Basic overview of the regulatory procedures for authorisation of veterinary medicines with emphasis on residues in food animal species

This document is a first attempt to collate and disseminate information relevant to regulatory procedures for authorizing veterinary medicines with emphasis of residues in food animal species. This document covers European Union (including the European Economic Area) and the United States of America. Information on other major markets are also being compiled and will be made public as they become available. This document has been produced by FAO Fisheries Department (Dr. Rohana Subasinghe) in collaboration with Dr. David Alderman of Centre for Environment, Fisheries and Aquaculture Science (CEFAS) of the United Kingdom. Any information regarding this document and FAO Fisheries Department's work on this area could be obtained by writing to Dr. Rohana Subasinghe, Senior Fishery Resources Officer (Aquaculture), Inland Water Resources and Aquaculture Service, Fishery Resources Division, FAO Fisheries Department – rohana.subasinghe@fao.org

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1 Preface

There has been recent discussion, stemming particularly from the ban of import of some aquaculture products in the European Union, which caused considerable economic losses to producers and processors of aquatic products. The recent ban resulted from the detection of residual levels of an antibacterial substance called Chloramphenicol. This is a broad-spectrum antibiotic used in human and pet animal medicine, and it is still being applied in some countries in animal production, including aquaculture. Chloramphenicol is also known to cause serious human health implications such as "aplastic anemia". However, the incidence of this disease is rare, according to Joint FAO/WHO Expert Committee on Food Additives (JECFA), and probably could not be attributed to residues in food.

Over the past years, FAO has been involved in various discussions, meetings, and workshops concerning the use of drugs and chemicals in aquaculture and aquatic food production. FAO encourages countries to raise fish in a sustainable manner applying good aquaculture practices and, where necessary, to promote the prudent and responsible use of feed ingredients and veterinary drugs that have shown to be safe.

On the basis of the recent communications that we received from many countries, it became clear that the public knowledge and understanding of the regulatory procedures for the authorization, use and control of antimicrobials, standards for residues, and trade (import/export) implications in different countries and regions is insufficient. Responding to the recent discussion on the prudent use of antimicrobials, the need for producing aquatic products with maximum consumer safety, and considering the lack of such knowledge and understanding among the general public, the FAO Fisheries Department undertook to compile information on various existing relevant regulatory procedures in different parts of the world. This report is the first step towards this goal covering European Union and the United States of America regulations. Other countries should also be reviewed, as we intend to continue this process. We will have more information on this broad and complex subject, widely available to the concerned public, in due course.

2 Summary

- Both Europe and the USA have strictly regulated controls on use of veterinary medicines, particularly for use in food animal species.
- Before any such medicine can be approved for sale a range of safety and efficacy requirements must be satisfied.
- Included in these is a requirement that residues of the veterinary medicine must be below a predetermined safe level when the animals are slaughtered. This level is the Maximum Residue Level (MRL) (Europe) or tolerance (USA).
- Certain compounds, including chloramphenicol and the nitrofurans are specifically prohibited for use in food animals in Europe and in USA.
- Programmes of sampling and analysis of the edible tissues of food animals produced in Europe and in the USA are carried out to ensure that producers do not slaughter animals until residues of any medicines used have fallen below the predefined safe levels (MRL).
- These programmes also check for the presence of any residues (no matter how small) of drugs that are prohibited for use in food animals. Action is taken if either MRL is exceeded or prohibited residues are found.
- Both Europe and USA require that countries exporting food animal products into their markets operate a programme of checks for residues that will ensure that imported food is safe for their consumers.
- If imported food is found to contain residues in excess of MRL or to contain any residues of prohibited drugs, again action will be taken. This will normally result in a prohibition of imports from the country concerned until the cause of the unsafe residue has been traced and action to guarantee that no further breach will occur has been taken.
- Producers wishing to export to Europe or USA must take care that sufficient time has elapsed between medication and slaughter ensure that no residues in excess of the MRL are present in the edible tissues and must never, in any circumstances, use prohibited medicines. In the case of aquaculture these are chloramphenicol and nitrofurans. Malachite green residues are also unacceptable. Use of prohibited substances on any part of a production unit or processing/handling risks transfer of residue to export animal tissues.
- Regulatory authorities in exporting countries can assist producers by developing tighter regulation of supply of veterinary medicines, enforcing that regulation and operating compliance and residue monitoring programmes.

