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POINTS TO CONSIDER REGARDING EFFICACY REQUIREMENTS FOR MINOR SPECIES AND MINOR INDICATIONS

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Purpose and background of the document

In the EU, Member States, CVMP, VMRFG, FVE and other organisations have raised concerns on availability of veterinary medicinal products. The present regulatory situation in the European Union requires an extensive investment to secure the research and development of products for food-producing animals – especially for minor food-producing species. This problem is not unique for the EU: the FDA has also published its guidance document on the topic (January 1999) " FDA Approval of New Animal Drugs for Minor Use and Minor Species".

In food-producing animals the major obstacle to ensure sufficient availability of medicines has been the lack of MRLs, even for a number of substances considered essential for treatment of animals. In addition, for rare indications or for minor species, the efficacy requirements are considered too extensive for the veterinary pharmaceutical industry. Existing products are also withdrawn from the market due to a declining market sector and rationalisation of the industry.

A more pragmatic approach concerning the requirements for efficacy documentation for products for minor species and minor indications are needed to avoid case-by-case decisions and to provide appropriate guidance to industry. These guidelines aim at reducing requirements for proving efficacy and target animal safety, however, still providing acceptable assurance on efficacy and target animal safety. Such a reduction of requirements for proving efficacy and target animal safety should free up resources for companies to develop medicines for niche markets.

The Efficacy Working Party (EWP) was asked by the CVMP in October 1998 to develop a minor species and minor indication policy paper for efficacy testing on pharmaceutical veterinary medicinal products. The EWP forwarded the document to the CVMP in July 2001.

The existing guidelines and position documents on efficacy and target animal safety concerning possible minor species/minor indications in the EU are:

- Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species, EMEA/CVMP/153a/97-FINAL
- Update of Position Paper on Availability of Veterinary Medicines, EMEA/CVMP/411/00-FINAL.
- VMRFG list of Orphan Drugs in the Veterinary Field, Pharmaceuticals Necessary for Veterinary Use, which are Lacking or May Be at Risk, October 1999.
- Guideline for equine anthelmintics: Specific requirements
- Guideline for anticoccidials used for the therapy of coccidiosis in chickens, turkeys and geese.
- Guideline for veterinary medicinal products controlling varroa jacobsoni and acarapis woodi parasitosis in bees.
- Guideline for efficacy of veterinary medicinal products for use in farmed aquatic species.

The above-mentioned guidelines were produced for practical purposes, as no clinical practice guidance was present at that moment. They do not relax the requirements for studies in minor species.

1. DEFINING THE PROBLEM

1.1. Defining a major or minor species

For the establishment of MRLs, the following classification for food producing animals has been made by the CVMP, based on the importance of these animal species in the EU:

Major food-producing species:

- Cattle and sheep (meat)
- Cattle (milk)
- Pigs
- Chickens (including eggs)
- Salmonidae

As a consequence of this definition, other animal species by default are classed as minor:

Minor food-producing species:

- Other ruminants, minor ruminants (bovidae including caprinae) and their milk, deer including reindeer
- Sheep milk
- Other avian species (game birds and ratites) and their eggs
- Other fish species
- Other mammalian species (horse and rabbit)
- Honey bees

Major species require a full data set for the establishment of MRLs. For the minor species extrapolation can be made from MRLs from the corresponding major species, providing that there are 3 major species.

The MRL legislation and its related CVMP document on the definition of major species / minor species are aimed at to ensure consumer safety. However, efficacy requirements and target animal safety requirements are aimed at proving efficacy and animal safety in the target animal.

Examining the European population data for the species and comparing it to data provided by the national experts at the EWP for minor species confirms the split between major and minor species. For mammalian species in the EU a threshold value of 15 million animals would confirm the listing above (see tables 1 - 3), except for rabbits, which are estimated to number >260 million for meat and fur production and >15 million as pets but restricted by geographical distribution to certain markets.

Poultry and fish are a different issue because of the huge animal numbers involved. In this case the threshold number should be higher: at 200 million for poultry and at 100,000 tons fish produced annually in the EU. These thresholds would place chickens and salmonids as major species and the remainder as minor species. The use of consumption figures were also considered for other animal species than for fish but it was concluded that these data are biased due to internal trade and import of food.

