European Medicines Agency
Veterinary Medicines and Inspections

London, 15 October 2007
Doc. Ref. EMEA/CVMP/EWP/85954/2007-CONSULTATION

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

CONCEPT PAPER ON THE REVISION OF THE GUIDELINE FOR THE EFFICACY OF VETERINARY MEDICINAL PRODUCTS (PHARMACEUTICALS) FOR USE IN FARMED AQUATIC SPECIES

AGREED BY EFFICACY WORKING PARTY (EWP-V)	July 2007
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	10 October 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2008

The proposed guideline will replace guideline "Efficacy of veterinary medicinal products for use in farmed aquatic species" (7AE22a Volume VIIA)

Comments should be provided electronically to vet-guidelines@emea.europa.eu

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KEYWORDS	Guideline, Veterinary medicinal product, Fish, Efficacy

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1. INTRODUCTION

The current guideline on "Efficacy of veterinary medicinal products for use in farmed aquatic species" was adopted early in the 1990s and last revised in 1994.

Between 1994 and 2004, farmed fish production increased by 76 % in Europe, topping at almost 1.500.000 t in 2004 (Source: FAO Fisheries Global Information System). While fresh water fish and salmonids still dominates the scene, marine species such as turbot, sea bass, sea bream, flounder and cod, that were only emerging from experimental tanks in 1994, are now farmed to significant amounts in many countries, in some areas becoming the predominant agricultural production.

2. PROBLEM STATEMENT

Despite the considerable growth of the aquaculture industry, few pharmaceutical medicinal products have been developed and authorised for farmed aquatic species in recent years.

As development and approval of medicinal products intended for fish have not been able to keep up with the immediate need for effective treatment in the fast expanding aquaculture industry, products authorised for other species have been used according to the cascade.

Anaesthesia, bacterial infections and parasite infestations are currently the predominant field of interest for product development. For treatment of ectoparasites such as sea lice some products exist, but to our knowledge no products are authorised for use against other important parasites in fish, such as trematodes, tapeworms or protozoans.

Currently authorised products are mainly indicated in salmon and/or trout. In salmons, management of infectious disease has shifted from treatment with antibiotics to vaccination. However, there is an increasing need for pharmaceuticals to treat diseases which are not satisfactorily covered by vaccines, most particularly diseases emerging in newly farmed species (cod, halibut, sea bass and bream, sturgeon, perch, etc.).

To encourage the development and authorisation of veterinary medicinal products for use in farmed fish, legislation has provided an extended Data Protection period (13 years). It also provides for an additional period of protection (1 year) for additional food producing species. MUMS Guidelines have introduced the possibility of reduced data requirements, if justified. All these factors will hopefully result in increased submission of applications for medicinal products for fish.

However, industry awareness of the "Fish-guideline" has faded and until recently the guideline could only be found on the Eudralex website, but is now included on the EMEA website. Some feedback from Industry has also indicated that the current guideline could be improved by including more specific guidance.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Since the release of the guideline in the early 1990s, guidance documents have been updated and a number of new guidelines have been developed, which supersede / could replace some of the more general information included in the current guideline by way of references (i.e. NtA,, Guideline on GCP, pharmacokinetics and antimicrobials).

The guideline does not address vaccines. Also, the current guideline is intended for all aquatic animal species, but bivalve molluscs are not subject to therapeutic treatments, and crustaceans or echinoderms production is negligible in Europe. The title should be modified accordingly.

Keeping the broad target group of all aquatic species will furthermore prevent the guideline from giving clear and precise advice applicable for products intended only for finfish, as advice would mostly have to be more general. A revised guideline should, therefore, focus on the particulars relevant for the development and documentation of efficacious medicinal products for farmed finfish, to facilitate the authorisation of such products.

The different challenges encountered when developing and documenting local versus systemic treatment, water-borne versus in-feed treatment, and treatment under fresh water or saline conditions should be addressed.

A more practical approach including relevant examples, in the guideline text itself or as attachments, should be considered.

Taking into account current MUMS guidelines, some advice should also be provided in regard to possible extrapolation of data between species/reduction of documentation requirements, where relevant.

Comments related to the present guideline:

General

The title of the guideline should be changed to reflect that both efficacy and target animal safety of pharmaceuticals are addressed. The term "farmed aquatic species" should be replaced by "farmed fin-fish".

The guideline should be restructured as following:

Preclinical: pharmacokinetic/pharmacodynamic, dose-finding, target animal safety.
Clinical: experimental dose-determination/confirmation studies, field studies.

Section 1 General considerations

Several sections/subsections in the current guideline (i.e.1.1, 1.2, 5.2, 6.4) could be replaced by an introductory section covering general points to consider when planning, conducting and reporting preclinical and clinical studies in farmed finfish.

