European Medicines Agency
Celebrating ten years – 1995 – 2005

"A Scientific Perspective on the Future of Medicines"
11 March 2005

Topic: Community Authorisation for Veterinary Medicines-the Contribution to Animal Health in the EU

Prof. Paul-Pierre Pastoret
Biothechnology and Biological Sciences
Research Council, UK

Community Authorisation for Veterinary Medecines – The contribution to animal health in the European Union.

Professor Paul-Pierre Pastoret
Biothechnology and Biological Sciences Research Council, UK

1. Introduction

The market for veterinary medicinal products in the European Union differs markedly from the market of its human counterpart for several reasons.

The total market for veterinary products only accounts for roughly four percent of the total pharmaceutical market in the European Union; nevertheless veterinary medicinal products play an essential role in both animal and public healths as I shall illustrate it.

Another striking difference is the place of vaccines which amount to approximately 25 % of the veterinary products even if it is often very specific ones with tiny markets. Among the pharmaceuticals, the market is shared mainly by other major categories of products, namely antibiotics, antiparasitic and antiinflammatory drugs.

Veterinary medicinal products are intended for use in many different target species, domestic or wildlife, from salmons to foxes. In most animal species, particularly in food producing animals, there are several categories according to the purpose of the production system. As far as the evaluation of veterinary medicinal products is concerned, there are therefore major differences between what is called companion animals – or pets – like dogs, cats and even horses, and food producing animal species unevenly distributed within the European Union.

Due to all these specific constraints, it was therefore not obvious, ten years ago, to put together human and veterinary medicinal products under the same European umbrella. Nevertheless, as stated by Reinhard KROKER, the first chairman of the Committee for Veterinary Medicinal Products (CVMP), there was an obvious advantage of scale in being located in the same agency together. Both scientific and practical. Scientifically, there are obvious links between both Medicines. Practically, sharing major resources such as administrative support, information technology, human and financial services, offered real benefits in terms of cost savings. Other benefits came from being able to address logistical and regulatory problems common to both scientific committees (CPMP and CVMP); it was especially important to share knowledge about immunologicals, biotech products, antibiotic resistances and transmissible spongiform encephalopathies.

2. Why and how to use veterinary products

As already mentionned the scope of regulations differ in many instances between human and animal health products. Veterinary medicinal products have a wider objective both in terms of species and use.
Veterinary medicinal products are developed for many different purposes and under many constraints if aiming towards a global market:

- to protect animal health;
- to protect public health;
- to improve animal welfare;
- to prevent food poisoning in humans;
- to implement animal diseases control policies;
- to improve production of food producing animals;
- to reach sustainability in agriculture;
- to alleviate poverty;
- to protect the environment and maintain biodiversity.

As a consequence, when developing a veterinary medicinal product, one must take into account numerous, often contradictory, requirements.
In animal health, within the European Union, the emphasis is nowadays more placed on the various aspects of safety and animal welfare, rather than on food security and the improvement of animal production.Therefore, apart from being efficacious, veterinary medicinal products must be safe not only for the target animal itself, but also for other species sharing the same agro- or eco-systems, including human beings. A product must not be harmful for the environment and its use in food producing animals cannot result in the presence of undue amounts of residues.

3. Contribution of the EMEA to the determination of Maximum Residue Limits (MRLs)

As a result of the new trends in the sector of food producing animals industry, one of the first major task and major achievement of the Committee for the evaluation of veterinary medicinal products was to determine the Maximum Residue Limits of products for use in food producing animals. For already existing substances a definitive Maximum Residue Limit had to be determined unless the substance was no longer marketed within the European Union. A Maximum Residue Limit had also to

be established for all new veterinary substances for use in food producing animals apart from immunologicals devoid of concerned excipients.

This had of course beneficial aspects by protecting the consumers eating food derived from food producing animals, but had also detrimental effects on the availability of substances essential for animal health and welfare, creating problems of orphan diseases and minor species and of the regulatory status of horses.

4. Contribution of the CVMP to the policies for the control of animal infectious diseases within the European Union

The alarming Epizootics of Foot-and-Mouth disease in United Kingdom and other European countries, and a greater perception that future control strategies might involve a policy of "vaccination for live" have contributed the Committee for Veterinary Medicinal Products initiating a position paper on requirements for vaccines against foot-and mouth disease. Slaughter policies to control animal infectious diseases are less and less popular in the European Union – a soft way to tell it - and there is a trend to use so-called marker vaccines associated with a companion diagnostic test, allowing to distinguish vaccinated from infected animals.

