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Guideline on Data requirements for Immunological veterinary medicinal products intended for minor use or minor species/limited markets

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1. Introduction (background)

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 inappropriate use of antimicrobials 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 and increasing 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. 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.

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.

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.

2. Scope

This guideline applies to new applications for authorisation, line extensions and variations 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.

If the vaccine contains a genetically modified organism (GMO) according to Directive 2001/18/EC as amended, the full set of data with regard to Directive 2001/18 EC should be provided. It is however acceptable to fulfil part of the requirements through data which has been gained with similar GMO constructs already authorised.

3. 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."

4. Requirements for Immunological veterinary medicinal products for minor use/Limited markets

4.1 List of IVMPs to be considered as products intended for minor uses/limited markets

Annexed to this guideline a list of minor uses/limited markets 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 on the CVMP level at regular intervals. 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.

4.2 Specific requirements for IVMPs for minor uses/limited markets

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 provisions for the use of other tests than those described in Ph. Eur. should be facilitated.
- The data on preservative systems could be used for all products of similar IVMPs from the same manufacturer.
- For laboratory trials, the GLP requirements could be lifted, if justified.
- 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.

TABLE 1: SPECIFIC REQUIREMENTS FOR IVMPS FOR MINOR USES/LIMITED MARKETS

A cross (=X) means that the named reduction of the normally required data is accepted

All items not mentioned require the full data according to Annex I of Directive 2001/82/EC

n/a means not applicable

No.	Subject	Proposed reduction	New authorisations		Line extensions	
			Live	Inactiv.	Live	Inactiv.
I. SUMMARY OF THE DOSSIER						
I.C.	Expert reports	No expert reports required	X	X	X	X
II. ANALYTICAL DOCUMENTATION						
II.B.3	Validation of production procedure	▪ Validation studies with R&D batches allowed (to be checked against production batch results later, i.e. post-authorisation)	X	X	n/a	n/a
II.C.2	Starting materials of animal origin	▪ for Master seeds : Extraneous agents testing: only for those agents that may occur in source species	X	X	n/a	n/a
II.D.3 / II.E.3	Results of 3 consecutive production runs	▪ Results of 2 runs (R&D batches allowed) sufficient	X	X	n/a	n/a
II.E.1	Finished product control tests	▪ No repetition of the test for inactivation, when already performed at an earlier stage ▪ Batch safety test for major use/species also valid for minor use/species ▪ Batch safety test: no age requirement and for fish the size should be	n/a X X X X	X X X X X	n/a n/a n/a - n/a n/a	n/a n/a n/a n/a n/a

			New authorisations		Line extensions	
		justified ▪ Extraneous agents testing: allowed to be done on final bulk ▪ Batch safety test may be carried out on the final bulk				
II.F	Stability	▪ Results of 1 batch sufficient (results of another additional batch to be provided post-authorisation). R&D batches are acceptable. The data on one presentation will be acceptable for all presentations provided the presentation is the largest one ▪ Stability data obtained with combined products can be used for 'smaller' combined or single products derived thereof	X X	X X	n/a n/a	n/a n/a
III. SAFETY DOCUMENTATION						
III.C.	Laboratory studies	▪ May be combined with laboratory efficacy studies (if necessary, GLP requirement may be lifted). This means: no min/max dose/potency requirement, no passage level requirement	X	X	X	X
III.C.1	One dose administration	▪ May not need to be carried out; overdose test may cover this aspect	X	X	X	X
III.C.2 III.C.3	Overdose administration Repeated dose administration	▪ If repeated administration is required both these tests could be combined (overdose followed by a single dose). The post-mortem examination can be performed at the very end. If data on one dose administration are not provided and if relevant any warnings required as a result of the overdose study should bee given in the SPC.	X	X	X	X
III.C.4 and 5	Reproducibility and immunological functions	▪ Omission of studies of the effect on reproduction or the immune systems will be accepted. If not performed, relevant warnings should be given in the SPC	X	X	X	X
III.C.6.1	Spread of vaccine strain	▪ Restriction of required amount of data, e.g. literature data may suffice. In case there is not sufficient scientific literature available the test has to be performed.	X	n/a	X	n/a
III.C.6.2	Dissemination in animal	▪ Study not necessary if agent does not spread from animal to animal except for zoonotic diseases	X	n/a	X	n/a