3 Introduction

This report presents a précis of the regulatory procedures for authorisation of veterinary medicines in Europe and the USA. In particular it concentrates upon the requirements for consumer safety in regard to presence of residues of veterinary medicines in the edible tissues of food animal species. In both Europe and the USA the regulations in regard to veterinary residues and consumer safety are "third country" regulations requiring that countries wishing to export into those markets demonstrate that procedures are in place to ensure that the products exported meet the same standards as those enforced internally.

In Europe, national animal products are monitored by Member States for presence of residues of veterinary medicines in food animal species to ensure compliance with the residues regulations. This monitoring programme and its results must be submitted to and approved by the European Commission annually and sampling normally takes place in slaughterhouses (for large animals) or at wholesale or farm level for aquaculture. Similar monitoring plan requirements are required from those countries that wish to export to the EU.

In addition to obligatory monitoring, Member States are free to monitor for all types of contamination, including veterinary medicine residues, in the retail food chain. Such retail monitoring programmes not only include products from national production, but also imports from other parts of the EU and from third countries. It is this retail level monitoring that has recently detected residues of prohibited residues in imported aquaculture products from Asia within the EU. Where monitoring of any type detects the presence of residues that are not in compliance with the current EU requirements, the foodstuff concerned is regarded as unfit for human consumption. Within the EU the Member State concerned is required to take action, if from a third country, the European Commission will take action.

This document is intended to explain the reasons for and background to the operation of veterinary medicines authorisation and residues monitoring programmes in the EU and USA. The reason that these programmes are in place is very simple. They are programmes designed to protect the safety and health of target animals, their environment and most particularly the consumers of the products from those animals. The origins are wide, from the thalidomide disaster of the 1960's to increasing worries about misuse of antibiotics and the transfer of antibiotic resistance from animal production to humans and to the spread of drug resistant organisms such as MRSA. In Europe the regulations were introduced to provide a uniform level field within the EU (and the European Economic Area [EEA]) removing what might otherwise have impeded internal trade. However they are applied equally to food animal production within the EU and to food imported into the EU. It is therefore difficult to see how these regulations could be seen as impermissible trade barriers.

4 European Union (EU) and European Economic Area (EEA)

The process of harmonising the legal controls on veterinary (and human) medicines between the member states of the European Union has now been underway for over 20 years. This has meant that the legislation of 15 countries, some with radically different approaches to the control of medicines, has had to be modified and adapted to produce a single uniform legislatory environment across all member states. The progress towards the creation of the open market within the European Community in 1993 increased the needs for the harmonisation of medicines regulation across the Community (Alderman, 1999a, b). Much of the law created during this process also has wider European Economic Area application.

This harmonisation process has been carried out at a time when the regulatory environment would inevitably have had to become more demanding as greater consumer safety requirements were introduced during the 1990s. The net result has been the introduction of what seemed to many to be a remorselessly increasing range of new controls on veterinary medicines.

The basic Directives of European legislation on veterinary medicinal products have been frequently and substantially amended over time. Very recently in the interests of clarity these Directives have been codified by assembling them in a single text (European Parliament and Council Directive 2001/82/EC). Therefore only a very brief overview of the original legislation will be presented here in order that the way in which regulation has been developed may be understood.

The first stages of the harmonisation process commenced with Directive 81/851/EEC "On the approximation of the laws of the Member States (MS) relating to veterinary medicinal products". This was the first stage in bringing together the disparate medicines legislation of the (then) twelve MS. A second Directive (81/852/EEC), made provision for harmonisation of the analytical, pharmaco-toxicological and clinical tests and trials of veterinary medicinal products.

The European Medicines Evaluation Agency (EMEA) was formed in 1993 (Council Regulation 2309/93). The EMEA is responsible for both human and veterinary medicine, and the previously established Committee for Veterinary Medicinal Products (CVMP) is now a committee within its structure. The EMEA is responsible for the determination of applications submitted under Centralised Procedures within the EU; currently, in the veterinary area, only applications for biotech products and new molecules are obliged to use this route which was established by Council Regulation 2309/93/EEC.

