Veterinary Medicinal Products Authorised for Rabbits in the European Union
Causes for Insufficient Availability and Consequences on Human and Animal Health

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List of Abbreviations

ADI	Acceptable Daily Intake
AVC	Association of Veterinary Consultants
BEUC	European Bureau of Consumer Unions
CMS	Concerned Member State
COGECA	General Committee for Agriculture Cooperation in the European Union
COPA	Committee of Agricultural Organisation in the European Union
CVMP	Committee for Medicinal Product for Veterinary Use
EC	European Commission
EFSA	European Food Safety Authority
EIA	Environmental Impact Assessment
EMA	European Medicines Agency
EPEC	European Policy Evaluation Consortium
EU	European Union
FEDESA	European Federation of Animal Health
FVE	Federation of Veterinarians of Europe
GPUE	Pharmaceutical Group of the European Union
IFAH	International Federation for Animal Health Europe
HMA	Heads of Medicines Agencies
MRL	Maximum Residue Limit
MRP	Mutual Recognition Procedure
MUMS	Minor Uses Minor Species
NOEL	No-Observable-Effect-Level
OIE	World Organisation for Animal Health
SME	Small and Medium Sized Enterprise
SmPC	Summary of product characteristics
T	Tons
TEC	Tons in Carcass weight Equivalent
VMP	Veterinary Medicinal Product
VMRFG	Veterinary Mutual Recognition Facilitation Group

1. Introduction

Since the last decades the European legislation of veterinary medicinal products (VMPs) became more complex and the requirements for the marketing authorisations have considerably increased. With a view to ensure a high level of safety and efficacy for target animals and protection of consumers, the main amendments of the Community legislation of VMPs followed two lines: firstly an increase of compulsory comprehensive studies to demonstrate the quality, the safety and the efficacy of VMPs and secondly the obligation to establish a maximum residue limit (MRL) for all pharmacologically active substances intended to be used in food-producing species. The new regulation stated indeed that a VMP may be authorised or used in food-producing animals only if pharmacologically active substances contained therein have been assessed as safe according to the Council Regulation (EC) No 2377/90 [1] laying down a Community procedure to evaluate the safety of residues (Article 6 (1) of Directive 2001/82/EC [2]). As a result, the Member States were requested to withdraw the marketing authorisations for all old VMPs containing substances which have not been included in Annexes I (MRL established), II (MRL considered unnecessary) or III (provisional MRL established) of the Regulation by 1st January 2000 [1].

This increase in requirements led of course to an increase in costs for the development of new VMPs, as well as for the maintenance of existing marketing authorisations, forcing many companies to abandon the development of new products, or to no longer defend existing marketing authorisations when return of investment is not given. As a result, many companies decided to withdraw the marketing authorisations of those VMPs with limited sales potential or to give up some claims rather than to perform additional studies in order to meet the new requirements of product quality, safety and efficacy. For obvious reasons, VMPs for minor use and minor species (MUMS) were particularly concerned and often, when investments were made to defend the marketing authorisation, only the indications for the main species were maintained. Thus, conjointly to the growing developments in regulation, the lack of availability of a range of VMPs, particularly VMPs for MUMS, became a significantly rising concern in the European Union (EU).

The European Commission (EC) and the European Medicine Agency (EMA) with its Committee for Medicinal Products for Veterinary Use (CVMP) became concerned in regard of the seriousness of the problem since the end of the nineties, corresponding with the approaching of the 1st January 2000, deadline for the establishment of MRLs for all pharmaceutically active substances used in VMPs for food producing species. Discussions and consultations in view to provide provisions for increased availability began as early as

1998. Pre-1st January 2000, extreme efforts have been made to establish MRLs for as many old substances as possible and to identify which indications in which species will not be covered with authorised VMPs in the future (EMEA/CVMP/151/99-FINAL [3], EMEA/CVMP/731/99-FINAL [4], EMEA/CVMP/130/00-FINAL [5], EMEA/CVMP/411/0-FINAL [6]). Despite these efforts, more than 100 well known pharmacologically active substances have been identified as not complying with the residue Regulation and consequently, all VMPs containing these substances have been prohibited in the Community (COM(2000) 806 final [7]).

A European consultation conference on this important topic hosted by the European Commission took place in Brussels in July 1999. This conference successfully highlighted the main problems and several recommendations were reviewed and discussed. Following this conference, a task force to consider the recommendations and to prioritise in detail the actions that have to be taken has been created by the EMA. The task force consisted of representatives of the EMA, the EC, the CVMP, the Veterinary Mutual Recognition Facilitation Group (VMRFG) and Interested Parties (a representative of the Federation of Veterinarians of Europe (FVE), a representative of the European Federation of Animal Health (FEDESA) and a third seat to be shared amongst the Association of Veterinary Consultants (AVC), the Pharmaceutical Group of the European Union (GPUE), the Committee of Agricultural Organisation in the European Union (COPA), the General Committee for Agriculture Cooperation in the European Union (COGECA) and the European Bureau of Consumer Unions (BEUC), depending on the agenda). The task force met four times between October 1999 and July 2000. The main recommendations agreed upon were the following (EMEA/V/PHJ/uh/33379/99/Rev1/Corr [8], EMEA/V/38491/99 [9], EMEA/V/7306/00 [10], EMEA/V/18383/00 [11]):

- a facilitating extrapolation of MRLs to minor species
- a more flexible approach for the use of the “cascade”
- the establishment of a policy analogous to “orphan drugs” for human use in the veterinary sector
- a new provision for medicines for horses
- more financial incentives for research and development
- the installation of a fast-track procedures under mutual recognition.

Based on these recommendations, the EC laid down a Communication to the Council and the European Parliament on availability of veterinary medicines [7], proposing short term (MRL extrapolation) and medium term (revision of existing legal instruments) measures. In

parallel the CVMP communicated its concerns and proposals on open issues in several documents:

- A CVMP note for guidance to facilitate establishment of MRLs for minor species coming into effect in April 2001 (EMEA/CVMP/187/00-FINAL [12]). This note for guidance calls for a possibility to extrapolate the MRLs from major to minor species, and for 3 major species to all food producing species with a view to reduce a part of the development costs of the new drugs by maintaining high safety margins for public health.
- Furthermore, in January 2002 the CVMP approved the extrapolation of existing MRLs to all food producing species (including fish) for 12 substances for which identical or slightly different MRLs had been set in three major species (EMEA/CVMP/069/02 [13], EMEA/CVMP/065/02 [14]).
- Further recommendations have been communicated by the CVMP and its Efficacy Working Part (EWP) in the "Position Paper regarding availability of products for minor uses and minor species" (EMEA/CVMP/477/03/Final [15]), such as data requirements for marketing authorisations for MUMS products, free scientific advice, and extrapolation of MRLs to minor species.
- Guidelines on data requirements for VMPs intended for MUMS on quality, safety and residues, efficacy and target animal safety have been adopted by the CVMP in 2006, with the aim to establish appropriate standards and reduce requirements (EMEA/CVMP/QWP/128710/2004 [16], EMEA/CVMP/SWP/66781/2005 [17], EMEA/CVMP/EWP/117899/2004 [18]).

All the initiatives taken have contributed to moderate the problem of lack of availability of VMPs in the EU but, unfortunately, they have not managed to completely solve the problem. As already mentioned above, this concern is more acute for VMPs for MUMS with limited sales potential. Rabbits (food-producing and pet rabbits) are a typical example of target species, which is highly affected by the lack of availability in the EU, because of their low financial value and the reduced sales potential. Thus, the first part of this thesis aims at describing the current availability of VMPs authorised for rabbits in France, France being representative of the Member States of the EU. A second part aims at discussing the principal causes for the lack of availability of VMPs, which account for the current situation. Finally, the consequences of the lack of availability of VMPs on animal and human health, as well as the future perspectives to improve the current situation are discussed.

2. Current Situation in France

2.1 Rabbit Population

Having for a long time bred rabbits only for their meat and fur, man has attached to them more affective and sentimental value within the last decades. Today, rabbits are indeed fully considered as pets. Being a valuable model for toxicological studies, they are also extensively used in laboratory work.

According to a scientific report of the European Food Safety Authority (EFSA) adopted in 2005 [19], European rabbit meat production was estimated to be around 520,000 TEC (Tons in Carcass weight Equivalent) in the EU and is concentrated in the Mediterranean Countries. Differences in culinary and cultural consumption habits are important among different European regions. With about 80'000 tons (T) of carcass produced each year, France is the fourth largest rabbit meat producer in the world, after China (450'000 T), Italy (225'00 T) and Spain (108'000 T) [20]. The yearly consumption of rabbit meat in France is, however, rather moderate with an estimated 1.2 kg per person, thereby representing only 1.2% of meat consumed [19]. Two thirds of French rabbit meat is produced on commercial farms, while the remaining production comes from in-house farms [19]. Approximately 10% of rabbit meat produced in France is exported. With 90% of the entire export volume, the Member States of the EU and specifically Italy, Belgium and Spain, are the principal importers of French rabbit meat. In return, but to a lesser extent, a part of the rabbit meat consumed in France is imported from several Member States of the EU such as the Netherlands, Germany, and Hungary [21].

Even though meat remains the main goal of rabbit production, rabbits are also bred for their fur. France is the first producer of rabbit fur in the EU with an estimated annual skin production of around 70 million [22].