			New authorisations		Line extensions	
		▪ Restriction of required amount of data, e.g. literature data may suffice In case there is not sufficient scientific literature available the test has to be performed.	X	n/a	X	n/a
III.D	Field studies	▪ If laboratory studies sufficiently show no safety risk, field studies are not required. It should be sufficiently justified that data from the laboratory studies are representative for safety under field conditions. Safety data from the field may be required as a follow-up measure.	X	X	X	X
III.E	Ecotoxicity	▪ General data from bibliography may be used	X	X	X	X
IV. EFFICACY DOCUMENTATION						
IV.C	Laboratory studies	▪ May be combined with laboratory safety studies (if necessary, GLP requirement may be lifted). This means: no min/max dose/potency requirements wherever formulation of the final product is standardised, no passage level requirement ▪ For line extensions, omission of studies such as duration of immunity , effect of MDAs etc, is acceptable, provided that it is made clear in the SPC that the data are not available.	X n/a	X n/a	X X	X X
IV.D	Field studies	▪ Field efficacy studies may replace laboratory efficacy studies, when justified ▪ If sufficient laboratory studies are performed: field studies are not required. Efficacy data from the field may be required as a follow-up measure.	X X	X X	X X	X X

References

The following legislation, guidelines and notes for guidance are relevant to this Guideline:

- (1) Directive 2001/82/EC of the European Parliament and of the Council as amended by Directive 2004/28/EC
- (2) Rules Governing Medicinal Products in the EU: Volume 7B "Guidelines for production and control of immunological veterinary medicinal products"
- (3) Points to consider regarding availability of products for Minor Species and Minor Indications (EMEA/CVMP/610/01-CONSULTATION)
- (4) CVMP Position Paper regarding availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03)
- (5) CVMP immunologicals guidelines
- (6) VICH immunologicals guidelines

Table 2: Minor uses/limited markets for IVMPs

Infectious agent	Disease	Animal species
Actinobacillus equuli	Various disease conditions	horse
Adenovirus	Egg Drop Syndrome	turkey
	Hemorrhagic Enteritis	turkey, chicken
	Enzootic Bronchopneumonia	cattle
	Fox encephalitis	foxes
Aeromonas hydrophila	Haemorrhagic Septicemia, Aeromonas Septicemia, Ulcer Disease, Re-Sore Disease	fish
Aeromonas salmonicida	Furunculosis	trout, cod and halibut
Arterivirus	Equine viral arteritis	equidae
Babesia canis	Piroplasmosis	dog
Bacillus anthracis	Anthrax	cattle, sheep, goat, equidae, pig, mink
Birnavirus	Infectious pancreatic necrosis	Salmonids, cod and halibut
Bordetella bronchiseptica	Bordetellosis	rabbit
Borrelia burgdorferi sensu stricto + spp	Borreliosis	dog
Brucella abortus	Brucellosis	cattle
Campylobacter fetus	Campylobacteriosis	cattle
Calicivirus	Rabbit haemorrhagic disease (RHD)	rabbit
Chlamydophila abortus	Chlamydiosis	sheep, goat
Clostridium botulinum	Botulism	cattle, fox, racoon dog, mink, swan, goose, duck
Clostridium chauvoei	Various disease conditions	pig, cattle, equidae, goat, rabbit
Clostridium haemolyticum	Various disease conditions	pig, cattle, equidae, goat, rabbit
Clostridium novyi	Various disease conditions	pig, cattle, equidae, goat
Clostridium perfringens	Various disease conditions	pig, cattle, goat, rabbit
Clostridium tetani	Tetanus	pig, cattle, dog, rabbit
Clostridium septicum	Various disease conditions	pig, cattle, equidae, goat, rabbit
Clostridium sordelli		pig, cattle, goat
Corynebacterium spp		cattle, pig
	Pseudotuberculosis	sheep and goat
Corynebacterium pyogenes		cattle, sheep, goat, rabbit

	Disease	
Coxiella burnetti	Q-Fever	cattle, sheep, goat
Dichelobacter nodosus	Foot rot	sheep and goat
Dictyocaulus viviparus	Dictyocaulosis	cattle
Erysipelothrix rhusiopathiae	Erysipelas	turkey, sheep
Escherichia coli	Colibacillosis	sheep, goat, equidae, dog, chicken, rabbit
Equines Rotavirus	Equine rotavirus infection	equidae
Flavivirus	Louping ill	sheep
Flavivirus	West Nile disease	equidae
Flavobacterium spp		salmonids
Giardia lamblia	Giardiosis	dog
Haemophilus paracuniculis		rabbit
Haemophilus paragallinarum	Infectious Coryza	chicken
Haemophilus parasuis	Glässer´s Disease	pig
Haemophilus somnus		cattle
Herpesvirus	Canine herpes infection	dog
	Equine Rhinopneumonitis, Equine Herpes Virus 1 and 4 infection	horse
	Duck plaque	duck
	Herpes v. meleagridis	turkey
	Marek's Disease	turkey
Lactococcus garviae	Lactococcosis	salmonids
Klebsiella pneumoniae	Endotoxaemia	horse, dog
Leishmania sp	Leishmaniasis	dog
Leptospira spp.	Leptospirosis	pig, cattle
Mannheimia haemolytica	Enzootic Bronchopneumoniae	pig, horse, sheep, goat, rabbit
Microsporum canis	Microsporosis	horse, dog, cat, rabbit, guinea pig
Microsporum canis var. distortum	Microsporosis	horse, dog, cat, rabbit, guinea pig
Microsporum canis var. obesum	Microsporosis	horse, dog, cat, rabbit, guinea pig
Microsporum gypseum	Microsporosis	horse, dog, cat, rabbit, guinea pig
Mycobacterium paratuberculosis	Paratuberculosis	cattle, sheep, goat, zoo animals
Mycoplasma agalactiae	Contagious agalactia	sheep, goat
Mycoplasma hyorhinis		pig
Mycoplasma capricolum	Contagious agalactia	goat

