European Medicines Agency
Veterinary Medicines and Inspections

London, 12 July 2007
Doc. Ref. EMEA/CVMP/IWP/279839/2007

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON DATA REQUIREMENTS FOR IVMPS INTENDED FOR MINOR USE OR MINOR SPECIES/LIMITED MARKETS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	IFAH - Europe	
2	Association of Veterinary Consultants	UK
3	The Impfstoffwerk Dessau	Germany
4	Federation of European Aquaculture Producers	Belgium
5	The Spanish Medicines Agency	Spain
6	Norwegian Medicines Agency (NoMA)	Norway
7	Pharmaq AQ	Norway

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
IFAH-Europe welcomes this guideline on Minor Uses Minor Species (MUMS) for Immunological Veterinary Medicinal Products (IVMPs). We very much appreciate the practical approach taken here in defining what MUMS IVMPs are. Instead of using the rigid definitions for 'minor use' and 'minor species' of the "Position Paper regarding availability of products for minor uses and minor species" (Doc. Ref.: EMEA/CVMP/477/03), which would not be helpful for a number of IVMPs for which relevant but only small markets exist, it has been chosen to define MUMS IVMPs in terms of their relevance for animal (and human) health and the economics of their potential markets (size, price, etc.). This approach is really helpful for improving availability of 'small' IVMPs on the European market.
Although the general approach is positive, the guideline's scope is only for new submissions and line extensions of existing products. We consider that the scope of this guideline should include existing products that have been registered before this guideline comes into force but fall within the scope of the MUMS definition. In fact according to the title of this guideline, and as defined in the above mentioned position paper (EMEA/CVMP/477/03), any application submitted for a IVMP intended for minor uses or minor species should be considered within the scope of this guideline. National or Mutual Recognition Procedures (MRP) registrations already exist within the European Union (EU) for many of the pathogen-disease-animal species combinations named in the draft. Some of the currently registered MUMS IVMPs are old products which are unlikely to be re-developed for territory extensions or variations to match current MRP expectations. To extend the scope to existing products would allow to update and renew old products under the same standards AS for new applications, as well as to re-develop products to match current MRP expectations and reach other EU MSs. Furthermore, since the efforts and costs of variations are certainly relevant for MUMS products too, the scope of this guideline must be extended and include variations, as well.
We would also appreciate to see firmer statements, especially for the safety/efficacy parts to not lose the positive aspects of this proposed guideline. Experience demonstrates that wordings like "Clinical studies may combine safety and efficacy" or "Field data could replace laboratory studies" will create divergent interpretations in MS if conditions/criteria are not clearly established or specific examples included. Finding a way to enforce the decision of the RMS would be extremely useful. Alternatively, we can suggest organising a review of the technical options proposed by the manufacturer through the CMD(v) or the EMEA scientific advice procedure. This advice would be binding for a given period of time.
Other aspects of MUMS IVMPs registrations are not covered by this draft guideline and should also be discussed: 1. Administrative - Regulatory procedure for MUMS IVMPs could be progressed on a quicker timetable as the dossier will contains less data to review. - Existing MUMS IVMPs national licences could be used for an MRP with reduced dossier content (emphasis on quality and 5-years PSUR) and help these MUMS IVMPs to be available in more EU countries. - In the original IFAH-Europe proposal, reference was made to waiving or reduction of fees. This idea has not been taken over in the proposed guideline. IFAH is however convinced that this will form an indispensable part of measures to encourage the development of MUMS IVMPs. There are limits to the reduction of requirements for MUMS products and the influence of these reductions on the development costs is therefore restricted. To really give the availability of MUMS medicines a boost, we believe that waiving or reduction of fees is an important contribution. In addition, the requirement to provide package material in all languages should be omitted for MUMS products.

2. Technical

-There are numerous links between part II and the clinical parts (III and IV). Examples are validation of the potency test (linked to efficacy study) and the batch safety test (linked to overdose laboratory study). The table should stay consistent regarding proposed removed requirements and their impact on other parts of the dossier.

- Generally in the development of a vaccine, efficacy studies form the bulk of the studies performed, and are a major proportion of the cost especially for combination products. The amount of efficacy data required is therefore a key determinant to develop a vaccine for a particular species. We consider that more details on what may or may not be required is essential to make these guidelines useful.

- Another way to enable more vaccines to be authorised for minor species would be to allow extrapolation of efficacy data from one species to another closely related species. For example if a full data package was available for salmon, and then a limited study to show primary efficacy in other salmonids, e.g. trout, should be sufficient for authorisation. Other examples are: chicken and partridge or quail; dairy small ruminants (sheep or goats); dairy cows and dairy buffaloes, etc ...

3. Positive list of MUMS IVMPs

- The two tables provided, one listing IVMPs being considered as MUMS products and one listing potential reductions of the requirements for a Marketing Authorisation dossier, are very useful tools (in the latter table we gratefully recognise much of the table presented earlier by IFAH-Europe for this purpose). We would like to understand the process and frequency for revision of this positive list of MUMS IVMPs to make it more predictable to applicants: a procedure for the revision of the positive list should be included in the guideline.

- Without neglecting other MUMS markets, a special situation exists for the fish vaccine which is a small market with limited profitability and high business risk from the manufacturer's perspective. As a general comment we would like to point out that in the few Ph Eur monographs for vaccines for fish published to date, there is a requirement for safety to be shown for three batches. This is not required for any other species, and should not be required for other fish vaccines for minor use, or for line extensions for fish vaccines already covered by monographs.