According to the Report from the Commission to the Council and the European Parliament regarding the statistics on the number of animals used for experimental and other scientific purposes in the Member states of the EU [23], a total number of 12.1 million animals were used in 2008 in the EU. Rabbits were estimated to account for 2.78% thereof, corresponding to roughly 335'000 animals, and nearly one third of these animals were used for experiments in France alone (96'427 rabbits). In comparison with meat and fur-producing rabbits, the population of rabbits for laboratory work is small but not negligible.

The number of pet rabbits in the EU is roughly estimated to be above 15 million [15]. A precise estimation is unfortunately not possible because of the missing data from individual countries. However, an increasing pet rabbit population is a trend, and according to the veterinary practitioners in France, they are increasingly important in the daily consultations. Indeed, about 3.7% of French households own a pet rabbit and consult regularly the veterinarian with their animal [24].

Even though their numbers are estimated to be high in the European Union (>260 million), meat- and fur-producing rabbits are classified as a minor species due to their low financial value. Pet rabbits are also considered a minor species due to the low estimated number of animals in the EU [15].

2.2. Rabbit Diseases and Health Conditions

Compared to other animals, rabbits are rather sensitive and susceptible to a lot of different diseases. Two principal systems are commonly concerned: the respiratory system (e.g. pasteurellosis, bordetellosis) that predominates in adults, and the digestive system (e.g. epizootic rabbit enteropathy, coccidiosis, colibacillosis, clostridiosis), more frequently affected in growing rabbits. Gastro-enteric diseases have mainly bacterial origin (enterobacteria like Escherichia coli, Salmonella spp., Klebsiella spp. and Clostridium) but can also be caused by viral agents (rotavirus) or parasites (Eimeria spp.). Digestive diseases have significantly increased in the last 15 years in the EU becoming the most common cause of mortality [19]. The second common cause of morality is respiratory disease mainly caused by Pasteurella spp. and Bordetella bronchiseptica. Myxomatosis and Rabbit haemorrhagic disease (RHD) are the main viral diseases encountered in rabbits and lead to epidemic infections with high mortality rates. Fortunately both diseases can easily be prevented by vaccination, commercial products being available in the EU. Further common diseases or health conditions found in rabbits include ear infection, scabies, abscesses, obesity, nutritional diseases, dental problems (malocclusion, infection) and sore hocks, which are most frequently due to poor hutch hygiene. Rabbits are also often infested with worms (e.g. Passalurus ambiguus) which are transmitted easily through contact with infected rabbit's coat or living quarters [25], [26].

These common ailments are almost always the result of poor husbandry and environment coupled with the onslaught of pathogenic agent (bacteria, viruses or parasites). Therefore, both prevention, beginning with a correct housing and proper nutrition, and treatment with VMPs are essential to assure rabbits' welfare. Unfortunately, like for almost all other minor species, the availability of VMPs authorised for rabbits in the EU is insufficient.

2.3. Availability of VMPs Authorised for Rabbits

The number of authorised VMPs in France decreased from 7'800 in 1975 to 3'063 in 2005. Conjointly to the diminution of the number of authorised VMPs, there has been a concentration of manufacturers, and the number of enterprises decreased from 350 to 104. The first 10 enterprises provided 80.7% of the French veterinary product market in 2002 and 144 VMPs represented 50% of the whole turnover of VMPs in France [26]. The decrease in VMPs illustrates an obvious reduction of the therapeutic arsenal for all target species. As example of the lack of availability of VMPs in France, a list of antimicrobials considered as essential for rabbits by the World Organisation for Animal Health (OIE) [28] and their availability for food-producing rabbits in France is presented in Table 1.

Table 1: List of essential antimicrobials for food-producing rabbits and their availability on the French market

Antimicrobial Family	Indications	Active Substances	Authorised for rabbits in France
Aminoglycosides	Septicaemias digestive, respiratory and urinary diseases	Spectinomycin	No
		Streptomycin	No
		Dihydrostreptomycin	No
		Neomycin	Yes
		Paromomycin	No
		Apramycin	Yes
		Gentamycin	No
Anamycin-Rifamycins		Rifaximin	No
Ionophores	Coccidiosis (Eimeria spp.)	Lasalocid	No
		Salinomycin	No
Macrolides	Respiratory diseases	Tulathromycin	No
		Erythromycin	Yes
		Spiramycin	No
		Tylosin	No
		Tilmicosin	Yes
Orthosomycins	Digestive diseases	Avilamycin	No
Phenicols		Florphenicol	No
Pleuromutilins	Enterocolitis	Tiamulin	Yes
Polypeptides / cyclic	Septicaemias colibacillosis, salmonellosis	Bacitracin	Yes
		Colistin	Yes
		Polymixin	Yes
Quinolones	Septicaemias colibacillosis respiratory diseases	Flumequin	Yes
		Norfloxacin	No
		Difloxacin	No
		Enrofloxacin	No
		Marbofloxacin	No
Sulfonamides	Respiratory and digestive diseases, coccidiosis	Sulfadimerazin	No
		Sulfadimethoxine	Yes
		Sulfadimidine	Yes
		Sulfaquinoxaline	
Sulfonamides+ Diaminopyrimidines		Trimethoprim + Sulfonamide	Yes
Tetracyclines	Septicaemias, respiratory and digestive diseases	Chlortetracycline	Yes
		Doxycycline	No
		Oxytetracycline	Yes
		Tetracycline	Yes

Sources:
- Index of authorised VMPs in France, National Veterinary Medicines Agency [29]
- Dictionnaires des médicaments vétérinaires (DMV) [30]

The table shows an obvious lack of availability on the French market of several antimicrobial molecules considered as essential for rabbits by the OIE. Pet rabbits are not really better off since enrofloxacin is the only active substance listed above as not authorised for food-producing rabbits which is authorised for pet rabbits. The situation is even worse for dewormers, insecticides and antifungals since almost no VMP against parasites/insects is currently authorised for rabbits in France [29], [30]. France is not an exception and the same situation is to be found in other Member States of the EU, situation being even worse in small countries. One of the most preoccupant lacks of availability concerns the treatment of scabies. The disease which is very uncomfortable for the contaminated animals has indeed a very high morbidity and none of the following substances potentially effective against scabies parasites are currently authorised for rabbits: rotenone, fenvalerate, dympilate, amitraz, avermectine [27]. According to Annex 3 of the Report of Task Force of the Heads of Medicines Agencies (HMA) on availability of VMPs published in 2007 [31], VMPs for rabbits identified as being most needed by the FVE are medicines for the treatment of scabies and enterocolitis.

Other VMPs which are frequently used in pet rabbits, but very rarely in farmed domestic rabbits due to the high cost of the therapy, are sedatives, analgesics and anaesthetics. Pet rabbits are often stress-sensitive when handled and sedation is sometimes necessary for procedures, such as radiography, deep ear cleaning and dentistry. Common surgical procedures like spay, castration, and orthopaedic procedures require general anaesthesia. Many tranquilizers, sedatives, analgesics and anaesthetics are known to be safe for rabbits [32], but almost none of them are authorised for rabbits in France [29], [30].

3. Causes for the Lack of Availability of VMPs

3.1. Increasing Regulatory Requirements

3.1.1. Data requirements for all target species

The principal cause for the lack of availability of VMPs in the EU is found in increasing regulatory requirements. Directive 81/851/EEC [33], governing the authorisation of the veterinary medicinal products was adopted in 1981 and defined common requirements for manufacturing and marketing authorisations. Conjointly, Directive 81/852/EEC [34] madding dispositions in view to harmonise the analytical, pharmaco-toxicological and clinical tests and trials of VMP has also been adopted. At that time, the marketing authorisations were granted only on a national basis and despite the harmonisation of assessment's criteria within the EU, different decisions were made for the same product in the different Member States. Therefore, a new system for licensing veterinary medicinal products was proposed by the Commission and adopted by the Council of Ministers in 1993 [35]. The new system went into force on January 1st 1995 and important consequences were the creation of a European Medicines Evaluation Agency in London and the centralised Community procedure for both veterinary and human medicines. The Community legislation has been frequently and considerably amended over time and with a view of clarification and consolidation, the Directives have been merged in a single text: Directive 2001/82/EC [2] providing the legal framework for the authorisation, manufacturing, marketing, distribution and use of VMPs. Directive 2001/82/EC has then been further amended by Directive 2004/28/EC [36] and Regulation 726/2004 [37] in 2004.

With the evolution of the European legislation, the data requirements to obtain a marketing authorisation for a VMP have increased from a minimum data package to a huge range of comprehensive studies to demonstrate their quality, safety and efficacy. According to Article 12 of Directive 2001/82/EC as amended [2], and its Annex, the application dossier shall indeed consist of administrative information (Part I), and documentation demonstrating the quality (Part II), the safety (Part III) and the efficacy (Part IV) of the VMP. The presentation and the content of the dossier are described in detail in Volume 6B of Notice to Applicant for veterinary medicinal products [38]:

- **Part I : Administrative information**

  Part I shall present administrative information and the summary of the dossier. It consists of an application form with several annexes, the proposed summary of product characteristics (SmPC) and the expert reports on quality, safety and efficacy. For VMPs intended to be used in food-producing species, an expert report on residues is also requested. The expert reports shall provide a critical evaluation of the data presented in the respective parts.

