Availability of veterinary medicinal products for food producing minor animal species in the Mediterranean area

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Summary. In its historic role, the Mediterranean used to be the unifying element of heterogenic cultures, economies and societies surrounding its three continents’ borders. For the benefit of the leading idea laying behind the present paper and in order to reinforce its original role, the whole Mediterranean area has been deliberately considered as a geographic and legislative unicum relating to MUMS. Such an acronym, well established either in EU countries and internationally, stands for Minor Use/Minor Species and is generally accepted in scientific and regulatory debates to incorporate any reference to a non-core market of a veterinary medicinal product or to an animal species that, conventionally, has not been considered as a major one. Difficulties to develop and market new products have resulted in an internationally recognized severe shortage of drugs for MUMS and, as a consequence, in unacceptable animal suffering, loss of animal life, and financial loss to farm industry. Furthermore, inadequate treatment of sick animals may increase health risks to humans as well as other animals.

Key words: Mediterranean, veterinary drugs, food safety.

CIVILIZATION OF THE ANCIENT MEDITERRANEAN

Among the first human civilizations, two originated in the Mediterranean area: the Nile River Valley civilization which reached Mesopotamia and the trading society of the East coast which from Syria, Lebanon and Israel expanded throughout the Mediterranean Sea. Since early civilizations, agriculture and animal domestication have been recognized as the major pattern of change in the development of human organization. It resulted in a new way of living known as farming which included crop growing and herding sheep, goats, cattle, horses, camels, as source of food, transport, labour and companionship. The Middle-East is generally considered the starting point for Euro-Mediterranean agriculture. Founder species were the main plant and animal species first domesticated over a large area centered between the Euphrates and the Tigri Rivers and then transferred from the Middle-East to other Mediterranean countries through the Danube River and the Mediterranean Sea. Plant species such as wheat, oat, pea and animal species such as dog, pig, goat, sheep and cow were used as the starting basis for agricultural development within the whole Euro-Mediterranean area where cereals and many other domesticated species did not exist as wild species. In the Mediterranean area many sites mainly specialising in sheep and goat breeding, were established between 5000 and 3000 BC. The earliest Italian and French farming communities dated respectively from 5050 and 4250 BC, onwards. In the fourth millennium BC, Spanish agriculture was based on wheat, legumes, sheep and goats. Domesticated from the end of the second millennium BC, the camels became the primary source of transport, shade, milk, meat, wool and hides for the desert’ dwellers.
AN UNICUM OF BIODIVERSITIES IN THE MEDITERRANEAN

The Mediterranean is one of the richest areas in biodiversity with a remarkable variety of climates, environments and fauna. Landscapes have been shaped throughout the centuries by different farmers working and, as a consequence of the large breeding stock and practices peculiar of the many different countries surrounding the Mediterranean Sea, rich diversity of breeds, systems, and animal products is present in that area. While the breeding system more commonly adopted in several Euro-Mediterranean countries relies on rating and genetic selection, in most parts of the dry Mediterranean areas, pastoral systems for sheep, beef, cattle or goats still predominate. Although traditional breeding has been influenced by the globalisation process, the value of Mediterranean small scale and classical farming must still be recognized. Finally, the relation between animals and humans and their surrounding environment as well as traditional animal products for human consumption, still represent important socio-economical and cultural resources for all the Mediterranean countries.