Bees are considered to be a special case and should be accepted as a minor species.

Animal species numbers

Numbers of animals of potential minor species are listed in Annex I according to information from the members of the EWP and Eurostat (Agricultural Statistical Yearbook 1999 and 2000). On the basis of the tables the following food-producing species could generally be regarded as major species, based on their population numbers in the EU:

- Cattle (Milking and beef)
- Sheep (Both milking sheep and meat-producing sheep)
- Pigs
- Chickens
- Dogs
- Cats

The total animal numbers in European Union are summarised below in the Tables 1, 2 and 3.

Table 1. *Number of livestock in the European Union in December 1999 (millions of animals). Source: Eurostat.*

Cattle (total)	Dairy cows	Pigs (total)	Fattening pigs over 50 kg	Sheep	Goats	Chicken
83	21	124	47	96	12	1017

Table 2. *Estimates of numbers of some other food-producing animal species in the European Union (millions of animals).*

Milking sheep	Rabbit	Deer/ Reindeer	Horses	Farmed fish (tons produced)	Turkey	Duck and goose
20	over 260 millions	0.5	2.6	430,000 tons*	115	75

* Besides, Norway produces more than all the EU countries together. Majority of produced fish in the EU is salmonids (estimate: at least 300,000 tons, thus other fish species become minor).[1]

Table 3. *Estimates of numbers of some non- food-producing animal species in the European Union (millions of animals).*

Dogs	Cats	Pet rabbits	Minks (breeding animals)	Foxes (breeding animals)
41	39	Above 15*	4	0.5

* rough estimate because lots of data missing from individual countries.

1.2. Defining a major or minor indication

The proposed definitions of major / minor species are not entirely suitable for the identification of minor indications. For example some disease might have a very low prevalence in a major species and therefore can be considered to be a minor use. In addition, animals living in different parts of Europe may suffer from different kinds of diseases and the proposed major/ minor species definitions focuses solely on food producing animals and excludes companion animals.

This proposal considers the global animal numbers across Europe and does not take into account the variation of numbers within Member States. For example, the number of goats exceeds 1,000,000 in each of Spain, Italy and Greece (approx. 85% of the European population). However the pharmaceutical industry will regard the potential market as that of Europe and will not judge it by Member State.

It is proposed to establish a threshold value to define minor use. This could be based on the number of cases treated as in the human sector. However, this type of epidemiological data is not reliably collected across the Member States. So the alternative proposal is to establish a threshold based on sales value. This would need to be discussed with the pharmaceutical industry but a figure of 2 million Euros for total European sales would be a reasonable starting point. This would be the minimum sales needed to justify developing a product for a single indication for a new molecule or, for an additional use for an existing product. It is recognised that this threshold would need to be established by reasoned estimation.

The current legislative situation in the Member states with regard to requirements for minor species and minor indications

Directive 2001/82/EEC Art. 10 permits Member States in exceptional circumstances to allow extra label use of veterinary medicinal products or the use of a human product by a veterinarian when an authorised veterinary medicinal product is not available (cascade principle). Although this article is intended to be applied in life threatening situations, it is in fact used for all extra label use. Although such use is permitted, directives (e.g. 2001/82/EEC) are not intended to compensate for insufficient availability. For the veterinary medicine, extra label use, as well as the use of human medicinal products, can be recommended in books, articles and Formularies. Members States are aware of this situation, tolerate or even endorse it.

The EWP compiled information about the special procedures used in the Member States for licensing veterinary medicinal products for minor indications. Member States did not have clear definitions for minor use or minor indications.