- **Part II : Quality documentation**

  Part II describes in detail the composition of the VMP, the manufacturing methods, the control of starting materials, intermediate products (if necessary) and finished products, the stability of the product and the specific measures concerning the prevention of the transmission of animal spongiform encephalopathy. Sufficient details of the analytical test procedures shall be given in order to enable the competent authorities or official laboratories to repeat them and finally, all procedures shall be validated.

- **Part III**: **Safety documentation**

  Part III consists of safety (Part IIIA) and, if the VMP is intended for food-producing animals, of residue documentation (Part IIIB). Residue documentation will be discussed in detail in the next chapter (3.1.2. Additional data requirements for food-producing species). The main goal of the safety documentation is to demonstrate the potential hazard taken by the persons who may come into contact with the product (user safety) and the potential risks for the environment from the use of the product (environmental impact assessment). The safety of the VMP on target species should rather be presented in Part IV. Part III A should contain the following information:

  - **Pharmacological and toxicological studies:** description and results of pharmacological (pharmacokinetic and pharmacodynamic) and toxicological studies (single-dose, repeated dose, tolerance, teratogenicity, effects on reproduction, mutagenicity, carcinogenicity).

  - **User safety.** Annex I of Directive 2001/82/EC as amended [2], states that “the safety documentation shall show the potential risk which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal”. The Directive does not give details on data requirements and assessment methods but a “Guideline on user safety

for pharmaceutical veterinary medicinal products" [39] has been adopted by the CVMP to give guidance and advice for the applicant conducting risk assessments on user safety. The user safety shall include the description of potential harmful effects of substances contained in the VMP on the human being and the possible route of exposure (skin contact, inhalation, ingestion, accidental self-injection etc…). Furthermore, the appropriate user warning, which will be included in the SmPC and on the package leaflet, as well as risk management measures shall also be discussed.

- **Environmental impact assessment** (EIA): The requirement for an EIA for VMPs was implemented into the legislation in 1992 by Directive 92/18/EC modifying the Annex to Council Directive 81/852/EEC [34]. This modifying Annex states that the EIA shall be carried out in two phases. The first phase consists of an estimation of the potential exposure of the product (active substances and/or relevant metabolites) to the environment (Phase I assessment). If it is demonstrated in phase I, that the exposure is negligible, the assessment may be stopped here. If however, the potential exposure may induce a hazard for the environment, a Phase II assessment describing the impact of the concerned substances in the soil, water and air, as well as their potential to affect non target species in the environment (aquatic and terrestrial species, organisms) shall be provided. New provisions increasing data requirements concerning the potential effects of the product on the environment have been included in Directive 2001/82/EC as amended [2] and in Regulation (EC) 726/2004 [37].

- **Part IV : efficacy documentation**

  Part IV of the dossier concerns target animal safety and efficacy of the VMP. The results of all preclinical (pharmacokinetic, pharmacodynamic, target species tolerance studies) and all clinical studies performed in the target species shall be presented here.

3.1.2. Additional data requirements for food-producing species

3.1.2.1. Establishment of MRLs

The Regulation which had the most important impact on the availability of veterinary medicine has been the Regulation (EEC) No 2377/90 [1] adopted in 1990, which established the requirements for MRLs for veterinary medicines. VMPs used in animals, whose tissues and/or products are destined for human consumption may indeed generate residues of parent compounds or metabolites in these food-producing animals. In order to protect the health of the consumer, the Regulation (EEC) No 2377/90 implemented the obligation for all pharmacologically active substances contained in a VMP for food-producing species (incl. excipients with pharmacological activity) to be assessed regarding the safety of their residues. In other terms, a maximum residue limit of pharmacologically active substances which could safely remain in the tissue or food product derived from food-producing animals had to be established. Regulation (EEC) No 2377/90 has recently been replaced by Regulation (EC) No 470/2009 [40] which came into force in June 2009. The principal objective of the new Regulation was to improve the availability of VMPs for food-producing animals in the EU, to simplify the previous legislation and to improve harmonisation with international standards.

The maximum residue limit is commonly expressed in mg/kg or in micrograms/kg. The residues are considered as safe if they cause no adverse health effects when ingested daily by humans over a lifetime. The determination of MRLs is based on the Acceptable Daily Intake (ADI) which may be determined on the basis of toxicological or pharmacological data and may be calculated with the following formula:

ADI (mg/kg bw) = NOEL (mg/kg bw/day) / Safety factor (usually 100)

The lowest no-observable-effect-level (NOEL) is also defined from a variety of toxicological and pharmacological studies and represents the lowest exposure level at which there is no significant increase in the frequency or severity of any effect between the exposed animals and its appropriate control. The most sensitive parameter and the most sensitive test species have to be used. Moreover, often a safety factor of 100 to correct the intraspecies variability (difference in sensitivity within the human population) and the interspecies extrapolation (difference between tested animals and human) is applied. The determination of the MRLs also takes into account the potential consumer intake of residues and the bodyweight of the consumer. The potential consumer intake is determined on the basis of an estimated daily food basket of 0.5 kg of meat (0.5 kg meat comprises: *mammals*: 0.3 kg of muscle, 0.1 kg of

liver, 0.05 kg of kidney, 0.05 kg of fat / *poultry:* 0.3 kg of muscle, 0.1 kg of liver, 0.01 kg of kidney and 0.09 kg of fat) or 0.3 kg of fish + 1.5 kg milk + 0.1 kg eggs + 0.02 kg honey. The arbitrary bodyweight of the consumer has been defined as 60 kg. MRLs are established in such way that the maximum theoretical intake does not exceed the ADI [42].

Where MRL applications had been submitted and assessed by the CVMP, the corresponding substances are listed in Annex I-IV of Regulation 2377/90 [1] according to their MRL status:

- Annex I includes substances for which MRLs have been established.
- Annex II includes substances for which it has been concluded that no MRLs have to be established.
- Annex III includes substances for which provisional MRLs have been established. The substance presents no hazards for the consumer but minor outstanding issues are still open and further data have to be submitted by the applicant within a defined time frame before the substance can be included in Annex I.
- Annex IV includes substances prohibited for food-producing species because they are hazardous for the consumer at whatever limit.

In the new Regulation 470/2009 [40] the classification of pharmacologically active substances remains the same but a single Annex replaces the Annex I, II, III and IV of Regulation No 2377/90. Substances for which the CVMP has concluded that **no MRL evaluation** is required are listed in an “out of scope list” which is to be found in the CVMP publication “Substances considered as not falling within the scope of Regulation (EC) No 470/2009, with regard to residues of veterinary medicinal products in foodstuffs of animal origin” [41]. The list is not exhaustive and includes only substances for which a request for its inclusion has been submitted to the CVMP by a company or a national authority.

To support the evaluation of a new substance with regard to its residues in foodstuffs, new data thus have to be generated by the marketing authorisation holder of VMPs intended for use in food-producing species. Indeed, to establish a MRL for a pharmacologically active substance, a full package of safety and residue data, as described in detail in the Notice to applicants and Guideline “Establishment of maximum residue limit (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin” [42] has to be submitted to the EMA. The information has to be presented in two distinct parts of the dossiers:

- a **safety file** containing the pharmacological (pharmacodynamics and pharmacokinetics), toxicological (toxicity, tolerance, mutagenicity, carcinogenicity) and microbiological (where appropriate) studies carried out with the medicine in laboratory animals. This file includes the determination of the NOEL and ADI.

- a **residue file** composed of all data concerning the formation, nature, behaviour and disappearance of residues after the VMP has been given to a food producing animal, which are necessary to determine the withdrawal period. The file contains, among others, the proposals for MRL, the basis to determine the MRLs (proposal market residue, distribution in edible tissues), the objectives of MRLs and the validated analytical method (basis for official residue monitoring and surveillance).

Additionally, expert reports covering the safety and the residue files have to be included in the application. The application for MRLs has to be evaluated by the CVMP and approved by the European Commission. The MRLs are defined for each food commodities and for each target species. The obtained MRLs are published in the Official Journal of the European Communities and are consequently publicly available.

3.1.2.2. Establishment of withdrawal periods

Once MRLs are established, the withdrawal periods during which the animal must not be slaughtered (or during which milk or eggs must not be taken) for human consumption, have to be determined. The withdrawal period is the time which elapses between the last dose administered to animals and the time when the residues in the tissues or products is lower than or equal to the established MRL. The withdrawal periods depend on the pharmaceutical formulation of the finished product and therefore, shall be assessed during the evaluation of the application for marketing authorisation. In other terms, the MRL is defined for a pharmacologically active substance while the withdrawal periods are determined exclusively for a specific VMP. In order to avoid potential delay which may arise from doubts about the safety of residues, the EMA recommends to applicants to submit the applications for the establishment of MRLs as soon as the necessary documentation is ready, and in any case before the submission of the application for the marketing authorisation. Article 12 of Directive 2001/82/EC as amended [2] states that "*at least six months shall elapse between a valid application for the establishment of MRLs and an application for a marketing authorisation*". The CVMP has published a "Note for Guidance regarding withdrawal periods for animal tissues" [43] and milk [44] with a view to harmonise the approach to the calculation of withdrawal periods throughout the EU.