PRELIMINARY REMARKS TO DEFINING FOOD PRODUCING MINOR ANIMAL SPECIES

Healthy animals are of crucial importance to ensuring the quality and safety of food for human consumption. Today, farm animals can benefit from quite a large variety of veterinary medicinal products, including major categories of drugs, such as antibiotics and immunobiologics. A scientific determination must show that no unsafe residues in food will result when a drug is used in an approved manner in a specific animal species. In the last decade, internationally recognized difficulties in establishing maximum residue limits (MRLs) for several veterinary pharmaceuticals used in food producing animals, associated with the need to guarantee their availability in the market, have lead to a pragmatic inclusion of food producing animals in the two categories defined as major or minor species. The threshold of animal numbers and total consumption figures, as well as, in some cases, the low economic value of the single animal (as it is in the case of honey bee) have been used as inclusion criteria of an animal species in either of the two categories. It is worth of note that, given the EU definition of residues (pharmacologically active substances, whether active principles, excipients or degradation products, which remain in foodstuffs obtained from animals to which a veterinary medicinal product has been administered), it is evident that the basic categorization of animal species adopted to overcome major difficulties relating to MRLs’ demand for drugs is not fully applicable to immunological veterinary medicinal products (IVMPs). Indeed, it appears to be more appropriate to consider major/minor markets for such a peculiar category of veterinary products. The following are some practical examples which should clarify the different rationale used for IVMPs. The difficulty in establishing if egg drop syndrome vaccines must be considered products for major or minor animal species, should be overcome by solely considering major or minor markets of these vaccines in chickens and turkeys, respectively. Mixomatosis vaccines are largely available for rabbits but still the market remains a marginal one. Although limited number of vaccines and of poor quality profile, are available for major animal species such as chickens, coccidial vaccines should be considered as a major market for the industry. Clostridial vaccines represent a minor market even in major animal species such as cattle and pigs. Pasteurellosis vaccines should be considered as a minor markets for animals of both major and minor species.

EU LEGISLATION FOR MUMS (MINOR USE/MINOR SPECIES)

While EU legislation recognizes the lack of products for minor use (needed for diseases occurring in major animal species of a limited geographic area) or affecting certain “rare” species (in general, needed for treatment of very small number of animals), no formal definition of minor animal species has been given although the different attempts tried by EU Member States. Following the most commonly shared criteria, food producing animal species other than cattle (dairy and meat animals), sheep (meat animals), pigs, chickens (including laying hens) and salmonidae, are considered as minor animal species in EU. Where a substance is included in Annex I, II and III to Council Regulation (EEC) 2377/90 for a major animal species, extrapolations to the corresponding minor animal species (from cattle/sheep meat to other ruminant meat; from salmonidae to other fin fishes, etc.) can be made. A pragmatic approach has been suggested for honey bees due to the limited number of drugs currently available. Special considerations are envisaged for horses in relation to the highly valuable significance of such animal species. Some discrepancies to the EU approach based on the economic value of animals (in case of funding) or on the dietary intake (in case of extrapolation) can be foreseen. In USA, horses and turkeys are considered as major animal species, while Japan shares the same view of EU countries. By contrast, any category of sheep is considered as a major animal species in both USA and Japan. It is generally accepted that minor animal species usually constitute a marginal component of the diet of the average European consumers. Nevertheless, from Table 1 (www.fao.org/ag/aga/glpha/index.jsp), showing the consistency of those species in the Mediterranean area, it is evident that for certain subpopulations of EU countries as well as for the majority of population of non EU-Mediterranean area, they constitute a major portion of the dietary intake of animal derived products. By contrast, animal species such as pigs, which constitute major component of the diet for the majority of EU-Mediterranean populations, are only rarely reared in non Eu-Mediterranean countries. Finally, it is worth of note the increasing importance of small ruminants, ratites, wildlife and fish as emerging meat products in many countries all over the world.
BIOLOGICAL AND SOCIO-ECONOMIC IMPACTS OF ANIMAL DISEASES

It is not surprising that as well as for all the cultures that need animals for a variety of human usages, primarily as source of food, one of the major effort for the Mediterranean farmers has been to find ways to keep their animals healthy. The Ancient Egyptian art shows how people cared of their cattle and dogs’ health. Archaeological findings demonstrated the advanced level of development of fish culture in ponds among the ancient Romans.

In recent years the biological impact of animal diseases on human societies has had an extremely high profile, with the spread of diseases such as BSE and foot and mouth amongst animal populations, as well as the transmission of diseases such as HIV, Ebola, SARS and Influenza from animal to human populations. Reduction of animal populations caused by a disease in wild environments can dramatically modify the ecological balance of the area. Socio-economic impact of animal diseases are of major concern also. Diseases can reduce the productivity of animals used to produce food and may affect the economic well-being of many industries.