SPECIFIC COMMENTS ON TEXT		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
2. Scope		
1st paragraph	The scope of this guideline should be extended to existing products (see general comments).	Accepted in the way that the guideline also applies to line extensions and variations of existing licenses.
4.1. List of IVMPs to be considered as products intended for minor uses		
3rd sentence	It is indicated in the proposed guideline that the positive list table is not intended to be exhaustive and is subject to updating on a case-by-case basis. As manufacturers should not be discouraged from developing a 'small' product because they cannot obtain clarity on its MUMS status, an adequate, transparent and	Accepted, in the way that CVMP will consider changes of the list either regularly of on case by case. It is understood that CVMP will not delay the decision as long as all necessary data will be available.

	relatively rapid procedure for manufacturers how to address and for regulators how to manage proposals for additions to this list, seems a prerequisite here. We therefore propose that an annex containing such procedure will be added to this guideline (we would appreciate to be consulted on this). Authorities or manufacturers could initiate this procedure by providing a rationale to the modification. This should be assessed by CVMP within a given set of time.	
4.2. Specific requirements for IVMPs for minor uses		
	The wording of this section is open for interpretation by the use of the verbs "could" and "may be".	It is understood, that these formulations will be used in an approach favourable to the applicant
	This guideline provides guidance for monovalent products. The current industry trend is to limit the number of vaccinations and therefore to go for combination products. The text should provide guidance on the development of a combination product with for example addition of an infectious agent from table 2 to existing IVMPs not in this table. We would propose to have a reduced development for the combination product, not to have to re-document the entire new combination product.	Accepted. Last sentence of 4.1
Last paragraph; last bullet point	Benefit of treatment statistically significant: the wording of the last sentence must reinforce the idea of flexibility on statistical results.	accepted
Table 1: Specific requirements for IVMPs for minor uses		
Legend	A legend to explain the crosses and the dashes could be usefully added. A cross is sometimes used to accept a positive or negative statement which is sometimes confusing the reader.	accepted
I. Summary of the dossier	Administrative matters: waiving or reduction of the fees. Industry is convinced that this will form an indispensable part of measures to encourage the development of MUMS IVMPs.	Not accepted. Administrative items, such as fee waivers are not subject of scientific guidance.
II.B.	It should be added that the amount of details in the production steps description may be reduced. Experience is that often small details are asked during marketing authorisation procedures, resulting in a lot of less relevant particulars being laid down.	Not accepted. The description of production in application dossiers for IVMPs is that short, compared to application for human and pharmaceutical veterinarian products that further shortage cannot be accepted.

	This cause a burden, if small alterations in the production process are to be established through long and costly variation procedures. This is especially unfavourable in case of 'small' products.	
II.B.3	Validation of changes to the production procedure, if validated for the major use, does not have to be validated for the minor use. Some variations require batch safety studies or batch potency studies to show that the change in the production procedure has no negative consequences. Once done for major use, doing this for the minor use would not have to be necessary.	accepted
II.C.2	Concerning extraneous agents, vaccines for ducks and turkeys are to be controlled for specific pathogens but also for chicken pathogens (these last ones apply to all poultry vaccines), even if the process does not use chicken raw materials. Therefore we would propose to limit the extraneous agent test to non-specific techniques and possibly specific techniques limited to the contaminants of the target animals.	IFAH proposal to reduce EA testing to agents that occur in source species is acceted
II.D.3 / II.E.3 - live new authorisations	This section has a missing character (cross or dash) for results of 2 batches.	accepted
II.E.1.	We consider that the requirement for a second inactivation test should be removed for all inactivated products.	accepted
	The section has a missing character (cross or dash) for batch safety test for line extension live.	accepted
	Fish used in this test are selected by size and not age. This precision should be added.	accepted
	TAST removal for MUMS IVMPs of new a authorisation should not have to wait for production of 10 batches of product but could be granted on a reduced number of batches	accepted
II.F.	The stability data on a presentation should be sufficient to cover all presentations (for example 5 doses vials data to cover for 1 dose and 10 doses).	accepted

III.C	It is not clear from the table if it is intended that the lifting of the GLP requirement is only where safety studies are combined with efficacy studies. If this is the case, then other situations should also be covered – particularly for fish there are only limited GLP facilities and many minor species (for example cod) are not covered.	accepted
	Studies on effect on reproduction or on the immune system may not be required. If not done, relevant warnings should be given on SPC.	accepted
III.C.1	If data on safety of one dose administration are not provided, any warnings required as a result of the overdose administration should be given on the SPC in section 4.6 It is not clear why this line applies only to live vaccines and not to inactivated vaccines.	Accepted All products are covered
III.D and IV.D	The proposal of this guideline is to limit the work required for MUMS IVMPs. The current use of the adjective 'sufficient' should therefore apply on the safety results and not on the number of studies.	accepted
IV.	Studies such as Duration of Immunity, Effect of MDA etc may be omitted provided that it is made clear in the SPC that the data are not available.	Accepted for line extensions
IV.C		
Table 2 Minor uses for IVMPs		
	Fish IVMPs are special cases as indicated in the general comments above and we propose to extend the positive list. As more species are farmed, all of which will be minor, the diseases so far identified in current farmed fishes are likely to be identified in more species, so it makes sense to extend current specific marine species to extended wording to cover all marine fish rather than giving individual species. The similar approach should be considered for: - Equidae, to include horses, mules and donkeys;	Accepted. Table 2 was revised also on request of some IWP-members.

	- Other birds for human consumption: partridge, quail, pheasant, etc; - Dairy small ruminants: sheep and goats.	