As already mentioned above, residue documentation shall be included in Part IIIB of the application dossier. This part shall consists of

- A precise identification of the VMP concerned by the application
- Residues studies (pharmacokinetics, depletion of residues, determination of MRLs, establishment of the withdrawals periods for each commodity and each target species)
- Analytical methods (description, validation…)
- Conclusions on the results of residue studies and proposed withdrawal periods for the VMP concerned

A part of these documents are thus the same as those already submitted to the EMA for the establishment of MRLs. The documents shall clearly be identified either as having been already submitted to the EMA or as being new documents supporting the marketing authorisation application.

3.1.3. Consequences of increased data requirements

The main aim of the new legislation providing provisions for new standards for quality, safety and efficacy of VMPs and defining the content of the application dossier for a marketing authorisation (including establishment of MRLs and withdrawal periods) was an increase of the safety to animal, consumer, user and environment. As a result, the quality and the safety of the veterinary medicines have indeed increased and more informative and precise labelling and package leaflets have been introduced on the market. Furthermore, the reliability of the evaluation of the studies has improved and the harmonisation throughout the European Union has increased. However, the implementation of the new legislation with considerable increasing data requirements caused a marked increase of development costs for new VMPs and therefore, significantly contributed to the decreased availability of VMPs in the EU, specifically VMPs for food-producing species. Indeed, since 1st January 2000, after a transitional period of about 10 years foreseen in the Regulation [1], substances which were not exempted from the establishment of MRLs and for which no MRLs have been established (either definitive nor provisional), were no longer allowed for use in food-producing animals. As a result, many of the existing marketing authorisations containing such substances were withdrawn. Because of the high costs of the studies on residues, the industry has had difficulty to apply for the evaluation of substances, especially for the evaluation of substances not promising sufficient return of investment. Moreover, once the substance has been assessed by the CVMP, the results are publicly available and all other pharmaceutical companies can make reference to this. Therefore, not many companies have been ready to invest the financial revenue and time to generate data that can then be used

by competitors. This problem is particularly acute in relation to the availability of medicines for minor uses/minor species (MUMS), because of the limited market and subsequent small return of investment intended for such VMPs. Therefore, several measures which will be described in detail in the following chapter have already been taken by the EC and the EMA to promote the development of VMPs for MUMS, giving incentives to companies which develop such medicines.

3.2. Special Case: MUMS (e.g. Rabbits)

3.2.1. Definitions

There is no legislative definition in the European Union for the term "major and minor species". However, the CVMP made the following classification in their position paper regarding the availability of products for minor uses and minor species [45]:

- **Major food producing species**: cattle (dairy and meat animals), sheep (meat animals), pigs, chicken (including laying hens), salmon
- **Major companion animal species**: cats, dogs

All other species are, by default, considered as minor species. The minor use of a product will be considered on a case-by-case basis, taking into account the prevalence/incidence of the condition or disease, the geographical areas concerned, the importance of the product to avoid animal suffering, ethical considerations and the future market sales. In order to classify the VMPs in MUMS products, the applicant should submit a request for classification to the Veterinary Unit of the EMA. The request is forwarded to the next CVMP meeting for consideration, and the applicant is informed about the outcome immediately following the meeting. There is no fee requested for the classification.

Rabbits are, by default, classified as a minor species. With more than 260 million meat- and fur-producing rabbits in the European Union, the population is very important, but they are nevertheless considered a minor species due to their low financial value. With an estimated population close to 15 million, pet rabbits are also considered a minor species due to the low estimated number of animals in the EU [15].

3.2.2. Fee incentives

Once the classification is confirmed, the following fee incentives are provided to the applicant for a period of up to five years [46]:

- **Free scientific advice**: scientific advice is a key element in order to establish and validate a project-specific strategy and can be requested at any time of the life-cycle of a VMP. Without incentive the fee for a central scientific advice varies from 10’000 to 40’100 Euros, depending on the extent of the request.

- **Fee waiver or fee reduction for MRL applications**: a fee reduction of 50% is applicable for a MRL application for a new active substance (VMP exclusively

intended for MUMS or extension to a minor species where new data is available). The extension of MRLs to an additional minor species without provision of new data is free of change.

- **Centralised marketing authorisation application**: if the VMP is eligible for a centralised procedure, the applicant benefits from fee exemption in case of failure of the validation and, fee reduction for authorisation (50%) and maintenance (75%) of the marketing authorisation.

Small and medium sized enterprises (SME) benefit from additional incentives. The determinant criteria to benefit from a SME status are, the staff headcount, the annual turnover and the annual balance sheet of the enterprise. According to article 2 of Recommendation 2003/361/EC [47], the thresholds for SME are the following:

Medium sized enterprise:	a headcount smaller than 250 employees, an annual turnover ≤ 50 millions or a total annual balance sheet ≤ 43 millions.
Small enterprise:	a headcount smaller than 50 employees, an annual turnover or a total annual balance sheet ≤ 10 millions.
Micro enterprise:	a headcount smaller than 10 employees, an annual turnover or a total annual balance sheet smaller than 2 millions.

SME benefit from 90% reduction for scientific advice (in case of MUMS, outstanding 10% will be waived), scientific services, inspections and applications for an MRL. Furthermore, the payment of the application fees may be deferred until the end of the marketing authorisation procedure. If scientific advice has been used, the payment is due only in case of success (granted marketing authorisation) and, in case of a negative outcome of the validation, SME are exempt from application fees. Moreover, assistance with translations of the product information is provided by the EMA [48].

3.2.3. Reduced data requirements

The acceptable data requirements to demonstrate the quality, the safety and the efficacy of VMPs intended for MUMS are presented in the following CVMP Guidelines on data requirements for MUMS:

- Guideline on quality data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/QWP/128710/2004 [16].

- Guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/SWP/66781/2005 [17].
- Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/EWP/117899/2004 [18].

Article 2 of the Commission Regulation (EC) No 1234/2008 [49] concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products defines the extension of a marketing authorisation as "*a variation which is listed in Annex I of the Regulation and fulfils the conditions laid down therein*". The annex I lists three main categories:

- change to the active substance
- change to strength, pharmaceutical form and route of administration
- other changes, specific to VMPs to be administered to food-producing animals: change or addition of target species.

The addition of a food producing target species is therefore considered as an extension of the marketing authorisation, while the addition of a non-food producing target species is classified as a variation (Type II variation). The extensions defined in Annex I are not considered to fall within the scope of the Regulations on variations [49]. Any application for such a change will follow the same procedure as is necessary for a full marketing authorisation application. The legal basis for an extension application corresponds indeed to the legal basis of the initial application for the VMP. Usually, for an extension to a new food-producing target species, all preclinical and clinical data concerning the new target species have to be submitted. However, if the new species is a minor species, such as food-producing rabbits, a reduction of data requirements is possible since some data may be extrapolated from already registered major species.
Administrative data (**Part I**) shall always be submitted, in the same extent as is requested for the first granting of a marketing authorisation, and a reduction of the data package is not possible. Regarding the quality documentation, there is no requirement for a full **Part II** dossier, since a satisfactory set of supporting quality data already exists for the product. However, it will be necessary to consider the practical use of the VMP in the minor species and to update the quality documentation accordingly. For example, depending on the concentration of the original authorised VMP, correct dosing in the new target species (rabbit) might demand small volumes of the same solution. However, the grading of the scale of the

smallest syringe types available (insulin syringes) might limit correct reading of such small volumes. It is therefore necessary, to adapt the VMP concentration for practical use in the new target species, calling for an adaptation of the corresponding sections in Part II of the documentation. Similarly, if according to clinical data appropriate dosage for rabbits is reached with 1/10 of the already available tablets, a more suitable strength should be developed and corresponding quality data provided.

Data requirements for safety testing (**Part IIIA** – pharmacology, toxicology, user safety, EIA) may be reduced for the extension to a new target species. A table proposing possible reduced data requirements in comparison with standard data requirements is presented below.

Table 2: Data requirements for safety testing for an extension of the marketing authorisation for minor food-producing species (e.g. rabbits)

Part III.A Safety	Standard data requirements	Minimum dataset for minor food-producing species
III.A.2. Pharmacological studies (pharmacokinetics, pharmacodynamics)	Cross-reference to studies in Part IV. Details of pharmacological studies in laboratory animals and relevant observations in target species	Cross-reference to target species pharmacological studies submitted in Part IV
III.A.3 Toxicological studies		
A.3.1. Single dose toxicity	Normally 2 mammalian species but 1 can be replaced by target animal species. Normally 2 routes of administration To reduce animal numbers, alternative validated protocols and internationally recognized protocols will be accepted	No single dose studies are required but a summary of any observed adverse effects or toxicity, or absence of effects, seen in the target species studies, should be included. Studies should be submitted where they exist in the study archive or in published literature.
A.3.2. Repeat dose toxicity	90 day study (2 species, one must be non-rodent, oral administration) Chronic toxicity study	Same criteria apply. Not required for topical use if negligible systemic absorption.
A.3.3 Tolerance in the target species		Cross-reference to studies in Part IV
A.3.4 Reproductive toxicity including teratogenicity		
3.4.1. Study of the effects on reproduction	2-generation study in at least 1 species usually rodent	Not required for topical use if negligible systemic absorption
3.4.2. Embryotoxic/fetotoxic effects including teratogenicity	At least 2 mammalian species usually rodent and rabbit	Absence of studies could be accepted if a valid scientific justification is presented and there are adequate warnings to compensate for the absence of data.
3.5 Mutagenicity	Testing strategy in accordance with current state of scientific knowledge (VICH GL23)	Same criteria apply.
3.6 Carcinogenicitiy	Long term carcinogenicity study for substances required if: i) have a close chemical analogy with known carcinogens	Same criteria apply. Not required for topical use if negligible systemic absorption.