AVAILABILITY OF VETERINARY MEDICINAL PRODUCTS IN FOOD PRODUCING MINOR ANIMAL SPECIES

While there is a great variety of food producing minor animal species, they all share a significant need for pharmaceutical tools to improve their health and welfare. Regrettably, in the last decades, the massive use of drugs in food producing animal species has raised special concerns mainly relating to their residues in edible animal products, to contamination of environment with antimicrobials, disinfectants and pesticides, and to the potential for the development of antimicrobial resistance. Adverse effects of residues in the consumers of animal derived products may result in systemic toxicological effects, genotoxicity/mutagenicity and potential carcinogenicity. Contamination of waterways, aquifer and sewage systems has been associated with drug-resistant food-borne diseases have been linked to the use of antimicrobials (Salmonella and Campylobacter) as well as the potential for development of resistant pathogens and its impact on human health. Having regarded all these aspects, EU legislation has requested an extensive investigation to secure the research and development of high quality and efficacious products for food producing animals while assuring their safety for animals, humans and environment.

As a consequence, veterinary medicinal products have become more and more sophisticated and expensive, and it is well known that pharmaceutical companies shy away from the costly approval process to produce drugs for a market with low profit expectations. Whether the costs for the development, production and marketing of veterinary medicinal products are very high, investments are proportionally even higher for minor food producing species taking into account the limited market size and therefore there is a little

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ND = not determined.


*Table 1* | Consistency of populations of food producing minor animal species in the Mediterranean area
economic incentive for companies to seek approval for MUMS.

Among the consequences of an internationally recognized severe shortage of drugs for MUMS, animal suffering, loss of animal life, and financial loss to farm industry are reported. Furthermore, inadequate treatment of sick animals (millions of animals go either untreated or treatment is delayed), may increase public health hazards. The transmission of parasites or pathogens from animals to humans, or the shedding of infectious agents by untreated animals into the environment, may increase health risks to humans as well as other animals.

Drug are used in food animal production to treat infectious diseases such as mastitis, foot rot, pneumonias (general drug types are antibiotics, anti-inflammatory such as steroids, supportive therapy, milk let-down and parturition drugs, sedative/pain reducers, teat tips and sanitizing agents) and non infectious diseases such as nutrient deficiencies, indigestion, metabolic problems (general drug types are vitamins, minerals, energy additives, digestive stimulants). Drugs are also used for reproductive management such as for inducing estrus and heat synchrononization, calving (certain steroids) and uterine contractions, for maintaining pregnancy, for controlling reproductive infections (antibiotics) and treating various types of ovarian cysts. Other category of drugs used in food animals are production related, internal and external parasite drugs; anesthetics and tranquilizers. Preventive medical compounds include vaccine and sanitizers (insect preventatives in animal environment, and, to an extreme extent, even agricultural chemicals). Improper use of many of these products can kill, permanently injure or render the animal useless as a production unit. All of these reasons are important but of even greater significance is the production of safe food animal products the consumer can trust and buy with total confidence.

The following are examples for which a shortage of medicines has been identified in the Mediterranean:
- goats and sheep: antiparasitics, drugs to treat mastitis, vaccines against Q fever, contagious agalactia, anthrax, brucellosis (B. melitensis), Clostridium spp. salmonellosis (S. abortus ovis), Staphylococcus spp., blue tongue, contagious ectima, sheep pox;
- turkeys: drugs to treat histomoniasis, vaccines against coccidiosis and Newcastle disease;
- rabbits: antiparasitics, vaccines against coccidiosis and Clostridium spp.;
- ratites: vaccines against coccidiosis, salmonellosis (S. pullorum), Newcastle disease;
- bees: nosemosis and American foulbrood.