4.1 DEFINITIONS

Three definitions may be valuable to readers at this stage.

4.1.1 Veterinary medicinal product

From Directive 2001/81 veterinary medicinal product is defined as "Any substance or combination of substances presented for treating or preventing disease in animals. Any

substance or combination of substances which may be administered to animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in animals is likewise considered a veterinary medicinal product".

4.1.2 EU law : Regulations and Directives

European laws are of two types, Regulations and Directives. Regulations are laws effective throughout the EU, applying simultaneously in all Member States. Directives, in contrast, are pieces of community law, which Member States must implement in their national legislation by a specified deadline. In addition to Council Regulations, subsidiary Regulations made by the European Commission exist; these modify primary Regulations, relevant examples being the series of Commission Regulations placing substances in the different Annexes of Regulation 2377/90. Such Commission Regulations comprise the majority of items of legislation relating to veterinary medicines.

4.1.3 Marketing Authorisation

A veterinary medicinal product may not be marketed until a Marketing Authorisation has been obtained. The term "Marketing Authorisation" replaces the term "Product Licence" used previously.

4.2 Basic Criteria for Approvals

Applications for veterinary medicines approvals are assessed in the EU, as in most other regulatory regimes, against three basic scientific criteria. These are quality, safety and efficacy. The requirements for satisfying each of these criteria are presented in detail in the relevant volumes of "The Rules Governing Medicinal Products in the European Union". Relevant Volumes of the Rules are Volumes IV European Commission 1991) which defined guidelines for determination of Maximum Residue Levels (MRL) and VII covering general aspects of authorisation of veterinary medicines (European Commission 1995a, 1995b). Volume IV is about to be replaced by Volume VIII (draft European Commission 2001) updating MRL requirements.

Quality concerns the chemistry and pharmacy of all components of the veterinary medicine, including details of the processes of manufacture, packaging and stability under storage, especially in relation to formulation and intended route of application (i.e. bath or in feed).
Data are required to support manufacturer's claims of efficacy. This can sometimes be a difficult matter to demonstrate.

Although many of the quality requirements are in themselves safety considerations, safety itself is a separate specific consideration and forms by far the largest part of any new drug application. Applicants are required to demonstrate that the product is :

- safe to the consumer;
- safe to the user;
- safe to the target species;
- safe to the environment.

4.2.1 Consumer safety

The primary consumer safety consideration is addressed via Maximum Residue Limits (MRL), established by Council Regulation EEC/2377/90. The MRL defines the maximum level of residues of any component of a veterinary medicine that may be present in foodstuffs of animal origin without presenting any harm to the consumer. The EU definition is virtually the same as that adopted by the Codex Alimentarius Committee for Residues of Veterinary Drugs in Foods (see below) and the approach to evaluation of residues of veterinary medicinal products within the European Union is very similar to that employed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) that evaluates for Codex Alimentarius. There are certain specific differences between the evaluation of the safety of residues of veterinary medicines and the evaluation of other residues of food additives or contaminants.

It should be noted that, although there is no formal MRL regulation established in USA, the equivalent is the Tolerance established by the regulatory authorities. There is a conflict in terminology between the two regulatory regimes, in that within the EU the term tolerance specifically refers to target animal's tolerance of excess treatment doses and does not relate to residues or consumer safety.

Regulation 2377/90 provided that all pharmacologically active substances in veterinary medicines must be allocated to one of four annexes established under the Regulation. For new active ingredients, allocation to an Annexe was required beginning in January 1992 and for all existing veterinary medicinal products, both actives and excipients, a terminal date of 31 December 1996 for allocation was set. After that date, if no allocation had been made it was intended that products would have to be withdrawn for use in food species. This intention was too ambitious to generate the amount of new data required and, for a list of Defended Substances, a derogation from this requirement was extended until the end of 2000. From January 1992 no Marketing Authorisation could be granted unless an MRL had been set and no existing Marketing Authorisations could be extended beyond 1st January 2001 unless an MRL had been set.