GENERAL COMMENTS - OVERVIEW
The Association of Veterinary Consultants (AVC) welcomes the opportunity to comment on the Guidelines (GL) on data requirements for IVMP intended for minor use or minor species (EMEA/CVMP/IWP/123243/2006-CONSULTATION).
These GL are a complement to the already 3 existing GL on the quality, safety and efficacy requirements for Veterinary Medicinal Products (VMP) intended for minor uses and minor species. AVC had provided comments in October 2005 to those earlier proposed GL which came into effect on 1st February 2007.
In view of the specific characteristics of Immunological Veterinary Medicinal Products (IVMP), any reduction in requirements for IVMPs intended for MUMS, in order to reduce costs, shall be evaluated very carefully indeed. This is notably the case for the requirements on the quality of IVMPs containing live micro-organisms. Therefore, the quality requirements - Part II -, for MUMS IVMPs shall be similar to those for normal IVMPs. Reduction in costs will mainly be possible in Part IV, efficacy.
A comprehensive list of Minor Uses for IVMPs is presented. The list contains a great variety of animal species. For purposes of fruitful discussions it is recommended to distinguish between different animal categories: 1. Horses and cattle 2. Pigs, sheep and goats 3. Dogs and cats 4. Poultry and fur animals 5. Fish 6. Other species e.g. guinea pigs The reason for distinguishing these categories is that the cost is related to the value of the relevant category: eg using horses to generate data on efficacy and safety costs far more than using chickens.
The AVC welcomes the CVMP's production of these draft Guidelines specific to IVMP as a considered and useful attempt to encourage and support the development of IVMPs for minor species and/or minor uses. The AVC would like to congratulate the IWP, CVMP and EMEA on this initiative.

What is completely new in this GL for IVMP's, compared with the previous 3 guidelines for VMP, is that the IWP has proposed a list (Table 2) of minor uses for IVMP and has added that this list is not intended to be exhaustive. This avoids the discussions on the definition of "minor species": the list in Table 2 consists of minor uses in a large number of different "major" and "minor" animal species. This is welcomed and is a positive step in the right direction; even if the list could have been more accurate if the interested owners of the different sectors would have been consulted. See our comments here below.
As AVC has already commented in its report on the GLs for VMP, a "minor use" is sometimes difficult to define and will have to be decided on a case by case basis, resulting in regulatory uncertainty, which could deter application. It is therefore absolutely necessary that free pre-submission advice will be available to cover this topic so that realistic development decisions can be made.
Another important introductory remark which AVC is seeking to stress and which has also already been mentioned in our earlier comments is that any decision by the EMEA/CVMP, on the validity of "minor use" for a particular product should be binding for national authorities in order to avoid regulatory uncertainty. At present there is no clear mechanism for this to take place.
Based on information collected by AVC members, we are able to roughly estimate the costs reductions of preparing a dossier for minor use and/or minor species vs an application for a major species. This reduction may be as much as 2/3 reduction of the costs of preparing a dossier for a normal IVMP .Even if those are only very rough estimates, depending greatly on the animal species for which the vaccine is developed; this is nonetheless a very positive sign for the applicants and for the owners of such animals.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Outcome**
Part 1	**Part I: Summary of the Dossier** It is proposed, versus the existing requirements, that no expert reports are required for IVMP intended for MUMS. This will indeed cause a reduction in costs but AVC is not sure that this reduction will facilitate the evaluator review process. On the contrary, the minor uses are sometimes very specific indications and the opinion of an expert, who has an in-depth knowledge of this specific issue of a minor use, could help the	Not accepted. The comments from AVC analyse the cost reduction, when this guideline is applied. No scientific comments were provided. As the AVC members are involved in the production of expert reports it is understood that they did not want to loose their income. No scientific argumentation.

[1] Where available

	evaluators to conduct a more appropriate risk/benefit analysis.	
II.B.3.	**Requirements for Quality: Part II of the dossier** II.B.3. Validation studies Validation studies may be done with R&D batches but results obtained with production batches have to be submitted later. Comment: This will save time but not reduce costs.	No change in the draft NfG necessary
II.C.2.	II.C.2. Starting materials of animal origin. I: Master Seed shall be tested for extraneous agents that may occur in the source species. It is not required to test the MS for extraneous agents that may occur in the target species. Comment: The cost of testing the MS may be reduced by 50% and this is welcomed.	No change in the draft NfG necessary
II.D.3/II.E.3	II.D.3/II.E.3 Testing of 3 consecutive production batches The number of production batches is reduced to 2 batches and results obtained with RD batches are permitted. Note: It is not clear whether 2 batches are also allowed for live IVMPs, but this may be a typing error in the document. Comment: Even if the cost reduction will not be very substantial, this is welcomed.	No change in the draft NfG necessary
II.E.1.	II.E.1. Control tests on finished product. - Batch safety test. Data obtained from test on major species may be used for	No change in the draft NfG necessary

	MUMS. Batch safety test can be done on animal of any age. Batch safety test can be done on final bulk. Comment: This will reduce costs, the amount being dependent on the species category (see above in General Remark). The fact that the test can be done on the final bulk will reduce costs if the product is an independent entity.	
	- Extraneous agents testing. Test may be done on final bulk. Comment: This will reduce costs only if the final bulk can be stored for a long period and is used to prepare one than more final batch.	No change in the draft NfG necessary
	- Test on inactivation (inactivated IVMPs only) No test required on finished product. Comment: The cost of the test that can be omitted is not very substantial.	No change in the draft NfG necessary
II.F.	II.F. Stability Initially the results obtained with one batch are sufficient, but data on another batch shall be supplied later. Comment: This will save time and to some extend reduce costs.	No change in the draft NfG necessary
	Stability data obtained with combined products may be used. Comment: This will reduce costs because no specific testing needs to be done on the product itself. However if no combined product exists there is no advantage.	No change in the draft NfG necessary

<table>
<tr><td></td><td>Table I below gives a rough estimate of the cost reduction in € for the Section II (Quality) of vaccine development for major vs minor uses.