	ii) positive mutagenicity tests iii) suspect signs during toxicity testing studies designed in accordance with current state of scientific knowledge	
A.3.5 User safety	The requirements of the user safety guideline EMEA/CVMP/543/03 Final should be applied	Same criteria apply.
A.3.6 Environmental Impact Assessment		Ecotoxicity requirements should be addressed by referring to the VICH Phase I guidance as given in CVMP/VICH/592/98-Final

Source:

Guideline on Safety and Residue Data Requirements for Veterinary Medicinal Products intended for Minor Uses and Minor Species, EMEA/CVMP/SWP/66781/2005 [17]

Usually, a full package of safety and residue data as described above would be necessary for the **establishment of an MRL** for the new target species. However, in case of an extension to a new minor target species like rabbit, data requirements may be reduced. Indeed, normally only a residue file is required, because the ADI for a specific substance remains the same regardless of the target species or indications [50]. Furthermore, depending on the data already available for major species, previously established MRLs may be extrapolated to the minor species. Article 5 of the new Regulation (EEC) No 470/2009 [40] states that "*with a view to ensuring the availability of authorised veterinary medicinal products for conditions affecting food-producing animals the Agency while ensuring a high level of protection of human health, shall, (…) consider using (…) maximum residue limits established for a pharmacologically active substance in one or more species for other species*." This article provides the possibility to extrapolate the MRLs not only from one food commodity to another, but also from one species to another. For the extrapolation of MRLs for major species to minor species, it is usually sufficient to demonstrate that the method used for major species is basically applicable in the minor species [17]. For example, a request to extrapolate the already established MRLs of *dihydrostreptomycin* from all ruminants and pigs to rabbits has been submitted to the EMA. Taking into account all available data from other target species and making a risk analysis as described in the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin [12], the CVMP recommended the inclusion of *dihydrostreptomycin* for rabbits in Annex I of Council Regulation (EEC) No 2377/90 and a summary report regarding the extrapolation to rabbits has been published in December 2006 [51]. The residue data requirements for the application of the extension of the MRLs could thus be highly reduced compared to an application for the establishment of MRLs for a new substance. However, in

order to assure an optimal and correct preparation of the application, it is highly recommended to seek advice from the EMA or national Competent Authorities, since each situation is different and has to be considered on a case-by-case basis. This is especially important now since the new Regulation [40] is recent and not much experience has been collected.

Pre-clinical and clinical data (**Part IV**) are generally also requested for the new target species. Data justifying the recommended dosage, the duration of therapy and the route of administration, as well as appropriate data to demonstrate the tolerance in the new target species should be provided. Demonstration of the efficacy of the VMP for all proposed indications in the new target species is also necessary. However, bibliographic data originating from acknowledged scientific literature may be used to support the efficacy claims. Furthermore, extrapolation of pre-clinical data from major to minor species could be accepted, if scientifically justified. The extrapolation is usually possible only when the indications and the pharmacology of the VMP are similar in both major and minor species. Also, the availability of tolerance data of other target species may help to reduce the requirements for the new target species: when for example the VMP is known to have a wide margin of safety in other species, a specific target animal safety study may not be required. Efficacy data requirements for a new target species depend therefore on the available data regarding the safety of the active substance/VMP in other target species (toxicity studies, literature, pharmacovigilance data, efficacy studies…) and should consequently be determined on a case-by-case basis.

Reduced data requirements encourage companies to develop new VMPs for MUMS or to extend their existing marketing authorisations for major species to minor species or to minor indications. Extension of marketing authorisations is not only profitable to minor target species or animals suffering from rare diseases, but also to companies which would like to revitalize their old products. Indeed, companies sometimes use the extension of their existing marketing authorisation to relaunch their old VMPs. Extension of marketing authorisations to MUMS may be a good means for companies to have an advantage over competitors and to be on the leading edge of innovation. However, the investment in terms of money should of course not rise above the return on investment.

3.3. Increasing Costs and Small Return on Investment

3.3.1. Development costs

The above mentioned incentives are a great help for companies developing MUMS products but, unfortunately they are not sufficient to resolve the problem of a lack of availability. Indeed, even if data requirements may be reduced thanks to extrapolation from major species, they still represent a great investment for companies and many MUMS products still remain uneconomic to develop. Furthermore, due to the notion of global marketing authorisation stated in article 5 of Directive 2001/82/EC as amended [2], new data developed for the extension receive no data protection and will therefore be directly available for competitors. Consequently, the number of new products being licenced is decreasing considerably, while authorised generic products are still becoming more important. According to recent results of a survey published in the IFAH-Europe Impact Assessment Data Package of 2010 [52], "*In the MRP and DCP (combined) the number of applications for new products (article 12, "full" dossiers) fell from 51 in 2006 to 23 in 2009. However, the picture was very different for generic applications (article 13, "generic" dossiers); the number submitted to the MRP and DCP increased from 45% of full + generic applications in 2006 to 71% in 2009.*" These results illustrate an obvious decrease of innovation with regards to veterinary medicines in the EU.

The main incentive on data requirements for MUMS relies on the possibility to extrapolate available data from other species, laboratory animals or even human to new minor species. Developing a VMP containing a new active substance exclusively intended for use in rabbits, means that reduction of data requirements would be very limited and development costs would be almost similar to a new VMP for major species. Due to the costs of developing an entirely new medicine, this situation will only be encountered very rarely. Indeed, cost for developing a regulatory dossier which would meet European requirements for a major species is estimated to 15-30 million Euros or even more [31].

3.3.2. Registration and maintenance costs

In addition to the costs for development, high fees for the registration and for maintenance of marketing authorisations should be taken into account. As an example, registration and maintenance fees for a VMP authorised through mutual recognition procedure (MRP) in France - France acting as concerned member state (CMS) - are presented in Table 3. It should be noted that the fees have to be paid in each Member State concerned by the procedure (except for VMPs authorised through the centralised procedure where the fees

have to be paid to EMA). The fees are regulated at national level and may strongly vary from one Member State to another.

Table 3: Fees for VMPs authorised through MRP in France - France acting as CMS

New MA	**Fees (Euros)**
Complete application, new active substance	11'000
Complete application, known active substance/ fixed combination/ well-established use	7'700
Generic application	5'500
Informed consent	2'750
Variations or extensions of the MA	
Extension	7'700
Type II variation	3'000
Type IB variation	1'000
Type IA variation	500

Source:
Fees requested in France, National Veterinary Medicines Agency, 2012 [53].

For medicines for major uses, such registration and maintenance fees are not the most significant cost. However, for MUMS products, they are very important and often represent a barrier for the development of such VMPs, despite fees reduction or waivers granted by the EMA and other national competent authorities [54].

3.3.3. Manufacturing costs

The manufacturing costs are higher for VMPs with limited market potential because smaller batch size leads to higher costs per unit and, country specific packaging in the local language is necessary, all the same. Often, the cost of manufacturing batches outweighs the potential sales. Consequently, even if a VMP is authorised through a CP, mostly it will be launched in a selected number of Member States only. Indeed, companies market products solely in those Member States, where the return on investment is assured. According to a survey of IFAH-Europe member companies, "*centrally authorised products were in the market in only 50% of 25 EU Member States on average with very few on the market in the smaller countries*" [31].

3.3.4. Return on investment

Since the market for MUMS products is limited and the costs for development, registration and maintenance are still relatively high despite incentives, a return on investment can only be reached if the product is high-priced. This is barely possible, particularly in the agricultural

domain (e.g. rabbits). Indeed, farmers have to bear the total cost of any treatment and the financial value of food-producing animals such as rabbits is very low. Farmers do not invest in treatment that is more expensive than the value of their animals. Owners of pet rabbits are maybe ready to invest more money to save their animals but even if their population is currently rather increasing, the potential market of VMPs for pet rabbits remains very small. Data requirements for VMPs are very similar to those for human medicinal products in the EU. However, the turnover of VMPs is estimated to be only 3-5% of that of the human pharmaceutical sector and profit margins are smaller [31].The investment costs are therefore disproportionate to the value of the market and this disproportion is even higher for MUMS products.

4. Discussion:
Consequences of the Lack of Availability of VMPs

4.1. Consequences on Animal Health

4.1.1. Welfare of untreated animals

Animal welfare has grown increasingly important over the last decades in the EU and an EC Treaty's Protocol on Protection and Welfare of Animals [55], which recognises animals as "sentient beings" (with an ability to experience pain, suffering and distress) has been acknowledged by each Member State in 1997. The adoption of the Action Plan on the Protection and Welfare of Animals by the European Community in 2006 [56] confirms the important ethical value of the protection and welfare of animals in modern society. It is commonly agreed that, as a minimum requirement, all animals shall be provided adequate food, water, a suitable living environment, shall receive the opportunity to exhibit natural behaviour, shall be protected from fear and distress, and finally, shall be provided adequate health care (prevention of injury, illness, disease or infection).