The MRL for any substance is determined from data submitted by manufacturers or suppliers to the Safety of Residues Working Party, a sub committee of the Committee for Veterinary Medicinal Products (CVMP). This determination is ratified by the CVMP and adopted into law by a Regulatory Committee in the form of Commission Regulations. For veterinary medicines for use with food animal species in the EU the MRL is determined by an iterative process from a range of safety data, the most important of which is the Acceptable Daily Intake (ADI). The ADI is defined as the level of a substance that may be consumed daily without presenting a hazard to the consumer. It is based on a suitable no-observed effect level (NOEL) or from observations in humans, divided by a safety factor, often 100. For a discussion of MRL determination and ADI relationships see Woodward (1996) and the draft of Volume 8 of the Guidelines (European Commission 2001).

The Annexes to Regulation 2377/90 are as follows :

- Annex I: Full MRL can be set;
- Annex II: Safe, no MRL needed to protect the consumer;
- Annex III: Sufficient data to set a Provisional MRL, but additional data needed to allocate full MRL;
- Annex IV: On safety grounds no MRL can be set. Substances placed in this Annex are prohibited for use in food animal species, although they may still be used in pet species.
- Substances once of interest to aquaculture placed in Annex IV include chloramphenicol, the nitrofurans (including nitrofurazolidone and nifurpirinol) and dimetridazole.

It is important to realise that with Annex I, II and III substances, the presence of residues (including metabolites) below the MRL are disregarded, but the presence of any detectable residue, including metabolites, of any Annex IV substance in the tissues of any food animal species is regarded as evidence of use of a prohibited substance and is treated as a food safety matter, no matter how low the level of residues or metabolite residues detected may be.

MRL data packages are large and consist of two main parts, the safety file and the residue file. Much of the data in the safety file (e.g. mammalian toxicity studies and the ADI) may be reused for new species MRL applications. The unique part that is required for each species MRL is the residue depletion study. This requires the determination of the marker residue, which may either be the parent drug or a metabolite. Depletion of the marker residue characterises the depletion of the total residue (parent drug and metabolites) from the relevant tissues, such that the total residues in edible tissues will be below the safe concentration when the marker residue is below the MRL.

It should be noted that, in the EU as in the USA, for fish, edible tissues are defined as muscle with adherent skin in natural proportions (European Commission, 1991). A factor for consumption of 300 g (substituting for red meat as a dietary component) is taken to determine the fish meat contribution to the Acceptable Daily Intake (ADI) in the calculation of the MRL. Muscle and skin, in natural proportion, is therefore the target tissue for determining withdrawal periods in fish.

Although initial MRLs tended to cover a wide range of food animal species, later ones were much more species specific, so that a real risk existed of poor availability of well understood veterinary medicines for other than major species. Initially, for fish, applicants were required to present data for each active and excipient to enable the determination of individual marker residues.

As the problems of developing losses of veterinary medicines became evident, the CVMP produced a Note for Guidance, (Committee for Veterinary Medicinal Products, 1997) to help address the problem. The CVMP noted that, since the implementation of Regulation 2377/90, very few MRLs had been allocated for medicines for minor species potentially leading to animal welfare. A lack of authorised medicines could mean that the cascade system (see below) will be exploited in such a way that the majority of drugs used in minor

species came via this exemption. The Note for Guidance concerns the establishment of MRLs for minor animal species, stating that, since in the EU Salmonidae are a major food producing species. Therefore where a substance is already included in Annex I, II or III of Regulation 2377/90 for Salmonidae, then that MRL may be extended to relevant other minor species (i.e. other fin fish). A further Note for Guidance (Committee for Veterinary Medicinal Products, 1997) addressed the question of species specific marker residues. In this, the EMEA states that, although only a limited number of MRLs have been established for fish, where these have been evaluated, the marker residue determined in Salmonidae has been identical to that established in other animal species. A pragmatic approach should therefore apply to the establishment of MRLs for substances used in Salmonidae and other finfish as well.