	Disease	
Mycoplasma mycoides LC.	Contagious agalactia	goat
Mycoplasma bovis	Pneumonia	cattle
Mycoplasma synoviae		Turkey, chicken
Morbillivirus	Canine Distemper	mink, ferret, racoon dogs, foxes
Moritella viscosa	Winter ulcer	Salmon, cod, trout
Nodavirus	Viral Nervous Necrosis/ Viral Encephalo-Retinopathy	Cod, seabass, turbot
Ornithobacterium rhinotracheale	ORT	chicken, turkey
Paramyxovirus	Newcastle Disease+PMV1	other poultry species than chicken
	Paramyxovirosis	turkey
	Enzootic Bronchopneumonia	cattle
Parvovirus	Parvovirus hepatitis	duck, goose
	Mink enteritis	mink
Pasteurella multocida	Pasteurellosis	cattle, horse, sheep, rabbit, chicken, goat, duck
Pasteurella trehalosi	Various disease conditions	sheep
Photobacterium damselae subsp. piscida	Pasteurellosis/Photobacteriosis	marine fish: Gilthead:sparus aurata
Picornavirus	Duck Hepatitis	duck
Piscirickettsia salmonis	STS (salmonid rickettsial septicaemia)	salmonids
Pneumovirus	Turkey Rhinotracheitis / Swollen Head Syndrome	chicken, turkey
Poxvirus	Canary Pox	canaries
	Fowl Pox	chicken
	Pigeon Pox	pigeon
	Myxomatosis	rabbit
Poxvirus	Ecthyma	sheep, goat, zoo animals
Poxvirus	Immunomodulator	dog, cat, horse, pig, cattle
Renibacterium salmoninarum	BKD (Bacterial Kidney Disease)	salmonids
Rhabdovirus	Rabies	horse, sheep, goat, cattle, ferret, fox, racoon dogs
Reovirus	Tenosynovitis	chicken
Salmon Pancreas Disease Virus	Salmon Pancreas Disease	salmonids and sea trout
Salmonella abortus ovis	Salmonella abortion	sheep, goat
Salmonella dublin	Salmonellosis	dog, cat
Salmonella Enterica, various serovars	Salmonellosis	pig, cattle, horse, dog, pigeon
Salmonella typhimurium	Salmonellosis	cattle, sheep, goat, rabbit

	Disease	
Serratia marcescens	Endotoxaemia	horse, dog
Shigella flexneri	Endotoxaemia	horse, dog
Sleeping Disease virus	Sleeping Disease	trout
Staphylococcus aureus	Mastitis	cattle, sheep, goat
Staphylococcus spp	Mastitis	sheep, cattle
Staphylococcus spp	Pyodermatitis, conjunctivitis	dog, rabbit
Streptococcus parauberis	Fish streptococcosis	turbot, marine fish
Streptococcus spp	Mastitis	cattle
Streptococcus pneumoniae	Streptococcosis	horse
Streptococcus equi ssp. equi	Strangles	horse
Steptococcus equi ssp. zooepidemicus	Streptococcosis	horse
Streptococcus suis	Streptococcosis	pig
Tenacibaculum maritimum (Flexibacter spp)		Turbot, sea brass and sea bream
Teracapsula bryosalmonae	PKD (Proliferative Kidney Disease)	salmonids
Toxoplasma gondii	Toxoplasmosis	sheep
Trichophyton equinum	Trichophytosis	horse, dog, cat
Trichophyton verrucosum	Trichophytosis	cattle, horse, dog, cat
Trichophyton mentagrophytes	Trichophytosis	cattle, horse, dog, cat
Trichophyton sarkisovii	Trichophytosis	cattle, horse, dog, cat
Yersinia ruckeri	Enteric red mouth disease	trout
Vibrio anguillarum type 1,2	Vibriosis	trout, sea bass, sea bream, turbot
Vibrio salmonicida	Cold water vibriosis	Salmon and cod
Diagnostics		
Brucellin		cattle
Tuberculin, avian		cattle, sheep, goat, chickens, horse, pig
Tuberculin, bovine		cattle, sheep, goat, chickens, horse, pig
Antisera		
Clostridium tetani antiserum	Antitoxin	all tetanus sensitive animal species