PRACTICAL PROBLEMS FOR VETERINARY INTERVENTION AND PRESCRIPTION OF VETERINARY DRUGS

The use of drugs and vaccines without specific knowledge of disease patterns and immunology, makes their selection difficult. Thus, the role of the veterinarian in nearly all instances, is of crucial importance. Nevertheless, selection and use of medication for a specific treatment (which implies determination of causes and formulation of a correct diagnosis) and of vaccines for prevention of common diseases in food producing animals must be considered as a primary responsibility for the veterinarian in enhancing a health program together with good management. Indeed, good management practices improve environmental conditions, prevent animal stress that leads to diseases and generally reduce the need for drugs. Therefore, seeking a qualified veterinarian’s advice regarding drug use in any food producing animal is mandatory. Veterinarians should become more aware of their role and the consequences of their choices. While the use of registered veterinary medicinal products is mandatory, the use of a drug in a manner other than that listed on its label constitutes extra label use. This can occur, for example, when a product is used at a different dosage, by a different route of administration, for a different animal species or an unlabeled disease condition. Extra label use criteria are:

- a careful medical diagnosis made by an attending veterinarian within the context of a valid veterinary-owner/caretaker-patient relationship;
- a determination is made that there is no marketed drug specifically labeled to treat the condition diagnosed or drug therapy at the dosage recommended by the labeling has been found clinically ineffective in the animal to be treated;
- assurance that identity of the treated animals is carefully maintained;
- determination of a significantly extended time period for drug withdrawal prior to marketing meat and milk.

If a registered product does not exist, a veterinarian may exceptionally for a single animal or for a small number of animals use, hand out or prescribe:

- a veterinary product registered for another species or for the same species but for another disease, or, if this does not exist;
- a registered medical product authorised for use against disease in man, or, if this does not exist;
- a compound prepared at a pharmacy after a prescription from a veterinarian (extemperaneous drug).

APPENDIX
Provisions for MUMS

1. Extra-label use is possible: in general, the “cascade” system described in article 10 of EU Directive 2001/82 and amended by articles 10 and 11 of EU Directive 2004/28, allows extra label use or the use of a human product by a veterinarian when an authorized veterinary medicinal product is not available. Although the cascade principle should not be intended as a way to overcome insufficient availability of drugs, de facto represents an effective possibility to provide necessary treatments for sick animals where no suitable product is available. The main changes in the directive 2004/28 offer more specific options to address the non availability in exceptional circumstances and
are intended to increase availability of veterinary
drugs, including specific derogations for horses
from the provisions for food producing species.
2. Data extrapolation from major species is allowed
for MRL data only (EMEA/CVMP/153a/97).
3. Several guidelines are under preparation or have
been released for consultation by interested par-
ties concerning data requirements for dossiers for
veterinary medicinal products for minor species or
minor uses:
   i. draft guideline on the quality data requirements for
      veterinary medicinal products intended for MUMS
      (EMEA/CVMP/QWP/128710/2004-Consultation)
   ii. draft guideline on safety and residue data re-
       quirements for veterinary medicinal products in-
       tended for MUMS (EMEA/CVMP/66781/2005-
       Consultation)
   iii. draft guideline on efficacy and target animal
       safety data requirements for veterinary me-
       dicinal products intended for MUMS (EMEA/
       CVMP/EWP/117899/2004-Consultation)

MUMS category and definition is given for vet-
erinary medicinal products other than IVMPs. A draft
guideline on data requirements for dossiers for immu-
nological veterinary medicinal products for MUMS is
under preparation. Whereas it has been recognized the
impossibility to reduce requirements for quality data
for IVMPs, reduction of safety and efficacy data re-
quirements could be explored either in the case of line
extensions (from major species to another major spe-
cies as minor species use or to minor species) or de
novo products for MUMS.

Other new provisions in the amended legislation on
pharmaceuticals that are intended to provide an incen-
tive to industry to bring products for MUMS on the
market, are the prolonged data protection of 13 years
for products for use in fish or honey bees or other spe-
cies designated by the Committology procedure (arti-
cle 13 of EU Directive 2004/28), and the obligation
for EMEA to provide assistance to companies for the
submission of their application for veterinary medi-
cinal products which have limited markets or that are in-
tended for diseases with a regional distribution.

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