Considerable differences between the Member States exist concerning the specific authorisation procedures. Most of the Member States do not have a specific, clearly defined procedure to handle minor species/indications, but do allow the use of imported or, 'not in state registered' veterinary medicinal products on the basis of the Directive 2001/82/EEC (Article 10). For food producing species, the MRL Regulation 2377/90 is often referred to. Member States use the cascade system to meet the needs for the use of special drugs. Mostly, the concerned veterinary medicinal preparations are imported under strict conditions for a clearly defined use. Very few countries have a specific authorisation procedure in place and applications are mostly treated on a case by case basis. Authorisations given are always of limited duration (1-5 years), with renewals being possible. In the UK it was possible to obtain a provisional marketing authorisation with less requirements for Part IV of the dossier. Fees required differ considerably from one country to the other. In general, the required specific scientific information needs to be complete from a quality and safety point of view (as in a full dossier). Pharmacokinetics, target species tolerance and depletion confirmation studies are asked for by some countries. Most countries are initially less demanding on the Efficacy part (Part IV) of the dossier at the moment of application. However, additional data usually have to be submitted during the year(s) immediately following the initial application in order to obtain a renewal of the authorisation or to obtain a full Marketing Authorisation.

2. SUGGESTIONS FOR POSSIBLE SOLUTIONS

The gathered data potentially provides a clear identification of minor species / minor indications which would allow the establishment of specific efficacy and target animal safety guidelines.

It would be necessary to develop guidance on a minimum acceptable data package for efficacy for drugs identified for minor species/minor use.

In addition to such efficacy monographs for minor uses further measures could be envisaged:

- The marketing authorisation procedure for products intended for minor use could be simplified
- Fee reduction could be considered for the authorisation process and for scientific advice
- Based on preclinical data a provisional authorisation could be envisaged

2.1. Dossier requirements

As the starting point, the importance of the drug in question to avoid animal suffering, production losses etc. should be evaluated. Product specific data should be collected/produced in order to ensure target animal safety and efficacy. At least the minimum effective and the maximum tolerated doses should be known for the target animal species.
If relevant information is available, bibliographic data should be acceptable for dose confirmation, target animal safety and clinical efficacy. GLP/GCP compliance could be relaxed to permit the use of clinical reports as justification of efficacy.

For all products (human and veterinary), present on the EU market, a substantial data package is present - otherwise the product could not be authorised and marketed. This information usually covers the basic studies on the active substance from experiments in laboratory animals (pharmacodynamics, pharmacokinetics, toxicology, and mutagenicity). Depending on the application of the product specific preclinical and clinical data will be present.

In order to help defining an application for minor use and an acceptable efficacy data package an example is given in annex 2 (“decision tree”).

2.2. Simplifying the procedure

To avoid problems of inconsistent interpretation of guidelines that arise from the use of the Mutual Recognition Procedure (possibly leading to an increase of costs for the applicant) it should be considered to allow the use of the Centralised Procedure as an alternative for all "minor" animal species and / or indications with the possibility of a fee reduction.

2.3. Financial support

At present, there is an overall lack of veterinary epidemiological data for diseases in minor as well in major species. Such information is crucial to assess and to define minor use /minor indications and in light of animal welfare to identify indications which currently cannot be treated with the available medicinal products in EU. In the interest of maintaining animal welfare, the Community could be urged to take part of the responsibility to fund epidemiological studies aimed at identifying such minor use.

2.4. Provisional authorisations

Based on sufficient preclinical data a provisional authorisation could be considered awaiting more efficacy data over a period of e.g. one year with a possibility of renewal (Directive 2001/82/EEC, Art.

26). In this way applicants will be able to collect sufficient data in cases where animal numbers and / or the incidence of diseases are low.

References:

Communication from the Commission to the Council and the European Parliament 5/12/2000 – COM(2000) 806.final - on 'Availability of veterinary medicinal products'.

Guidance for Industry: FDA Approval of Animal Drugs for Minor Uses and Minor Species, January 1999.

Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species, EMEA/CVMP/153a/97-FINAL

Update on Position Paper on Availability of Veterinary Medicines, EMEA/CVMP/411/00- FINAL.

VEDDRA- Animal Species List, CVMP/PhVWP/024/99.

Drug availability for Minor Species (2), The Regulatory Affairs Journal, Jan.1998.

Availability of Veterinary Medicinal Products, The Regulatory Affairs Journal, Dec.1999.