This pragmatic approach recognises the difficulties imposed by the costs of developing data for MRL determinations against expectations of slight financial returns by potential applicants. A list of current MRLs is available of the EMEA web site – the current listing is

There is however one problem not properly covered by Regulation 2377/90, nor so far addressed by any other legislation, EU or national. This is that, without an application to set an MRL a substance is effectively in "limbo". Its use in food species is not authorised; equally it is not a prohibited Annex IV substance. More than most areas of veterinary medicine, aquaculture has used a range of "traditional remedies" whose use has persisted to the present day. Malachite green is the classic case – it is most unlikely that anyone will make a formal application to establish an MRL for this product. It can hardly be expected that, even if the effort were to be limited to the cost of assembling published data and then of submitting it for consideration by the Working Group on the Safety of Residues, any application for an MRL allocation could be funded by a commercial sponsor. However, without such an application and accompanying data package a substance like malachite green will not be scrutinised by the Working Group and therefore it will not be entered into Annex IV and will not become a prohibited substance. This appears to be a gap in the existing legislation that opens an avenue for failure of consumer protection. It is however true that in any tissue residue monitoring programme, substances such as malachite green, without MRL or authorisation in any food species would, if detected, be regarded as illegal residues.

4.2.2 Withdrawal periods.

The establishment of an MRL allows the setting of a withdrawal period for the product. The applicant normally proposes the withdrawal period for the Marketing Authorisation and presents data to support that proposal. The licensing authority of the Member State concerned assesses the data against the proposal and agrees with the proposal. Alternatively, the licensing authority may discuss and agree an alternative with the applicant or may refuse on grounds of inadequate data. In most food-animal species withdrawal periods are defined in days, but with fish the EU requires data to be presented from trials conducted at least two water temperatures relevant to the proposed conditions of use. If depletion of residues is found to be temperature dependant then a withdrawal period in degree-days will be set making the withdrawal period a function of temperature and time. If the data does not indicate a temperature effect on depletion then a day-based withdrawal can be accepted.

4.2.3 Target species safety, User safety, Environmental Safety

The requirements under these heads are not addressed in the present document, but the requirements can be found on the European Pharmaceutical Regulatory Sector portal at http://eudraportal.eudra.org/ or more specifically on the EMEA website (http://www.emea.eu.int/)

4.3 Cascade System (Off-label use)

Directive 90/676/EEC amended Directive 81/851 to establish the prescribing cascade, confirmed in Directive 2001/81/EC. This limits veterinarians treating food-producing animals to prescribing veterinary medicines containing only substances authorised for use in food producing species. Thus, where there is no suitable product to treat fish, a suitable product approved in other food animal species may be prescribed. Use of this prescription route requires the imposition of a standard withdrawal period by the veterinarian. For fish in the EU the standard withdrawal period has been set at 500 degree-days. The standard withdrawal period is also imposed on any special emergency authorisations for use granted whilst product data packages are still insufficient.

Significant restrictions exist in use of the cascade system. Even if used in different species, products may still only be applied by the exact route for which they are authorised. Thus cattle pour on and pig oral drench ivermectin formulations may not be "cascaded" for use on fish feed, only a formulation approved for use in feed for another species may be used in fish feed in this way. This particular product points to a potential hazard in that research has clearly demonstrated (Palmer *et al.*, 1997) that ivermectin in salmon can be extremely persistent, requiring withdrawals of at least 1000 degree days for full depletion to limit of detection. Thus an in-feed formulation of ivermectin approved for another species may be prescribed under the cascade provisions, but if the EU standard 500 degree-day withdrawal is observed, residues will be detectable if slaughter occurs before depletion has completed. Since there is no MRL set for ivermectin in salmonids, the presence of such residues at slaughter are in breach of the requirements of Regulation 2377/90, although no breach was involved before slaughter. It is incumbent on veterinary surgeons prescribing via the cascade route to take note of any known pharmacokinetic characteristics of the product that they are prescribing and, where necessary, apply an appropriately extended withdrawal period.

