (CVMP) – London – Member 1997-2001 **Vice Chair** 2001 – 2002, **Chairman** December 2002 – June 2010
- Strategic Planning group (CVMP) – London - **Chairman** 2001-2002 – Member 2002-2008
- Quality Working Party of CVMP- Brussels – Member 1994-1995
- Availability of medicines and MRL's risk assessment policy - Ad hoc Working Party (CVMP) - London - Member 1999 - 2004
- Summary of Product Characteristics - Ad hoc Working Party (CVMP) - London **– Chairman** 1999
- Scientific advice working party (CVMP) – London - Member 2004 – June 2010
- Benefit risk ad hoc Working Party (CVMP) – London - **Vice chair** 2005 -2008
- Task Force on Community Referrals (CVMP- CMDV) – London – Member 2009 – 2010

Antimicrobial Resistance:

- Interagencies Steering Committee (EFSA/EMA/ECDC/SCENIHR) – joint scientific opinion on antimicrobial resistance focused on infections transmitted to humans from animals and food (zoonoses) - **Chairman** - 2008- 2009
- Technical Consultative Group (TCG) for Setting up the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project – Member 2010 -2011
- European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) – Expert from 2009 – 2011

Telematics

- Telematic Steering Committee - 2000-2005
- Telematic management committee Brussels -2000
- Steering Committee for the feasibility Study for a Telematic Network between Administrations – Brussels - 1994

International level

Codex Alimentarius:

- CCRVDF (Codex Committee on Residues of Veterinary Drugs in Food) - **Head of the French Delegation – Chairman** of the working group on risk management 2003 – 2010
- TFAMR (Codex Task Force on Antimicrobial Resistance) - **Head of the French Delegation – Co-Chair** of the working group on risk management 2007 – 2010

JECFA

- JECFA (Joint FAO/WHO Expert Committee on Food Additives)- Rome - expert 2002- 2005

OIE (World Organisation for Animal Health)

- OIE collaborating Center on veterinary medicinal products - 1997 - 2011
- OIE adhoc group on antimicrobial resistance - 2003 – 2011
- OIE ad'hoc group Aquaculture, antimicrobial resistance 2009 -2011
- Organisation of Worldwide conferences on Veterinary medicinal products (First held in Africa in march 2008, **Chair** of the scientific committee)
- OIE Training of focal points for Veterinary Medicinal Products – 2011
- WAEMU: West African Economic and Monetary Union - Consultant – 2002 – 2011

WHO (World Health Organisation)

- Global patient safety challenge on Antimicrobial resistance – expert - 2010
- WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) – 2009 -2011

International cooperation on harmonisation of technical requirements for registration of veterinary medicinal products (VICH)

- VICH steering Committee – Member and representative of CVMP – 2008 - 2010

OIE/FAO/OMS

- Expert in various consultations on antimicrobial resistance: Geneva (2003), Rome (2008), Paris (2009)

Publications : 40 original publications and communications on research themes quoted above and more than 200 reports and guidelines concerning veterinary medicinal products.