Table I: Estimate cost reduction for the Quality Section

<table>
<tr><th>Requirement</th><th>Major species</th><th>MUMS</th><th>Saving</th><th></th></tr>
<tr><td>Quality total</td><td>69,000</td><td>29,000</td><td>40,000</td><td></td></tr>
<tr><td>Analytical</td><td>20,000</td><td>10,000</td><td></td><td></td></tr>
<tr><td>MS testing</td><td>10,000</td><td>5,000</td><td></td><td></td></tr>
<tr><td>Batch testing</td><td>15,000</td><td>10,000</td><td></td><td></td></tr>
<tr><td>Finished product tests</td><td>10,000</td><td>0</td><td></td><td></td></tr>
<tr><td>Safety test</td><td>3,000</td><td>0</td><td></td><td></td></tr>
<tr><td>Extraneous agents</td><td>5,000</td><td>2,000</td><td></td><td></td></tr>
<tr><td>Stability</td><td>6,000</td><td>2,000</td><td></td><td></td></tr>
</table></td><td>No change in the draft NfG necessary</td></tr>
<tr><td>Part III</td><td><u>III: Part III; Safety</u> Documentation

General Comment: The cost reduction depends very much on the animal species.</td><td>No change in the draft NfG necessary</td></tr>
<tr><td>III.C.</td><td>III.C. Laboratory studies

Laboratory studies for safety may be combined with the laboratory studies for efficacy, without any specific requirements for maximum and minimum potency and passage level of the vaccine strain. GLP requirements may be lifted.

Comment: This is a very useful modification of the requirements.</td><td>No change in the draft NfG necessary</td></tr>
<tr><td>III.C.1</td><td>III.C.1 Administration of one dose.</td><td>No change in the draft NfG necessary</td></tr>
</table>

	This test is not required because it will be covered by the overdose study. Comment: This is only applicable for live vaccines. Since single dose and overdose and repeated dose studies are usually done in one single experiment, the only cost reduction will be that fewer animals are used.	
III.C.2.	III.C.2. Administration of an overdose. This study can be used for post-mortem examination provided the overdose is followed by a single dose. Comment: This does not make a great deal of difference and will not result in a significant cost reduction.	No change in the draft NfG necessary
III.C.3	III.C.3 Administration of a repeated dose. This can be done in combination with the overdose study and needs not to be done if SPC does indicate a single administration. Comment: See comment III.C.1 applicable only for live vaccines.	No change in the draft NfG necessary
III.6	III.6. Live vaccines: III.C.6.1. Spread of vaccine strain Test only required if no satisfactory data are available from literature. Comment: This is very reasonable and will reduce costs.	No change in the draft NfG necessary
III.C.6.2.	III.C.6.2. Dissemination in animal	No change in the draft NfG necessary

<table>
<tr><td></td><td>Test only required if agent does not spread and it is not causing a zoonotic disease.
Satisfactory data available from literature may be sufficient.

Comment: This will reduce costs.</td><td></td></tr>
<tr><td>III.D.</td><td>III.D. Field studies.

Not required if results of laboratory studies are satisfactory.

Comment: This will reduce costs greatly: see Table II</td><td>No change in the draft NfG necessary</td></tr>
<tr><td>III.E</td><td>III.E Ecotoxicity

Bibliographical data may be used.

Comment: This will reduce costs, but not to a great extent.</td><td>No change in the draft NfG necessary</td></tr>
<tr><td></td><td>Table II below gives a rough estimate of the cost reduction in € for the Section III (Safety) and Section IV (Efficacy) of vaccine development for major vs minor uses.

Table II: Estimate cost reductions (euros) possible for safety and efficacy studies

<table>
<tr><th>Requirement</th><th>Major species</th><th>MUMS</th><th>Saving</th></tr>
<tr><td>Lab efficacy and safety testing</td><td>140,000</td><td>90,000</td><td></td></tr>
<tr><td>Shed and spread (live)</td><td>50,000</td><td>0</td><td></td></tr>
<tr><td>Field studies</td><td>80,000</td><td>0</td><td></td></tr>
<tr><td>Ecotoxicity</td><td>5,000</td><td>0</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Total safety</td><td>275,000</td><td>90,000</td><td>185,000</td></tr>
</table></td><td>No change in the draft NfG necessary</td></tr>
</table>

	and efficacy	
Part IV	**IV: Part IV: Efficacy** General Comment: The cost reduction depends very much on the animal species.	No change in the draft NfG necessary
IV.C.	IV.C. Laboratory studies. Laboratory studies for efficacy may be combined with the laboratory studies for safety, without any specific requirements for maximum and minimum potency and passage level of the vaccine strain. GLP requirements may be lifted. Comment: This is a useful modification of the requirements, but is only applicable to inactivated vaccines.	No change in the draft NfG necessary
IV.D.	IV.D. Field studies. Field trial data may replace laboratory data and if sufficient laboratory data are available field trials are not necessary. Comment: This is a very useful modification of the requirements, because it eliminates an entire set of experiments (See Table II here above).	No change in the draft NfG necessary
Table II	**Specific comments on the List of minor uses of IVMPs** (Table II) Different AVC members are in regular contact with the European representatives of the owners of minor species such as e.g. turkeys, rabbits, bees, aquaculture species, etc. Some AVC members contacted the FEAP (Federation of European Aquaculture Producers) and from it received a very detailed report. From this information, at least for aquaculture, and summarised in attached Table III, it may be concluded that,	No change in the draft NfG necessary

	for a number of diseases listed in Table 2 from the proposed GL, vaccines are registered already in the EU, at least in some Member States. It can also been seen that not all diseases of economical importance are present in the Table 2 from the proposed GL. The FEAP sent us also some more general comments on availability of VMP and IVMP for aquaculture and they proposed us to attach it to our own comments. See ANNEX I. We therefore propose that in future more contact should be made with the owners of minor species. The AVC members, who are regularly in contact with the owners of minor species, are prepared to facilitate this process.	