To assure rabbits' welfare, careful hygiene and correct husbandry are essential. Since stress is a contributing factor in developing illness, rabbits should be located far from nuisances such as noise, dust and the presence of other animals such as dogs and cats. They should also be protected from bad weather (rain and wind) and should be provided sufficient shade. Furthermore, rat and mice should be exterminated, since both species may be source of contamination with pathogenic agents. Feed and water hygiene is also very important, since both may contain numerous pathogens of rabbit disease. Cage and nest hygiene is basic, particularly while the does are nursing, to protect does and young from pathogenic agents. When basic and essential hygienic measures are neglected or, sometimes even when adequate measures are taken, diseases unfortunately may appear in rabbitries and quickly spread to the entire animal population. In absence of adequate VMPs in such cases, health care of rabbits cannot be assured any longer and untreated animals are exposed to suffering and premature death. At the worst, all rabbits in the affected rabbitry have to be culled.

4.1.2. Off-label use through the cascade

In case adequate authorised veterinary medication is unavailable in a country for the treatment of a particular condition in a particular target species, veterinarians are authorised

to use the prescribing cascade. The term "cascade" is used because a specified order applies, as stated in Paragraph 1 of Article 11 of Directive 2001/82/EC as amended [2]:

*"Member States shall take the necessary measures to ensure that, if there is no authorised veterinary medicinal product in a Member State for a condition affecting a **food-producing species**, by way of exception, the veterinarian responsible may, under his direct personal responsibility and in particular to avoid causing unacceptable suffering, treat the animals concerned on a particular holding with:*

(a) a veterinary medicinal product authorised in the Member State concerned under this Directive or under Regulation (EC) No 726/2004 for use with another animal species, or for another condition in the same species; or

(b) if there is no product as referred to in point (a), either:

(i) a medicinal product for human use authorised in the Member State concerned in accordance with Directive 2001/83/EC or und Regulation (EC) No 726/2004, or

(ii) a veterinary medicinal product authorised in another Member State in accordance with this Directive for use in the same species or in another food-producing species for the condition in question or for another condition; or

(c) if there is no product as referred to in subparagraph (b), and within the limits of the law of the Member State concerned, a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national legislation in accordance with the terms of a veterinary prescription."

For **non-food producing species** similar conditions apply and are stated in Article 10 of Directive 2001/82/EC as amended [2]. There are unfortunately no centralised data available on the use of the cascade (frequency, conditions, target species...) and its impact on animal health in the EU [57]. However, with the cascade system, substances are used without known efficacy and safety evaluation of the VMP on the target species and therefore unexpected side-effects or problems due to an inadequate dosage (e.g. overdose toxicity or on the contrary lack of efficacy) with sometimes fatal issues may occur. An example which has been reported by the National Veterinary Medicines Agency in France in 2004 is the use of fipronil (Frontline®) on rabbits [58]. From 1997 to 2003, 114 notifications on side effects of Frontline® used in rabbits have been reported in France, corresponding to 127 treated animals. About 44% of the cases had a fatal outcome and causality between side effects and use of the product (A probable or B possible) were found for 88% of the cases. Consequently, the Marketing Authorisation Holder included the warning "*Do not use in rabbits*" on each pack size of the product and informed distributors (veterinarians, pharmacists...) accordingly.

This is a typical example of a VMP, which is safe when used in designated target species (cats and dogs), but toxic when used in others (rabbits). In the United Kingdom, a total of 306 reports involving unauthorised use of authorised products were received by the Veterinary Medicine Directorate (VMD) during the year 2008. The majority of cases resulted from use of the product in an unauthorised target species (112 reports) or over-dosing (88 reports) [59].

According to Article 10 and 11 of Directive 2001/82/EC as amended [2], a veterinarian making use of the cascade administers the VMP under his *"direct personal responsibility".* It means that where unexpected losses occur due to the use of unauthorised VMPs, veterinary surgeons are considered responsible and are subjected to a legal implication. They are therefore confronted with a difficult dilemma when no authorised VMPs are available to treat their patients with unacceptable suffering.

4.2. Consequences on Human Health

4.2.1 Zoonotic diseases

Inadequate treatment of sick animals may increase public health hazards due to the risk of transmission of parasites or pathogens from animals to humans. Many infectious diseases can indeed be acquired through contact with animals or, indirectly, through contaminated tissues or products destined for human consumption (e.g. salmonellen in eggs). A lack of availability of appropriate VMPs against pathogen agents may thus increase the probability for humans to be contaminated. This is a very important problem worldwide and it is estimated that over 60% of known human diseases are caused by animals [52]. Animal and human health are indeed intimately connected and outbreaks of serious diseases like avian influenza, remind us of the crucial role played by VMPs and, that necessary measures have to be taken to always optimize the development of new and improved products. Unfortunately, this is sometimes compromised by current increased regulatory requirements.

Zoonoses transmitted by rabbits are quite rare and have apparently never been identified in intensive rabbit production. This is probably due to the fact that usually zoonoses are diseases of adult animals and early slaughter limits their spread [22]. Also, zoonotic diseases transmitted by pet rabbits are unusual but may nevertheless occur. The bacteria *Pasteurella multocida,* which resides in the oral cavity and upper respiratory tract of rabbits, for example, may cause cutaneous infection in humans. Clinical signs are generally a local inflammation with occasional abscess formation and ascending infection [60]. Other diseases like salmonellosis, yersiniosis and tularaemia are also potentially transmissible to humans, but rather rarely. More commonly, external parasites like Cheyletiella (mite acariasis) and Trichophyton (dermatophytosis) may be transmitted to humans and cause cutaneous lesions and pruritus.

4.2.2. Residues in food - Risk for consumers

Tissues and other products from food-producing animals may not only be contaminated by pathologic agents, but also by residues of VMPs. Due to the deficiency of authorised VMPs, the off-label use of products is increasing which may unfortunately jeopardise effective control of residues in food of animal origin and, consequently induce serious concerns for the safety of the consumer [12].

The following paragraph has been included in article 11 of Directive 2001/82/EC as amended [2], to reduce the risks of potential residues in meat and products of animal origin, when the cascade system is used:

"*2. Paragraph 1 shall apply provided that pharmacologically active substances included in the medicinal product are listed in Annex I, II or III to Regulation (EEC) No 2377/90, and that the veterinarian specifies an appropriate withdrawal period.*
Unless the medicinal product used indicates a withdrawal period for the species concerned, the specified withdrawal period shall not be less than:

- *7 days for eggs,*
- *7 days for milk,*
- *28 days for meat from poultry and mammals including fat and offal,*
- *500 degree-days for fish meat."*

Food-producing animals may thus only be treated under the cascade with VMPs containing pharmacologically active substances listed in Annex I, II or III to Regulation (EEC) No 2377/90 [1] resp. Table I of Regulation (EC) No 37/2010 [40]. The veterinarian shall set an appropriate withdrawal period, according to the available information on the VMP in the authorised species. However, unless the product indicates a withdrawal period for the species concerned, the minimal proposed withdrawal period may not go below the limit stated in the Directive.

The use of the cascade system to treat rabbits is frequent because of the insufficient availability of VMPs authorised for many conditions in this target species. Thus, veterinarians often apply VMPs authorised for other animal species. This may cause a significant problem when VMPs containing pharmacologically active substances, for which no withdrawal period has been determined, are used in meat-producing rabbits. Indeed, according to the cascade rules described above, a withdrawal period of 28 days has to be respected for rabbit meat. This requested withdrawal period is, however, not consistent with the life cycle of the food-producing rabbits, commonly slaughtered at the age of 60 days. When animals are treated after weaning (30 days) and for a duration of one week, the 28 days are not respected if the animals are slaughtered, as usual, at 60 days. If such a situation illegally occurs, there is a risk for the consumers, since it cannot be excluded that the meat still contains residues. If the withdrawal period is respected, rabbits are slaughtered later and consequently lose their commercial value, finally having a negative impact on farmers' revenue. Farmers and veterinarians are therefore often confronted to a dilemma: either to treat the animals to avoid suffering or not to treat to avoid a delay of slaughtering [52].

One of the most frequent and hazardous situation is found in the presence of antibiotic residues in food of animal origin. Antibiotics are indeed not only used as therapeutics to kill

the pathologic agents, but also sometimes in sub therapeutic levels to prevent infections. The use of antibiotics with a view to promote animal growth and improve feed production is, however, prohibited in the European Union since January 1st 2006 [61]. The administration of antibiotics is unfortunately often used in excess, and even misused (e.g. use of several antibiotics at the same time), particularly when no authorised product for the concerned target species and, consequently, no specific information about the use of the product in these target species is available. Antibiotic residues in food may have serious pathological effects in human, such as transfer of antibiotic resistant bacteria, carcinogenicity (sulfamethiazine, oxytetracycline, furazolidone), mutagenicity, nephropathy (gentamicin), hepatotoxicity, reproductive disorders and allergy (penicillin) [62]. The risks occurring from improper use of antibiotics are numerous and include not only the presence of residues in food destined for human consumption, but also the induction of bacterial resistance and the contamination of the environment.