The final restriction on the use of the cascade route of medication is that it is specifically restricted to use on a "small number" of animals. As Woodward (1996) commented, the interpretation of "a small number" is difficult when applied to aquaculture. With farmed fish all individuals in a cage or pond are at equal risk so that provided a proper diagnosis has been made, it might be reasonable to interpret "a small number" in aquaculture as applying to that cage or pond. In any case, proper records should be kept of such cascade use and such records are, in any case, now required under the provisions of Directive 96/23 (see Residues Surveillance below) to enable efficient monitoring of tissue residues in residue monitoring programmes.

4.4 Medicated Feedingstuffs

Where aquaculture medicines are applied in feed, then the provisions of Directive 90/167/EEC "laying down the conditions governing the preparation and placing on the market and use of medicated feeding stuffs in the Community" apply.

Drug formulations approved for incorporation in medicated feeds must be specifically approved for use via that route and must be in the form of a single authorised medicated pre-mix. Provision is made that if a feedingstuff already contains medication, no further medication of the same type may be added. These requirements also apply in full to products prescribed as medicated feeds employing the provisions of the cascade system.

4.5 Immunologicals

The original Directives 81/851 and 81/852 did not apply to immunological products such as vaccines. In January 1992 these were included in the EU medicines regulatory environment by the implementation of Directive 90/677/EEC. Requirements for testing the safety and efficacy of vaccines are detailed in the Rules Governing Medicinal Products in the European Union (European Commission, 1995b) that includes not only general requirements for vaccine production, but defines test procedures for bacterial and viral fish vaccines. The European Pharmacopoeia Commission (EP) (a Council of Europe body, rather than an EU or EC body) has also published a number of monographs on vaccine test protocols for the more important bacterial diseases of salmon. Where such monographs exist, they must be followed for testing any immunological product within the EU.

4.6 Licensing Authorities

Until recently almost all veterinary medicines licensing has been carried out by the authorities of Member States. In the U.K. veterinary medicines regulation is the responsibility of the Veterinary Medicines Directorate an executive agency of the Department for Environment, Food and Rural Affairs advised by the independent Veterinary Products Committee (VPC). The Licensing Authority per se is the Secretaries of State for Environment and Health. From 1 January 1998 what had been referred to as EU future systems came into operation. National procedures still exist however and the national Licensing Authority must determine applications made by this route within 210 days of receipt of an application.

Provision is made for applications for Marketing Authorisations to be made by a Centralised Procedure to the EMEA. This route is mandatory for some biotech products such as Genetically Modified Organisms (GMOs) and for the moment these and applications for new molecules are the only applications which are accepted centrally. The majority of applications are still made by the Decentralised Procedure. This may be in the form of a serial application in which an application is made to the Licensing Authority of one MS which if successful, may be followed by applications to other MS. Those MS Licensing Authorities have 90 days to accept authorisation of the first MS or to present cogent scientifically based reasons for any refusal. Alternately, parallel applications may be made simultaneously to several MS, once the first MS approves the others have 90 days to accept or produce cogent scientific objections. New applications are required for changes

in active ingredient, addition or change of indication or target species, change of MRL or change of withdrawal period

4.7 Residue Surveillance

There is, of course, little value in developing an elaborate and expensive system for ensuring that no unacceptable residues are present in food of animal origin (i.e. Regulation 2377/90) if no action is taken to confirm and enforce compliance. This next stage of the EU veterinary medicines harmonisation programme took the form of Directive 96/23/EC. This Directive introduced fish meat, poultry meat, milk and honey into Member States monitoring programmes that had previously been limited to red meat. It requires member states to produce a monitoring programme to search for illegal or excessive drug residues in fish meat. It is also a third country Directive (Article 29) in that countries exporting to the EU have to demonstrate that they are able to ensure that no unacceptable residues are present in fish meat exported to the EU by means of a suitable residues control and monitoring programme.

Any existing non-statutory programmes, have been replaced by a statutory programme in compliance with Directive 96/23. For farmed fish, a monitoring level of one sample (= one or more fish) per 100 tonnes of production is required. A maximum of two thirds of samples may be taken a wholesale level provided traceability to farm is guaranteed, the rest must be collected from the farm itself. Farms must keep full records of medications used and provide access to these during sampling inspections. Samples will be analysed for :

- for presence of residues of approved substances in excess of MRL;
- for residues of illegal substances and for substances which it is believed may be in use under the provisions of the cascade system or for other reasons (e.g. traditional remedies such as malachite green) but for which there is no MRL in fish;
- for presence of Annex IV substances.