VMRFG list of Orphan Drugs in the Veterinary Field, Pharmaceuticals Necessary for Veterinary Use which are Lacking or May Be at Risk, October 1999.

Annex 1

Number of animals in the EEA, food producing species

Mammals

Table 1

Countries	Sheep (milking sheep)	Goat	Rabbit	Deer/Reindeer	Horses
Austria	352,000 (none/few)	57,993	NA	39,086/0	75,347
Belgium	160,000 (none/few)	11,000	5,000,000	7164/0	29,712
Denmark	106,000 (1,000)	2000	2000	22,000/0	139,000
Finland	77,000 (none)	6,600	< 1000	189,700	56,100
France	9.4 millions (1,070,000)	1,187,000	84,418 t ≅ 28,000,000	NA	500,000
Germany	2,400,000 (few?)	120,000-130,000	62,000,000 (meat/fur)	25,000	400,000
Greece	6,860,000	3,900,000	1,411,100		100,229
Iceland	490,538 (none)	502	726	0/ca. 2,500	77,330
Ireland	8,000,000 (none/few)	13,500	0	16,000/0	52,000

Countries	Sheep (milking sheep)	Goat	Rabbit	Deer/Reindeer	Horses
Italy	10,890,000 (a lot: 10 million?)	1,347,000	NA	13,000/0	310,000
Netherlands	1,400,000 (none/few)	153,000	440,000	-/2 small farms	112,000
Norway	2,324,789 (during summer) (955,367 female breeders kept during winter)	68,714	3,400 (female breeders with ≥ 1 litter	550/183,100	26,959
Portugal	3.5 millions (a lot: 1 million?)	Total: 537.241 Female breeders: 456.431	1.673.702	68 farms 708 female breeders	96.471
Spain	23 millions (4,400,000)	2,600,000	100,000,000	0/0	260,000
Sweden	437,000 (200)	5,000	NA	20,000/227,000	250,000
United Kingdom	29,7 millions (few: 1 million)	80,000	75,000 (meat production)	38,000/0	173,000

Number of animals in the EEA, food producing species

Fish

Table 2

	Fish	Eel
Austria	4,800 t	fish produced in tons; eels will be combined
Belgium	91 fish farms	NA
Denmark	40,000 t	27,000 t
Finland	16,000 t	NA
France	37,400 t	NA
Germany	21,000t (trouts, carps, others)	NA
Greece	53,000 t	NA
Iceland	4,500 t (fish farming)	0
Ireland	40,000 t	NA
Italy	65,000 t	NA
Netherlands	2000 t	3000 t
Norway	Atlantic salmon: 427,324 ton (2000) Trout: 47,497 ton (2000) Arctic char: 426 ton (1999) Cod: 149 ton (1999) Halibut: 453 ton (1999) Blue mussels: 663 ton (2000) Oysters : 560,000 shells (2000) Scallop : 2,700,000 (2000)	NA
Portugal	7,170.3 ton	16,6 ton
Spain	Trout: 30,000 ton Marine fish : 9,000 ton Total marine fish with molluscs : 300,000 t	0
Sweden	7,000 ton	NA
UK	165,000 t (Salmonidis)	< 1 tonne – farmed 200 tonnes – wild i.e. caught

Number of animal in the EEA, food producing species

Birds

Table 3

Countries	Turkey	Duck and Goose	Ostrich/Emu	Pigeon, quail, fowl	Pheasant, partridge, Mallard duck	Other birds
Austria	645,000	121,900	no figures available	no figures available	no figures available	no figures available
Belgium	278,000	51,000	10600	6,050,000	194,000	232,000
Denmark	312,000	338,000	< 5000	85,000		NA
Finland	180,000	NA	NA	NA	NA	NA
France	705,605 t ≅ 85,000,000	255,415 t ≅ 60,000,000	1,200 t ≅ 20,000	70,826 t ≅ 67,000,000	15,500,000	7,100,000
Germany	7,300,000	No data	8000	86,000,000 (fowls)	No data	3,000,000
Greece	180,000	222,000	2,400	NA	NA	87,500,000
Iceland	500	1439	0	0	0	NA
Ireland	2,000,000	Duck - ~100,000 Geese – 25,000	0	0	0	NA
Italy	17,500,000	1,400,000	40,000	11,700,000		NA
Netherlands	1,400,000	6,000,000/year	<2000	NA	NA	NA
Norway	266,500 (for slaughter)	28,000 (for slaughter)	2300 (mostly breeders)	None/ Negligible	None/ Negligible	None/ Negligible