4.2.3. Antibiotics resistance

Even if the over-use of antibiotics in human medicine is recognised as the major cause of antibiotic resistance, over-use and misuse of antibiotics in intensive animal production is also considered an important factor. When animals are treated with antibiotics closely related to antibiotics used in humans, cross-resistances may develop and consequently, the pathologic agents may become resistant to human medicine, as well. Resistant bacteria are transmitted to people through direct contact with animals, via food of animal origin or,directly from person to person. It is also known that genes carrying antibiotic resistance can be transferred to other bacteria of the same or a different strain or species. This situation leads to a higher risk of infections with resistant bacteria in humans, which may have serious consequences particularly when no effective antibiotics are available anymore. One well-known example of multi-resistant bacteria is the emergence of a new strain of the methicillin-resistant *Straphylococcus aureus* due to an over-use of antibiotics in intensive pig farming. Resistant bacteria have been spread rapidly among pigs, to people in contact with animals and from these people to hospitals. The strain also contaminated chicken, cattle and calves [63]. Antibiotic resistance has also increased rapidly in food-poisoning *Salmonella* and *Campylobacter* because VMPs used in farming were very similar to those used in human medicine and cross-reaction occurred. This leads to a serious increase of new types of antibiotic resistance affecting humans. There is unfortunately no database collecting the antibiotic use in the European Union. It is thus not possible to know exactly the quantity, the frequency, the duration and the reasons of the administration of antibiotics in the EU, but it is known that the use of antibiotics is rather increasing, particularly in pig and chicken production. There is, therefore, a clear need for surveillance and early warning systems that

can pick up signs of increasing microbial resistance at a national level in each Member State of the EU.

It should, however, be noted that a professional and responsible use of antibiotics is important for animal welfare and is beneficial for human health due to the reduction of potential pathogen agents in food. This benefit may even overweigh the risk of antibiotics resistance. As described in the IFAH-Europe Impact Assessment Data Package of 2010 [52], "*a study done by scientists a the University of Minnesota College of Veterinary Medicine in which the potential risks associated with increased levels of antibiotic-resistant bacteria in meat were compared with the potential benefits associated with decreased risk of food-borne illness found potential benefits to human health associated with the use of antibiotics in chicken far exceeded the relatively low increased human health risks associated with antibiotic resistance*". Antibiotic resistance is thus not the major human health problem caused by the lack of availability of VMPs if the products are correctly used, but should nevertheless not be minimised.

4.2.4. Risk for the environment

Over-use or misuse of VMPs may also have an impact on the environment. Indeed, residues contained in urine and faeces may contaminate the soil when animal are pasturing or after spreading of manure and litter. Once released to land, substances may be washed off into surface waters or drain into groundwater, where they may have a negative impact on the environment and human health. For this reason an EIA is required to obtain a marketing authorisation for each VMP. However, the EIA is established based on the approved use in the target species and may be considerably different when applied in another target species. The use of a VMP not authorised for a concerned species may, therefore, represent a significant hazard for the environment and consequently, for human health, particularly in the agricultural domain where the exposure to the environment is high.

4.3. New Perspectives: the Regulatory Review

Over the past few years, a lack of availability of VMPs across the EU and consequent negative impacts on animal and human health have been intensively analysed, both by industry and regulators and critical problems have been identified. The insufficient availability of VMPs has been indeed one of the main key drivers for a premature review of the current veterinary legislation. During the co-decision procedure for the adoption of the revised legislation on the establishment of MRLs [40], the EC made a commitment in a Communication from the Commission to the European Parliament to review the VMP legislation in 2010 [64]. A public consultation has been carried out by the Directorate General for Health and Consumers (DG Health and Consumers) with a view to consult all stakeholders on their opinions about the deficiencies of the current VMP legislation and their propositions to improve the situation. All contributions have been carefully analysed and a summary of the outcome has been published [65]. The following eight main issues have been discussed in the public consultation:

- Innovation and data protection
- The authorised procedures
- Packaging and labelling
- Pharmacovigilance and monitoring
- Distribution channel
- Off-label use
- Harmonisation of already authorised VMPs
- New needs and new challenges

In parallel the European Commission mandated the consultancy GHK (part of the European Policy Evaluation Consortium (EPEC)) to collect the necessary data for the impact assessment of the revision of VMP legislation. This assessment has been carried out in two phases: a first phase to define the problems and to propose different policy options and a second phase to analyse the potential impact of the different proposals. A final report was published in July 2011 [57]. The main policy options recommended by GHK consultancy are:

- Single marketing authorisation valid in the entire EU
- Reduction of data requirements
- Systematical harmonisation of the SmPC for authorised products
- Simplify pharmacovigilance requirements
- Restrict requirements to renew a marketing authorisation

- Reduction of the amount of text required on packaging and labelling and acceptance of non-official languages
- Simplifying variations requirements
- Improved data protection: abolition of the concept of “global marketing authorisation” for new product developments, extension of the data protection for fish, bees and other species/indication to 20 years

For their part, the IFAH-Europe (International Federation for Animal Health Europe), representing the European Animal Health Industry also made its own assessment in view to present the industry’s point of view and published an Impact Assessment Data Package in May 2010 [52]. The most important proposals from IFAH-Europe are:

- Improved data protection for additional major innovations added to the first product
- Simplification of procedures: centralised procedures, MRP, DCP and national procedures should be replaced by a single regulatory procedure based on a single data dossier and a single scientific assessment which would result in a single decision for marketing authorisation in the EU (“1-1-1 concept”)
- Marketing authorisations of all existing products should be extended to the entire EU, using a simple administrative procedure and without re-assessment
- Pharmacovigilance system should be simplified
- Packaging and labelling requirements should be simplified (facilitation of multilingual labelling)

It is obvious that all stakeholders (regulators, industry, veterinarians, farmers…) agree about the main necessary changes and proposals to improve current legislation. However, they have different opinions on some details concerning the implementation of the solutions. Most regulators disagree, for example, with "1-1-1 concept" proposed by industry. In their opinion, at least two procedures, one for innovative products, one for generic products, should be maintained. They also mainly disagree with the proposition to extend the marketing authorisations to the entire EU using a simple administrative procedure [66].

Based on all available milestone documents, the EC is currently preparing the internal EC Impact Assessment Report for internal consultation within the EC. This Report will be finalised and published at the end of 2012. In parallel, the EC is also preparing its proposals for the amended legislation which is intended to be release also in late 2012. The co-decision procedure with the European Parliament and the Council is expected in 2013-2014. According to the final conclusion of the consultancy GHK, the new legislation will reach the

following objectives: reduce the administrative burden by approximately one third of the current levels, improve the availability of VMPs and a trend to implement a single market for VMPs [57].

5. Conclusion

A review of the current veterinary regulatory framework is urgently needed to overcome the problem of lack of availability of VMPs in the EU, particularly with regards to VMPs for minor use and minor species. Proposals from both, industry and regulators might suggest an improvement in availability, principally through a better balance between investments for development, extension and maintenance of marketing authorisations and return of investments.

A reduction of necessary investments may be reached with increased financial incentives for companies developing new VMPs or extending existing marketing authorisation to new minor species or minor indications, with simplifications of regulatory procedures, as well as, with a reduction of the administrative burden and data requirements. An improvement of the return on investments is, however, more difficult, particularly with regards to products for MUMS whose small market cannot further increase and with regards to VMPs for farm animals whose prices cannot rise above the economic value of animals. Better data protection for significant innovations is, however, one of the few proposals which may increase the return of investment and is therefore of high importance.

Coming decisions on the new veterinary regulatory environment are of particular interest, not only for stakeholders like industry, regulators, veterinarian and farmers, but also for minor target animals (e.g. rabbits) or animals suffering from rare diseases, whose welfare will hopefully improve with the expected increased availability of VMPs in the future. The proposal of the EC for the amended legislation is intended for the end of 2012 and is, in any case, eagerly-awaited by all parties involved.

6. Summary

Over the past few years there has been considerable concern about the lack of availability of veterinary medicinal products across the European Union and its consequent negative impacts on animal and human health. The principal cause of insufficient availability of veterinary medicine is clearly found in the implementation of stronger regulatory requirements in the veterinary legislation (new standards for quality, safety and efficacy as well as obligation to establish a maximum residue limit for all pharmacologically active substances intended to be used in food-producing species) that leads to increased costs for the development of new veterinary medicines and for the maintenance of existing marketing authorisations. This problem is particularly acute in relation to availability of medicines for minor uses/minor species, because of the limited market and subsequent small return of investment intended for such veterinary medicinal products. Rabbits are particularly concerned by this issue, not only because of the obligation to establish maximum residue limits for meat-producing rabbits, but also because of their limited economic value. This target species has therefore been chosen to illustrate the current situation of the insufficient availability of veterinary medicines in the European Union.

Without adequate veterinary medicine, animal health care cannot be assured and untreated animals may be exposed to suffering and premature death. Veterinary surgeons are, therefore, often enticed to consider the off-label use of medicines and consequently to administer substances for which no efficacy and safety evaluation in the target species have been performed. As a result, animals are exposed to unexpected side-effects with possible fatal issues. The lack of veterinary medicinal products has also an impact on public health, principally through the impossibility to manage zoonotic diseases and through the increased risk of residues in food of animal origin when unauthorised medicines are misused.