GENERAL COMMENTS - OVERVIEW
Principle of the Guideline/ Field of application: On principle we welcome the concerns and possibilities that the above named draft Guideline is addressing. Additionally we wish to make the following comments: National registrations already exist within the EU for many of the pathogen-disease-species combinations named in the draft. The decision to register them in further EU countries is frequently negative as this is only possible via an MRP process (cost, use, evaluation). Up to now there is no possibility of a simplified MRP or registration under the reduced data clause for these products. From our point of view it would not be justified and it cannot be in the sense of the EU drug legislation that in these cases, in addition, other vaccines with the same claims can be registered in the EU under a reduced data clause. Regular registrations involving a higher level of documentation would clearly be at a competitive disadvantage compared to those requiring a lower level of paper work. As a matter of urgency we feel it is essential that the above mentioned guideline does not only apply to new applications for registration and line extensions but it should also include vaccines with MUMS claims, which have already been registered within the EU. It should be possible for existing national registrations with MUMS claims to have further national processes in the EU or a simpler MRP process with priority over any new MUMS registration application (cascade ruling). Please consider and clarify:It must be possible for different producers to apply for and receive two or more MUMS authorisations for one and the same MUMS claim. For clarification the following scenario: **In any case, there must be no competitive disadvantage for products that have been well tested and documented.**

Other:

We consider the indication essential that different results can be achieved using R&D batches where production down the line must run under GMP conditions.

Table 1:

From our point of view the table is not clear enough in its statement. Please confirm: A cross means that the named reduction of the required data can be used.

Table 2:

Many of the named pathogen-disease-species combinations in the table do not represent cases for minor use. All cases should be excluded from the table that already have national or EU-registrations by several companies in Europe. We name the following vaccines as examples:

Trichophyton verrucosum	Trichophytosis	cattle
Paramyxovirus	Newcastle disease	pigeon
Calicivirus	RHD	rabbit
Rhabdovirus	Rabies	fox
Poxvirus	Myxomatosis	rabbit

From our point of view it could also be useful to dispense with this table altogether. The decision whether a MUMS ruling can be applied or not should be made case-by-case on the basis of clearly defined principles in each country.

Outcome

Most of the comments comply with the comments from IFAH and were therefore considered with IFAH's comment**.** It must be accepted, that products already on the market had higher hurdles than comparable IVMPs which will be placed on the market in future. Unfortunately, this cannot be solved.
Table 1 was revised in order to clarify the message.
The proposals for changes in Table 2 were considered as well.

GENERAL COMMENTS - OVERVIEW

The Federation of European Aquaculture Producers, with the aim of evaluating throughout European States the actual situation regarding the necessary availability of veterinary medicines to secure fish health and welfare, highlights the following points:

New Community registration procedures for medicines have resulted in a position where these are too expensive to be paid for by the aquaculture sector, leading to the following situation:

- A lack of interest from pharmaceutical companies;
- The wide availability, at low cost, of many principle active compounds but for which no licensing dossier is available;
- Not all aquaculture species can be included within MUMS (Minor UsesIMinor Species) and, therefore, cannot be the object of facilitation within the licensing process of medicines that are needed by the sector.

With reference to these afore-mentioned issues, the FEAP requests consideration of the following opinions:

- There is a need for a European review of the status of implementation, at the level of the Member States, of the EC Directives 2001182 and 2004128 on the licensing of veterinary medicines;
- Discussion is needed with DG Enterprise on the involvement of the pharmaceutical companies that are Lpecialised in aquaculture VMPs;
- A more direct 'information" channel is required between the aquaculture sector and the EMEA on MUMS-related issues.

These issues and recommendations form the basis of an argument for the creation of a Working Group on the availability of veterinary medicines for aquaculture that could include representatives from DG Fish, DG Sanco and DG Enterprise, and stakeholders from the production and the pharmaceutical industry.

This Resolution was approved unanimously by the Assembly of the Federation of European Aquaculture Producers at its 38th Annual General Meeting held in Copenhagen on 27th May 2006.

Outcome:
The comment is more a political statement. No scientific comment on the draft NfG was made.

GENERAL COMMENTS - OVERVIEW

For some time there has been considerable concern amongst all parties connected with animal health in the EU, especially the veterinary profession, about the decrease in the availability of authorised veterinary medicinal products. This problem is particularly acute in relation to availability of medicines for minor uses/minor species, where there are no authorised products for some uncommonly encountered disease conditions in major species or no authorised products at all for many indications in certain minor species. The EMEA at the behest of its Management Board began discussions and consultations on this increasing problem in 1998 and, since that time, the CVMP has worked on the matter and was active in initiatives to address the problem of lack of veterinary medicines and to define the problem in some depth and make suggestions for possible solutions.

The CVMP and its Efficacy Working Party (EWP) developed a document called Points to Consider Regarding Availability of Products for Minor Species and Minor Indications (EMEA/CVMP/610/01-Consultation), which was released for public consultation in February 2002. Having reviewed comments received from interested parties following the release of that document, the Committee developed its Position Paper Regarding Availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03). That document aims to define the problem in some depth and makes suggestions for possible solutions. The proposals are characterised as short, medium and long-term goals.

One of the main goals for CVMP is to review dossier requirements for veterinary medicinal products intended for minor uses or minor species and, if possible, to establish standards for demonstration of quality, safety and efficacy for these.

The breeding and the farming of minor species is an important reality in European livestock production. These production activities can only be sustained if they are performed under the appropriate conditions especially with respect to animal health and welfare as well as food safety. The need for veterinary medicinal products (VMPs), especially immunological veterinary medicinal products (IVMPs), for minor use or minor species is self evident in order to avoid the spread of infectious diseases from smaller segments of the livestock sector to larger ones. There has also been increased recognition of the role that many species play in the transmission of zoonoses and this has underpinned the need to pre-emptively control these diseases in the animal host rather than solely focus on the human population. Additionally, recent concerns about the development of antimicrobial resistance through overzealous use of antimicrobial use in humans or animals has led to an increased awareness of the potential benefits to be obtained through disease control by vaccination.