Countries	Turkey	Duck and Goose	Ostrich/Emu	Pigeon, quail, fowl	Pheasant, partridge, Mallard duck	Other birds
Portugal	1.263.076	758.298	< 3500 breeders (<> 42,000/year for slaughter) (1999)	NA	249,000 (pheasant) 884,600 (partridge) (1999)	1350 ton (1997)
Spain	200,000	100,000	100,000	1,227,000 quails	2,815,500 (partridge)	10,323,000
Sweden	500,000	Duck 5,000 Goose 30,000	6,000	NA	500,000	NA
United Kingdom	28,000,000 slaughtered p.a. (Total carcase weight – 264,000 t)	19,000,000 slaughtered p.a. (18m ducks, 1m geese) (Total carcase weight: 44,000 t 41kpk ducks, 3kpk geese)	15,000	7,000,000 pigeons shot p.a. No data on quail	32,098,500 (25m pheasants, 7,028,500 partridges, 70kpk Mallard ducks)	Insignificant

Number of animal in the EEA, food producing species
Honey Bees

Table 4

Countries	colonies
Austria	330,672 colonies
Belgium	(8500 bee holders)
Denmark	100,000 colonies
Finland	40,000 colonies
France	1,500,000 colonies
Germany	1,000,000 colonies
Greece	1,380,070 colonies
Iceland	practically 0
Ireland	
Italy	1,200,000 colonies
Netherlands	80,000 colonies
Norway	100,000 colonies
Portugal	228.573 colonies
Spain	1,854,000 colonies
Sweden	110,000 colonies
United Kingdom	200,000 colonies