Vaccines against Foot-and-Mouth disease are often seen by their manufacturers, and to some extend by their official users, as a "special case" due to the specific nature of the disease against which they provide protection. First of all due to the number and antigenic diversity of virus strains that might be used alone or in combination.

From a legal and regulatory perspective, Foot-and-Mouth disease vaccines are immunological veterinary products and therefore subject to the requirements of the pharmaceutical directive, demanding that all veterinary products placed on the market within the European Union must be authorised by means of a marketing authorisation and lays down the minimum requirements in terms of quality, safety and efficacy that medicines must meet to obtain an authorisation. Nevertheless, the directive provides an exemption from the requirement for an authorisation when a product is to be used in the event of "serious disease epidemic"

provided there is no authorised medicine for use against the disease concerned and provided the European Commission is informed of the detailed conditions of use. The term "serious disease epidemic" is not further defined but clearly applies to outbreaks of Foot-and-Mouth disease.

The European Commission itself utilises this exemption to allow use, without an authorisation, of vaccines prepared using concentrated antigens maintained in the strategic antigen reserves of its Foot-and-Mouth disease antigen bank.

The work done by the CVMP in concertation with other partners such as the group 15V of the European Pharmacopoeia will help to provide Foot-and-Mouth disease vaccines better adapted to the epidemiological situation and push forward a policy of "vaccination for life".
Fortunately, according to the new European pharmaceutical regulation, Immunological veterinary medicinal products for the treatments of animal diseases that are subject to community prophylactic measures may also be granted such authorisation.

5. Contribution of the CVMP to the improvement of animal welfare

Viruses, especially RNA viruses, are constantly evolving and can best be qualified as populations of quasi-species. This biological feature may have a strong impact on the design of vaccines as exemplified by equine influenza vaccines.

Equine influenza remains among the main acute contagious respiratory diseases of horses world-wide. Equine influenza is represented by two subtypes: Influenza A/equine 2 virus (H_3N_8) which is the most important cause of respiratory illness in the horse, and Influenza A/equine 1 virus (H_7N_7) which is still circulating subclinically but is almost considered as extinct. However, a divergence in the evolution of A/equine 2 (H_3N_8) viruses has occurred since 1987 and two families of viruses are now circulating. These were designated European-like and American-like, although representatives of both families had been isolated in both continents. There is increasing evidence from field studies that antigenic drift in the gene coding for the haemagglutinin (HA), which is the major surface protein of these influenza A strains, eventually renders vaccine

strains obsolete and is likely to compromise vaccine efficacy. A new outbreak associated with a possible breakdown of existing vaccines may require a change in the formulation of such vaccines.

In order to overcome this problem the CVMP, as a first step, did prepare a definition of a new active substance, with regard to immunologicals; and as a further step prepared a guideline on the harmonisation of requirements for equine influenza vaccines.

Equine influenza vaccines are well characterized products,and it is unlikely that the replacement of one strain by another would lead to such substantial changes as to justify a new full set of safety and efficacy tests to be carried out. In addition, there is a need to consider reduction of the number of animals used in the testing of medicinal products whenever possible (implementation of the three R rules: reduction, replacement, refinement). Therefore, provided there have been no or few adverse reactions with the previous formulation, a two-fold approach was proposed for the testing of the new formulation:

- cross references to the original dossier would be accepted for those parts which remain unchanged;
- where necessary, the analytical, safety and efficacy sections of the original dossier would need to be amended and new additional data generated.

On top of it,the use of two *in vitro* methods was suggested, in concertation with the European Directorate for the Quality of Medicine:

- Single Radial Diffusion (SRD) to measure vaccine bulk antigen content in terms of HA content;
- Single Radial Haemolysis (SHR) to measure serological responses.

6. Contribution of the CVMP to international harmonisation of requirements

The EMEA is one of the regulatory bodies involved in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). The objectives of the VICH are along the same lines as those proposed for the ICH, its human counterpart.

The VICH intends to:

- provide a forum for a constructive dialogue between regulatory authorities and the veterinary medicinal products industry on the real and perceived differences in the technical requirements for product registration in the EU, Japan and the United States of America, with the expectation that such process may serve as a catalyst for a wider international harmonisation;
- identify areas where modifications in technical requirements or greater mutual acceptance of research and development procedures could lead to a more economical use of human, animal and material resources, without compromising safety;
- make recommandations on practical ways to achieve harmonisation in technical requirements affecting registration of veterinary products and to implement these recommandations in the three regions. Once adopted the VICH recommendations should replace corresponding regional requirements. These recommendations should focus on the essential scientific requirements needed to address a topic and should eliminate unnecessary or redundant requirements;
- the VICH should be conducted in a transparent and cost-effective manner and should provide the opportunity for public comment on recommendations at the draft stage.