Despite this increasing recognition of the need for vaccines for a variety of diseases in a great number of animal species, there has been no corresponding increase in the number of Marketing Authorisations for these vaccines. There is a general recognition by all stakeholders that this is mainly due to the lack of anticipated financial return on investment for vaccines intended for minor use and in many cases for minor species.
The main goal of the efforts mentioned is therefore to increase the availability of authorised veterinary medicinal products for these minor uses, whilst ensuring animal health and consumer protection.
The concept of considering separately major and minor species and major and minor uses was not considered to be the most appropriate approach for immunological veterinary medicinal products and the only practical approach to the definition of minor use was seen to be a case-by-case approach based on the importance of the product to avoid animal suffering, production losses due to non-availability of treatment, as well as estimates of future market sales and taking into account the species concerned.

Comment 1:
In our opinion, the concept of considering separately major and minor species is also suitable for Immunological veterinary medicinal products because this concept is based on the species itself without taking account if the product is pharmacological or immunological. In fact the critical point is that there is no anticipated financial return on investment for pharmacological or vaccines intended for minor species and for minor use.

Comment 2:
It is amazing that there is no a clear definition of minor species after six years of discussions. Anyway, the new subgroup to discuss this matter at CVMP is welcomed. Anyway our opinion about this classification is as follows:
Major species: Bovine, Ovine (meat production), Porcine, Broilers and layer hens, horses (not meat production), dog, cat, Salmon.
Minor species: Goat, Ovine (milk production), Bees, Rabbit, Rest of avian species except Broilers and layer hens, horses (meat production), pets except dog and cats (p.e: reptiles) and species of acuaculture except salmon.

Minor use: Specific indications in major species where stakeholders do not invest due to the lack of anticipated financial return on investment for vaccines or pharmacological products. This specific indications will be described in table 2.

In some instances, such as products for game-birds or exotic pets, such an approach might seem unnecessarily complex. However, taking into account both the species and the condition to be treated will allow correct decisions to be made in complex situations, such as vaccines for diseases that affect equally both major and minor species.

Comment 3:
In our opinion, the vaccines for diseases that affect equally both major and minor species are not a problem at all because there will be a vaccine available (for major species) that could be also extended to minor species taking account specific guidelines about MUMS
The CVMP therefore considered establishing a list of indications/diseases that can be categorised as minor use for a given species across the European Union in relation to immunological veterinary medicinal products. This approach has the advantage of clearly identifying what indications can be considered to be minor use in relation to immunological veterinary medicinal products.

Comment 4:
This list of indications does not clearly distinguish between major and minor species because there are many diseases that could affect many species. For this reason, try to establish a list of indications/diseases create confusion in this matter instead of clarifying the differences between major or minor species. For example, it is amazing that clostridial diseases appear as a minor use indication for rumiants

Our proposal is that the minor species should be included in this guideline and all indications in this minor species should be deleted from the list.
The aim of this guideline is to define acceptable data requirements for the demonstration of quality, safety and efficacy for IVMPs intended for these minor uses. For new active substances, and for those where limited information is available relating to their use in any animal species, comprehensive information relating to use in the target species will be required.
The guidance provided in this document is as precise as possible. In addition, the CVMP is willing to give consideration to the development of specific additional guidance to facilitate the development of specific IVMPs for minor use should proposals for such guidance be deemed necessary.

SCOPE
This guideline applies to new applications for authorisation of immunological veterinary medicinal products, defined as minor use immunological veterinary medicinal products.
This guideline does not cover IVMPs, where vaccination is only allowed under emergency conditions (e.g. FMD, CSF, AI), based on decisions of the relevant EU bodies and where guidelines, specific for these products, apply.

LEGAL BASIS
This guideline has to be read in conjunction with the introduction and general principles (4) and Title II of the Annex I to Directive 2001/82/EC, as amended. This Annex is currently under revision.

One of the intentions of the revised legislation for the authorisation of veterinary medicines as laid down in the preambles Nr. 9 and 10 of Directive 2004/28/EC is to facilitate the authorisation of certain veterinary medicinal products:

"(9) The costs of research and development to meet increased requirements as regards the quality, safety and efficacy of veterinary medicinal products are leading to a gradual reduction in the range of products authorised for the species and indications representing smaller market sectors."

"(10) The provisions of Directive 2001/82/EC also need, therefore, to be adapted to the specific features of the sector, particularly to meet the health and welfare needs of food-producing animals on terms that guarantee a high level of consumer protection, and in a context that provides adequate economic interest for the veterinary medicinal products industry."

Requirements for Immunological veterinary medicinal products for minor use

4.1 List of IVMPs to be considered as products intended for minor uses
Annexed to this guideline a list of minor uses of IVMPs is provided in Table 2. This list is intended to give a clear indication to all stakeholders on what constitutes a minor use for IVMPs. The list is not intended to be exhaustive and the list will therefore be subject to updating as a result of future experience. Where a product is not covered by the annexed list, a case-by-case decision is necessary to consider whether or not the minimum requirements are applicable to a particular application.

Comment 5:
This table has been reviewed completely.

4.2 Specific requirements for IVMPs for minor uses

Generally, the requirements as mentioned in Annex I, Title II to Dir2001/82/EC as amended, apply to every veterinary medicinal product, including those for minor uses. However, some reductions in requirements could be acceptable and these are listed in Table 1. Please note that the numbering of the tests relies on the current Annex I.

In addition, following reductions in requirements can be considered, on a case-by-case basis :

- The use of other tests than those as described in Ph.Eur. could be facilitated.
- The data on preservative systems could be used for all products of similar IVMPs from the same manufacturer.
- Field studies (if necessary) can cover safety and efficacy aspects in one trial. A more flexible approach may be taken in relation to compliance with Good Clinical Practice (GCP), provided sufficient justification.
- Literature may be used to support the safety and efficacy claim, provided these data were raised by testing the product, the application is made for. Bibliographic data should preferably originate from acknowledged scientific literature ideally from peer-reviewed journals. Exceptions must be justified.

Should adequate documentation not exist in the literature, the efficacy of the product should be demonstrated in appropriately designed studies. The type and number of studies to be conducted will depend on the deficiencies in available data.