Number of animals in the EEA, Non-food-producing species

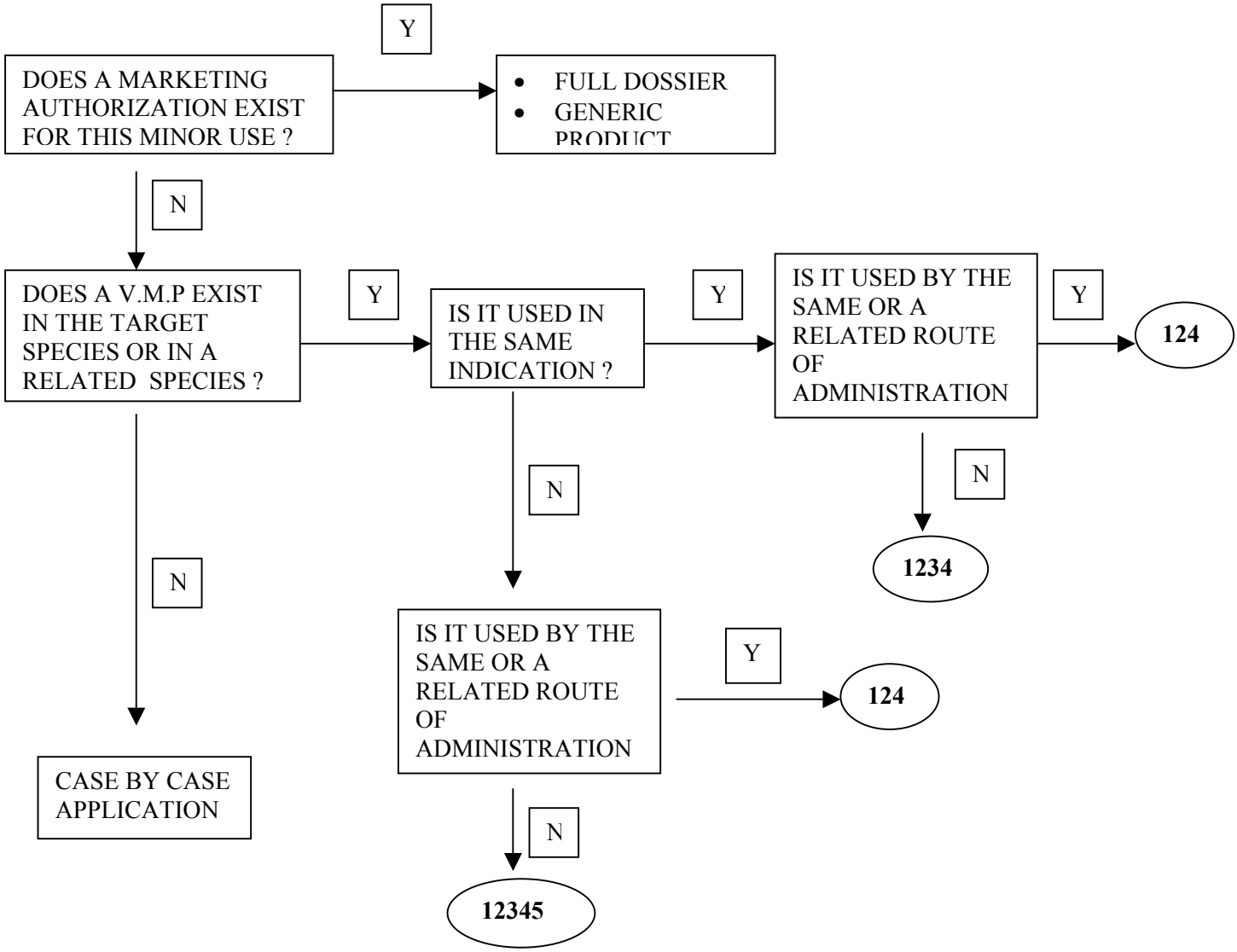
Table 5

	Dogs	Cats	Mink	Fox	Rabbit (pet)
Austria	581.000	1.400.000	no fur production	no fur production	133.000
Belgium	1.500.000	1.390.000	42.165	191	*150.000 (estimate = 1/10 of dogs)*
Denmark	550.000	800.000	2.200.000	11.000	*55.000 (estimate = 1/10 of dogs)*
Finland	500.000	550.000	Breeding minks: 450.000	Breeding foxes: 380.000	50.000
France	8.100.000	8.700.000	practically zero	no husbandry	1.800.000
Germany	10.000.000	6.300.000	No data	No data	>10.000.000
Greece	Dogs and cats: 2.500.000 *(estimated that 1.3 million are dogs and 1.2 million are cats)*				*130.000 (estimate = 1/10 of dogs)*
Iceland	5.000	10.000	33.532	3.923	ca. 100
Ireland	600.000	400.000	0	0	100.000 - 150.000
Italy	7.000.000	7.000.000			900.000
Netherlands	Dogs and cats: 3.500.000 *(estimated that 2 million are dogs and 1.5 million are cats)*		565.000 breeding	7600	*200.000 (estimate = 1/10 of dogs)*

Norway	260.000	30.000 ear-marked Real number probably > 300.000	47.000 (female breeders)	70.000 (female breeders)	Estimate 26.000 No official number, probably below number of dogs.
Portugal	<1.300.000 (year 2000)	<800.000 (year 2000)			*130.000* *(estimate = 1/10 of dogs)*
Spain	3,700,000	2,200,000	?	0	?
Sweden	800.000	1.200.000	270.000	1.500	*80.000* *(estimate = 1/10 of dogs)*
United Kingdom	6,700,000 (1999)	7,700,000 (1999)	1,200 killed each year (Fur farms to be closed in 2003) Live mink: approx. 1,450	Nil	1,600,000

Annex 2

EXAMPLE OF A DECISION TREE FOR A MINOR USE APPLICATION



These data are based on data of a full efficacy dossier.

1. PK data
2. PD data
3. Dose determination
4. Dose confirmation
5. Resistance
6. Clinical trials (experimental, field)
7. Tolerance studies