Standard protocols should be encouraged to facilitate the comparison of study results and extrapolation between species.

As water quality has been identified as the most important element for maintaining healthy animals and ensuring valid experimental results, the effect/impact of water temperature, O_2 contents, salinity etc. should be addressed in more detail.

The concept and use of the term "degree-days" could be described (e.g. effect-duration of antiparasitic treatment).

The possible impact/importance of feed composition in regard to in-feed treatment could be highlighted.

Section 2 Tolerance

In the current guideline this section mainly addresses toxicological studies aimed at establishing the lethal dose in the target animal and reference is made to the OECD Guideline. The text should be revised and reference could be made to the general principles outlined in the guidelines on target animal safety studies. Specific recommendations and requirements concerning target animal safety in fish should be included.

The dose-levels to be recommended must take the nature of the substance/treatment into account, i.e. water-borne treatment e.g. carried out in sea cages or raceways must usually have a very broad margin of safety due to the difficulty of accurate dosing/estimation of water volume.

The required number of fish in each treatment group should be discussed / addressed.

Section 3 Pharmacology

The principles outlined in the pharmacokinetics guideline also apply to fish and reference should be given. However, some specifics for fish should be highlighted. Pharmacokinetic studies in fish are necessary to determine pharmacokinetic parameters under different environmental conditions. Temperature related studies might be necessary and recommendations for minimum and maximum temperatures could be given. If the product is intended for in-feed treatment possible impact of the feed composition has to be considered and investigated, if appropriate.

Some examples of useful methods should be given. Distribution patterns may be illustrated using whole body- and micro autoradiography, while various disposition features including metabolism and mass-balance can be studied using cannulation of blood vessels, urethra and the gall bladder.

The required number of fish per sampling should be discussed.

Section 4 Microbiology and parasitology

This section could be taken out and reference made to the guidelines on antimicrobials, anthelmintics and ectoparasiticides. If special points to consider for fish are identified, they could be included under the relevant sections.

Section 6.1.2 Dose determination/Dose confirmation trial

The tank effect should be taken into consideration and the need of duplicate groups be highlighted.

Section 6.2.3.1 Challenge studies

Challenge models (cohabitant, water-borne, injection) and their relevance to natural conditions (time of challenge / time of treatment / infection pressure etc.) should be discussed.

Section 6.3 Field trials

More practical advice / specific points to consider should be given.

Numbers of individual fish to be examined should be discussed / addressed. It has been observed that the number of examined individuals in studies including thousands of fish has often been unnecessary small, compromising the efficacy evaluation.

4. RECOMMENDATION

The CVMP recommends revising the current guideline to consider the above-mentioned issues. Upcoming procedures / applications for veterinary medicinal products in fish should be used to further identify areas for improvement.

Revising the guideline should also be seen as an opportunity for interested parties to indicate areas where more guidance is needed and / or to give their opinion on how best to meet the requirements. Input from independent scientists, scientific associations and institutes and from the pharmaceutical industry is highly encouraged. Issues put forward could be further discussed in a focus group meeting with invited experts.

5. PROPOSED TIMETABLE

31 December 2007	Deadline for comments from interested parties
1-2 Q 2008	First draft guideline to be discussed in EWP
2-3 Q 2009	Focus group meeting
4 Q 2009	Expected date for adoption by EWP
4 Q 2009	Draft guideline for discussion and adoption for public consultation to CVMP

6. RESOURCE REQUIREMENTS FOR PREPARATION

Member States to provide input via EWP.

Rapporteurs to prepare the draft guideline.

Focus group meeting with invited experts from involved working parties, scientific associations/Institutes and Industry.

Drafting group meetings, as required

7. IMPACT ASSESSMENT (Anticipated)

The proposed revision is not intended to increase the requirements for documentation, but to give clearer and more practical guidance on study requirements. This would diminish the risk for industry having to perform additional studies caused by inadequacies in the documentation submitted for marketing authorisation applications. Thus the revision of the guideline would benefit both industry and regulatory authorities.

Engaging all interested parties in the discussion could establish / encourage a closer communication between the national competent authorities, independent scientific bodies and industry and facilitate the authorisation of more veterinary medicinal products for farmed finfish, thus improving availability.

8. INTERESTED PARTIES

Pharmaceutical industry.

Regulatory authorities.

Scientific associations, e.g. European Association of Fish Pathologists (EAFP), International Society of Aquatic Animal Epidemiology (ISAAE), International Association for Aquatic Animal Medicine (IAAAM).

International organisations, e.g. World Organisation for Animal Health (OIE) - Aquatic Animals Commission; International Council for the Exploration of the Sea (ICES) - Working Group on Pathology and Diseases of Marine Organisms; Food and Agriculture Organization of the UN (FAO) - Fisheries and Aquaculture Department, Federation of European Aquaculture Producers (FEAP).