- It is recognised that existing studies may not satisfy current GCP requirements. Such studies should be considered acceptable if the design is appropriate to the stated objective of the study.
- The Applicant should test for treatment differences using appropriate statistical methodology. It should be possible in all cases to demonstrate a benefit of treatment (either relative to a control or, where appropriate, relative to pre-treatment data) that is statistically significant. However, the practical limitations of data collection for a minor market product will be taken into consideration.

Outcome:
Most of the comments were agreed by the IWP and incorporated in the final text. Concerning table 2, ES agreed to the final version of June 2007.

GENERAL COMMENTS - OVERVIEW
The Norwegian Medicines Agency welcomes the initiative to establish data requirements for minor use and minor species. Introduction of the concept "minor market" is considered useful. However, we would like to stress the importance that the whole EU/EEA area should be considered when the decision is taken on whether a specific combination of species/indication qualify for "minor market" status. If this principle is not used it will lead to an unacceptable situation where MAs for "minor market" products from one country enter the MRP with CMSs where the product would be "major market". To accept such a product with a reduced data package would be impossible, as it would lead to double standards for similar products, since the CMS would have applied a requirement for a full data package for similar products with national MAs. If a decision to grant "minor market" status is taken nationally by one member state, it must be on the condition that there will be no following MRP including MSs that would not accept the "minor market" status for their countries. Allthough establishing data requirements for "minor market" products is a step in the right direction, the availability problem cannot be solved only by adjusting requirements for MA. It is at least as important to ensure that products can be put and kept on the market in "small market" countries without unacceptable costs. Thus national fee policies, possibility for a common European package in one language and flexibility regarding allowing foreign packages on the market under a national MA are also factors that must be regarded as part of the solution.
Regarding scope of the guideline: 1) As Line extensions are covered (ref table 1), this could also be made clear in the text under point 2. Scope. 2) We assume that the guideline does not cover products containing live GMOs, e.g. vector vaccines. This should be clarified under point 2. Scope.
Regarding Table 2: It is advised that the list should be a conservative one in the start. It will later be easier to add examples than to delete them, so any indication/species where there is dispute or doubt should not be put on the first version of the list to be published in the final document. When indications for salmonid fish are included in the list, the precise identification of the species should be given, e.g. Atlantic salmon instead of salmon. Concerning trout, it should be decided whether rainbow trout is regarded as major or all trout species are regarded as minor. The NoMA would tend to regard rainbow trout as a major species when the whole European market is considered.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE: 4. 1. List of IVMPs to be considered as products intended for minor use

Line no[2]. + paragraph no.	Comment and Rationale	Outcome
line 2-4	It is stated that the list will be subject to update. It should be clarified if the updates will only consist of adding new indications/species to	Accepted. It is understood that the regular update of table 2 will cover all aspects (disease and species)

[2] Where available

	the list or if some indications/species might also be deleted. One could well imagine that an emerging disease is "minor" in the beginning, while it might later spread within and between countries and eventually become "major". The NoMAs position is that it should be possible to remove indications/species from the list.	
GUIDELINE SECTION TITLE: Table 1: Specific requirements for IVMPs for minor uses		
Line no[3]. + paragraph no.	**Comment and Rationale**	**Outcome**
Page 6/16, II.E.1	Regarding second bullet point: For some species, the tolerance is different in young individuals compared to adults. This is valid e.g. for Atlantic salmon, and for this species also the vaccine volume per se will be an extra burden for the target age group compared to larger individuals. Vaccines only intended for young animals of sensitive species should be tested in the target age group. Therefore the text should be amended.	accepted
Page 7/16, III.C.2	The text should be reworded for clearness.	accepted
Page 7/16, III.C.3	First bullet point should be reworded for clearness.	accepted
Page 7/16, III.D	It may not be justified to completely omit field studies for oil adjuvanted fish vaccines. Current knowledge suggests that the degree of local reactions is influenced by the combination of adjuvance system and antigen, and that short time laboratory studies cannot necessarily predict degree of reactions seen over time in the field. For this option to apply it should be sufficiently substantiated that safety data from laboratory studies are appliccable for field situation.	Accepted. As the comment only relies on fish vaccines, it was difficult to take it on board word by word. The revised text covers the sense of the comment
Page 8/16, IV.D	First bullet point should be amended, as this option should be justified on a case by case basis.	accepted
Page 8/16,	Second bullet point should be amended, as laboratory studies cannot	accepted

[3] Where available

IV.D	replace field studies for all diseases, e.g. diseases with multifactorial etiology. For this option to apply it should be sufficiently substantiated that efficacy data from laboratory studies are appliccable for field situation.	
GUIDELINE SECTION TITLE: Table 2: Minor uses for IVMPs		
Line no[4]. + paragraph no.	**Comment and Rationale**	**Outcome**
Page 10/16	Birnavirus: IPN/salmon. This example should be removed from the table. In Norway alone the sales volume for multivalent oil adjuvanted vaccines, used mainly for Atlantic salmon, was approx. 19000 liters in both 2004 and 2005. This represents 190 million doses/year. Full data requirements apply on a national basis for these vaccines. The majority of these vaccines contain the IPN antigen. The NoMA cannot accept a "minor market" status for any of the antigens included in the commonly used vaccines for Atlantic salmon in Norway.	The comments on table 2 were considered at the revision of the draft. Unfortunately, the NO representative did not attend the March and June meetings of IWP.
Page 11/11	Clostridium chauvoei, Cl. haemolyticum, Cl. novyi, Cl. perfringens, Cl. tetani, Cl. septicum: Various disease conditions/sheep. For these examples the species sheep should be removed from the table. Vaccines containing these antigens are routinely used for a large population of Norwegian sheep. Products exist on the market.	The comments on table 2 were considered at the revision of the draft. Unfortunately, the NO representative did not attend the March and June meetings of IWP.
Page 13/16	Moritella viscosa: Winter ulcer (wound disease)/salmon. This example should be removed from the table. Moritella viscosa antigen is included in most of the commonly used vaccines for Atlantic salmon in Norway.	The comments on table 2 were considered at the revision of the draft. Unfortunately, the NO representative did not attend the March and June meetings of IWP.
Page 15/16	Vibrio anguillarum, type 1,2: Vibriosis/salmon. For this example the species salmon should be removed from the table. All Atlantic salmon farmed in Norway are vaccinated against V. anguillarum serotype O1 and O2a . All 190 million doses/year of	The comments on table 2 were considered at the revision of the draft. Unfortunately, the NO representative did not attend the March and June meetings of IWP.