7. Contribution of veterinary vaccines to public health and environmental protection

In developed countries, partly as a result of overproduction, public concern for food security has been replaced by a major concern about food safety. This concern has increased following the BSE outbreak. People are concerned about food poisoning, the presence of drug residues following treatment of food-producing animals and the possible transfer of antibiotic resistance from bacteria causing disease in livestock to those which affect man.

Veterinary vaccines may help to solve many of those problems. The best example of a veterinary vaccine used for public health purposes is the vaccination of wildlife against rabies; the primary goal was not to protect wildlife species from rabies but to prevent human exposure and the disease

in the human population. The CVMP contributed to this goal by the evaluation of such a vaccine under the centralised procedure.

Being considered as products working by natural mechanisms, vaccines, except for some of their excipients, do not need to have an MRL (Maximum Residue Limit) determination associated with a withdrawal period. Since vaccine prevention works after a lag period, the use of vaccines intrinsically contains a withdrawal period.

Veterinary vaccines can be used to prevent food poisoning as demonstrated by the "in ovo" vaccination of poultry against salmonellosis, in order to decrease carcass contamination. Vaccines against sheep cysticercosis have been developed experimentally and may lead to the development of similar vaccines to control bovine cysticercosis and thus *Taenia saginata* infestation in humans.

Bacterial resistance to antibiotics is an emerging problem for both the animal and public health sectors. Several antibacterial vaccines used in veterinary medicine disappeared after the second world war, and were replaced by antibiotics. The resistance to antibiotics in the animal health sector with possible implications (albeit rarely) for human health as well as the resistance of several parasites to anthelmintics may lead to the reappearance or the appearance of antibacterial and antiparasitic vaccines.

The use of vaccines may also contribute to avoid the adverse effect of some antiparasitic drugs on the entomo-fauna. Even if other pathways such as selection of food-producing animals for genetic resistance to disease are followed, the story of Marek's disease in chickens demonstrates that vaccines are often more economical to procure an animal's resistance to pathogens.We must nevertheless pay attention to what can be expected from the availability of the entire genome sequences of dog, chicken, cattle, pig and prototype species of fishes.

8.Contribution of veterinary science to technological developments

As previously exemplified by Foot-and-Mouth Disease vaccines and illustrated as follows by vaccines against Classical Swine Fever (CSF), veterinary science embraced the opportunities offered by the new

biotechnologies to develop new concepts for the control of animal infectious diseases.

Large scale vaccination against Classical Swine Fever using classical, atttenuated vaccines, is no longer allowed in the European Union; slaughter policy is the rule. Nevertheless, several countries in the Union have to face regular outbreaks mainly due to the existence of a reservoir in wildlife, the wild boar (*Sus scrofa*). One solution could be to use marker vaccines. Sub-unit marker vaccines have been developed by expressing the major protective immunogen of Classical Swine Fever Virus (a Pestivirus) (CSFV), protein E2, in a baculovirus expression system.

These sub-unit vaccines would allow vaccinated animals to be distinguished from infected ones by serology. These vaccines have been evaluated and accepted by the EMEA. The companion diagnostic test is based upon the detection of antibodies directed against another major immunogen (Non-Structural protein NS2) not contained in the vaccine. Unfortunately, independent experiments showed that the system is yet to be improved. Those sub-unit vaccines being inactivated vaccines are not as efficacious as the previous attenuated ones. Moreover, the available companion diagnostic tests are not yet fully reliable and therefore impede the practical use of these vaccines.

Improved marker vacccines could, nevertheless, help to solve the problem of Classical Swine Fever in Europe since it seems difficult to control the disease without vaccination.

9. Conclusion: a quick look on the centralised applications

A quick overview of the centralised applications evaluated by the CVMP at the EMEA allows to draw some conclusions.

Of course all the applications for products developed using biotechnologies must be examined through the centralised procedure and therefore there is a vast number of immunologicals. There is also a trend to apply preferably for products intended for use in companion animals with only few comfort ones. As far as food-producing animals are concerned, new products are designed to fight against pathologies of major importance.

During the last ten years, through its initiatives, evaluations and advices the Committee for the Evaluation of Veterinary Medicinal Products has been fully committed to the improvement of animal health in the European Union and elsewhere above expectation. I wish the new enlarged veterinary Committee and the EMEA as a whole many more successful years.