Significant failures in the current veterinary legislation have been pointed out both by the industry and regulators and the lack of availability of veterinary medicinal products has been one of the main key drivers for a premature review of the legislation. The proposals to improve the legislation consist mainly of simplification of procedures with a trend to a single market for veterinary medicines in the European Union, reduction of data requirements and administrative burdens, improvement of data protection for major innovations and increased incentives for companies developing new medicines. All stakeholders (regulators, industry, veterinarians, farmers…) agree about the main necessary changes and proposals but, they have different opinions about some details on the implementation of the solutions. Taking into account available information and proposals received by all stakeholders, the European

Commission is currently preparing its proposals for the amended legislation which is intended to be released in late 2012. The co-decision procedure with the European Parliament and the Council is expected in 2013-2014. The outcome of this "Review 2012" will have considerable consequences on registration of veterinary medicines and therefore, is eagerly-awaited by all parties involved.

7. References

1. Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits for veterinary medicinal products in foodstuffs of animal origin.

2. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

3. Position Paper on Availability of Veterinary Medicines agreed on 17 March 1999, EMEA/CVMP/151/99-FINAL.

4. CVMP Update of the Position Paper on availability of Veterinary Medicines agreed on 14 October 1999, EMEA/CVMP/731/99-FINAL.

5. CVMP Update of the Position Paper on Availability of Veterinary Medicines agreed on 9 February 2000, EMEA/CVMP/130/00-FINAL.

6. CVMP Update of the Position Paper on availability of veterinary medicines agreed on 21 June 2000, EMEA/CVMP/411/00-FINAL.

7. Communication from the Commission to the Council and the European Parliament: Availability of Veterinary Medicinal Products, COM(2000) 806 final.

8. European Task Force on Availability of Medicines 1st Meeting – Thursday 14 October 1999. Minutes, EMEA/V/PHJ/uh/33379/99/Rev 1/Corr.

9. European Task Force on Availability of Medicines 2nd Meeting – Tuesday 7 December1999. Minutes, EMEA/V/38491/99.

10. European Task Force on Availability of Medicines 3rd Meeting – Tuesday 7 March 2000. Minutes, EMEA/V/7306/00.

11. European Task Force on Availability of Medicines 4th Meeting – Tuesday 20 June 2000. Minutes, EMEA/V/18383/00.

12. Note for Guidance on risk analysis approach for residues of veterinary medicinal products in food of animal origin, EMEA/CVMP/187/00-FINAL.

13. Implementation of the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin, EMEA/CVMP/069/02.

14. Press release Committee for Veterinary Medicinal Products 73rd meeting, EMEA/CVMP/065/02.

15. Position Paper regarding Availability of Products for Minor Uses and Minor Species (MUMS), EMEA/CVMP/477/03/Final. 2003.

16. Guideline on quality data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/QWP/128710/2004.

17. Guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/SWP/66781/2005.

18. Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/EWP/117899/2004.

19. European Food Safety Authority (EFSA) – AHAW Panel, The Impact of the Current Housing and Husbandry Systems on the Health and Welfare of Farmed Domestic Rabbits, Annex to EFSA Journal, 2005. **267**: p. 1-31

20. Fortun-Lamothe L., Gidenne T., Filière cunicole française et systèmes d'élevage, INRA Prod. Anim., 2008. **21**(3) : p. 219-220

21. Pendariès C., La filière lapin souffre du repli chronique de sa consommation, Agreste Conjoncture, Panorama au 3 décembre 2010. **8** :p. 9-14.

22. Lebas F. et al., The Rabbit: Husbandry, Health and Production, FAO Animal Production and Health Series No.21. 1997.

23. Report from the Commission to the Council and the European Parliament: Sixth Report on the Statistics on the Number of Animals used for Experimental and Other Scientific Purposes in the Member States of the European Union, COM (2010) 511 final.

24. Delteil V., Le lapin domestique est de plus en plus présent dans les cliniques vétérinaires, La Semaine Vétérinaire, Supplément ASV 33, 2009. **1382**.

25. Licois D., Pathologie d'origine bactérienne et parasitaire chez le lapin: apports de la dernières décennie, Cuniculture Magazine, 2010. **37**: p. 35-49.

26. Vial. J. Les principales maladies bactériennes du lapin: revue bibliographique de l'utilisation des molécules antibactériennes; importance de leur innocuité, Thèse de doctorat, 2006.

27. Dehaumont P, Moulin G, Evolution du marché des médicaments vétérinaires et de leur encadrement réglementaire: conséquence sur leur disponibilité, Bull. Acad. Vét. France, 2005. **158** (2): p. 235-136.

28. OIE List of Antimicrobials of Veterinary Importance, adopted by the OIE International Committee in May 2007.

29. Index of the Veterinary Medicinal Products authorised in France, National Veterinary Medicines Agency, available from: http://www.ircp.anmv.anses.fr/

30. Dictionnaire des Médicaments Vétérinaires (DMV), WK-Vet, available from : http://www.wk-vet.fr/mybdd/?moteur=156

31. Report of Task Force on Availability of Veterinary Medicines, 2007. Heads of Medicines Agencies.

32. Borkowski R, Karas A.Z, Sedation and anaesthesia of pet rabbits, Clinical Techniques in Small Animal Practice, 1999. **14**(1): p. 44-49.

33. Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products.

34. Council Directive 81/852/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products.

35. Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the evaluation of medicinal products.

36. Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products.

37. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

38. Rules Governing Medicinal Products in the EU: Notice to Applicants, Volume 6B, Presentation and content of the Dossier, 2004. European Commission.

39. Guideline on user safety for pharmaceutical veterinary medicinal products, EMA/CVMP/543/03-Rev.1.

40. Regulation (EC) 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residues limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council.

41. Substances considered as not falling within the scope of Regulation (EC) No 470/2009, with regard to residues of veterinary medicinal products in foodstuffs of animal origin, EMEA/CVMP/519714/2009-Rev.9.

42. Rules governing medicinal products in the EU: Notice to applicants and Note for Guidance, Volume 8, Establishment of maximum residue limit (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin, June 2003. European Commission.

43. Note for Guidance: Approach towards harmonisation of withdrawal periods, EMEA/CVMP/036/95 Final.

44. Note for Guidance for the determination of withdrawal periods for milk, EMEA/CVMP/473/98 Final.

45. Position paper regarding availability of products for minor uses and minor species, EMEA/CVMP/477/03/Final.

46. EMEA Guidance for companies requesting classification as MUMS/limited market, EMEA/CVMP/370663/2009.

47. Commission Recommendation 2003/361/EC of May 2003 concerning the definition of micro, small and medium-sized enterprises, Official Journal L 124 of 20.05.2003.

48. Commission Regulation No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises, Official Journal L 329/4 of 16.12.2005.

49. Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, Official Journal L 334/7 of 12.12.2008.

50. Maximum Residue Limits Questions & Answers: Introduction, available from EMA website.

51. Dihydrostreptomycin (Extrapolation to rabbits), Summary Report (5), EMEA/CVMP/46923/2006-Final.

52. IFAH-Europe Impact Assessment Data Package, Review of the European legislation governing veterinary medicinal products, 2010

53. Fees, National Veterinary Medicines Agency, available from: http://www.anmv.anses.fr/?cat=10.

54. Meads R., Benchmarking the Competitiveness of the European Animal Health Industry, Business Decisions Ltd (BDL), Regulatory Affairs Journals, 2003. **14**(5): p. 357-8.

55. Treaty of Amsterdam amending the Treaty on European Union, the Treaties establishing the European Communities and certain related acts – Protocol annexed to the Treaty on the European Community - Protocol on protection and welfare of animals, Official Journal C 340 of 10.11.1997. European Communities.

56. Commission communication of 23 January 2006 on a Community Action Plan on the Protection and Welfare of Animals 2006-2010 (COM(2006)0013).

57. Assessment of the Impact of the Revision of Veterinary Pharmaceutical Legislation, GHK Consulting, on behalf of the European Policy Evaluation Consortium (EPEC), 2011.

58. Etude des effets indésirables observés à la suite du traitement des lapins avec des spécialités à base de fipronil, Rapport d'expertise de pharmacovigilance relatif à l'AVIS CNPV -04 du 15.06.2004, Commission nationale de pharmacovigilance vétérinaire.

59. Suspected adverse reactions, Veterinary Record, 2009. **165**: p.162-164

60. Harkness JE, Rabbit husbandry and medicine, Vet Clin North Am Small Anim Pract, 1987.**17**: p. 1019-44.

61. Castanon J.I.R, History of the use of antibiotic as growth promoters in European poultry feeds, Poult. Sci., 2007. **86**(11): p. 2466-2471.

62. Nisha A.R., Antibiotic Residues – A Global Health Hazard, Veterinary World, 2008. **1**(12): p. 375-377.

63. Turner J., Antibiotics in farm animal production. Public health and animal welfare, Compassion in world farming, 2011.

64. Communication from the Commission to the European Parliament, COM (2008) 912 final (2007/0064 (COD) Brussels, 8.1.2009).

65. Report on the European Commission's Public Online Consultation: Better regulation of veterinary pharmaceuticals: how to put in place a simpler legal framework, safeguarding public and animal health while increasing the competitiveness of companies. Unit SANCO D3-Pharamceuticals.

66. Clayton R., The review of the veterinary medicines legislation: an update, Regulatory Rapporteur, 2012. **9**(2): p.4-7.

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Villars-sur-Glâne, den _____

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