[4] Where available

	multivalent vaccines contain these antigens. Depending on the outcome of major/minor species status for rainbow trout, possibly modification of the term "trout".	

GENERAL COMMENTS - OVERVIEW

Being a small/medium size company developing fish vaccines for the aquaculture business, the initiative to develop guidelines for dossier requirements to facilitate development of safe and effective immunological products of high quality to minor use/minor species is much appreciated.

Our comments are limited to fish vaccines only

It is stated in the introduction that "For new active substances, and for those where limited information is available relating to their use in any animal species, comprehensive information relating to the use in the target species will be required." If this means that vaccines containing such new active substances will be out of the scope of this guideline, then the benefit with respect to new fish vaccines will be considerably reduced.

The aquaculture business is in rapid development and diseases caused by "new" pathogens are frequently emerging, especially as the business is expanded to new marine fish species or current species transferred to new regions with different environmental and climatic conditions. In general, the challenges within the aquaculture business, with poikilothermic animals are rather different from those seen agriculture (land based animals). A separate MUMS guideline for aquatic species may be needed to cover the needs for safe and effective IVMPs within the aquaculture segment. Also, there are a wide variety of fish species, it may therefore be wise to include order of fish rather than fish species, for example vaccines for salmonids rather than vaccine for Atlantic salmon.

The guidelines provide some reductions in the dossier requirements. However, it is not major changes compared to a full dossier, so the impact on development of IVMPs to minor use might be limited. It will be important to clarify that the acceptance of use of R&D batches and number of batches required are consistent throughout the guideline. The proposal to accept stability data from more complex vaccines is constructive as well as the proposal to omit the requirement for expert reports.

Table 2, Minor use for IVMPs. The table as it is presented in this guideline is not consistent with respect to classification of either minor species or minor use and the spread of the disease. The diseases listed for salmon are common/widespread, and the production of salmon is extensive. Thus, it does not seem reasonable to list those diseases in this guideline.

An example is vibriosis which is the most common disease for fish globally. Species like salmon and trout would according to our opinion not fall within the scope of this guideline for this particular disease. However, one could argue that vaccines approved for salmon could automatically be authorised for trout in sea water as well as those species are affected by the same disease.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no[5]. + paragraph no.	**Comment and Rationale**	**Outcome**

[5] Where available

2.	It is not clear whether new active substances are within the scope.	Accepted, scope was revised
4.1.	The procedure to update the list could preferably by clarified better: national level or EMEA/CVMP level.	accepted
4.2	It is important for the industry to have predictable guidelines. The benefit of the guideline is reduced by the fact that many of the reductions in the requirements will be performed on a case-by-case basis. It is recommended that the reductions listed on page 5 are included in table 1.	Not accepted. Section 4.2. is complementary to table 1
Table 1	General: The table will become more accessible if it differentiates between No and not applicable	accepted
II D.3/II.E.3	Please clarify that the requirements for 2 batches in first bullet point applies to second bullet point.	accepted
II.E.1	Bullet point 2, seams reasonable to add "or size" which is more relevant for fish	accepted
II.F	Please clarify that a R&D batch is acceptable. Ref II.E.3	accepted
II.C.1	"One dose administration: May not need to be carried out; overdose test may cover this aspect" Is it an omission that this point is not checked for inactivated vaccines?	Text revised for clarification
III.C.2.	Inconsistency between II.C.1 and this point? as the previous section allows omission of one dose administration	accepted
III.D	Please clarify that "sufficient lab studies" in this context are as outlined above	accepted
Table 2		
General comments to Infectious agent, Disease and Animal species listed related to fish		
The list of infections agents, is not complete. There are several minor infectious agents and fish species that are not listed, as for example *Piscirikettsia salmonis*, *Flavobacterium psycrophilum, Flavobacterium columnaris*, Panceatic diesae virus, ISA virus, HSMB virus and many more. On the other hand,, Vibriosis caused by *V. angullarum* type I and II which are the most wide spread disease in fish are listed as minor. Also birnavirus is listed as minor for salmon. Birnavirus does also cause problems in many other fish species (turbot, cod, and other marine fish species) The infectious agents for fish will normally be infectious to more than one fish species. Therefore the qualification of minor species, should be linked primarily to fish species rather than disease agent. We do therefore proposed that the criteria of minority should be linked primarily to fish species, and linked secondary to Infectious agent. Since new emerging fish species are being introduced yearly, and the fact that new diseases occur all the time, we would recommend that the list		

should include fish species and Infectious agents that are ***not*** minor rather than minor species.

Proposed list for Fish species listed as *not* minor:

Seawater salmonids (salmon and trout in sea water)

Proposed list for Infectious agents listed as *not* minor:

Vibriosis caused by *Vibrio anguillarum*

Furunculosis caused by *Aeromonas salmonicida*

Infectious Pancreatic Necrosis caused by Infectious pancreatic necrosis virus (birnavirus)

Thus vibriosis in Atlantic salmon would not be regarded as a minor species, while vibriosis in cod would be regarded as minor species.

Infection cause by ISA virus would be minor on both cod and salmon.

Outcome:
The comments on table 2 were considered at the revision of the draft.