As indicated above, this is a third country Directive, would be exporting states must satisfy the European Commission that they have in place a residue monitoring programme equivalent to that in place in EU MS. Article 29(1) of Directive 96/23/EC states that inclusion and retention on the lists of third countries provided for in Community legislation from which Member States are authorised to import animals and animal products covered by this Directive shall be subject to submission by the third country concerned of a plan setting out the guarantees which it offers as regards the monitoring of the groups of residues and substances referred to in Annex I of the Directive. Article 8(3) of the Directive requires that by no later than 31 March each year, Member States shall forward to the Commission their monitoring plan results and that third countries must also comply.

The most recent list of such approved monitoring plans was given in the Annex to Commission Decision 2001/487/EC which includes a listing of those third countries whose residue monitoring plans for aquaculture products had been approved.

Plans and results of veterinary residue monitoring programmes must be submitted to the European Commission for approval and, additionally some MS publish the results of their monitoring programmes. One readily accessible example of this are the results of the UK monitoring programme were routinely published before and since the implementation of

Directive 96/23 and are now available on the internet at http://www.vmd.gov.uk/. Very brief summaries of the MS residues monitoring programmes for 1998 and 1999 are at http://europa.eu.int/comm/food/fs/sfp/fcr/reports/reports_en.html. The reports of the European Commission's Food and Veterinary Office which carries out audits and on-the-spot checks on food safety controls in MS and in countries exporting to the EU are at http://europa.eu.int/comm/food/fs/sfp/fcr/reports/reports_en.html

It should also be understood that the requirements of Directive 96/23 are minimum requirements and MS may and do carry out additional monitoring programmes both on national and imported products. In some MS, both the responsible Veterinary Medicines authorities and Food Safety bodies may have such additional monitoring programmes, normally carried out at wholesale or retail rather than farm levels. Provided that identical standards are required for monitoring national and imported food animal products, and that the definitions of safety comply with the current Annexes to Regulation 2377/90, then any level of monitoring above the minimum set by Directive 96/23 may be used.

If in any of the residue surveillance programmes illegal residues are detected (i.e. residues of Annex I or III substances above MRL at slaughter, or Annex IV or other specified residues at any time), MS authorities are required to take follow up action to prevent re-occurrence. Legal action against violation may ensue although the tendency within any MS will be towards action to prevent re-occurrence unless the violation is clearly as a result of deliberate action. Additional analytical and monitoring costs are likely to be charged to the violator.

In the case of third country imports, violation may result in banning imports either at the MS level or at the European level, followed by inspection by veterinary officials. Imports will be barred until the cause of the violation is dealt with and proper assurances to prevent re-occurrence are in place. Reports of Inspections by the Food and Veterinary Office are available at: http://europa.eu.int/comm/food/fs/inspections/vi/reports/index_en.html

5 United States of America

In Europe the regulatory authorities for veterinary medicines tend to be separate bodies to those for human medicines. In the USA, under The Federal Food, Drug, and Cosmetic Act (as amended by the FDA Modernization Act of 1997), all drug approvals, both human and veterinary are the responsibility of the US Food and Drug Administration (USFDA). The USFDA Center for Veterinary Medicine (CVM) is responsible for veterinary medicine authorisations. The term "drug" under the Food. Drug, and Cosmetic Act means articles intended for use on the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals and articles (other than food) intended to affect the structure or any function of the body of man or other animal animals. Biologics (i.e. vaccines) approvals are the responsibility of the US Department of Agriculture (USDA) (http://www.aphis.usda.gov/vs/aqua/aquaphis.html) as are most monitoring programmes for veterinary medicine residues in red meat and poultry, through its Food Safety and Inspection Service (FSIS). Monitoring for veterinary residues in minor species (which includes fish) are the responsibility of the USFDA. These various bodies co-operate in a programme to approve and monitor the use of veterinary medicines, identify improper use and take action to prevent future illegal use.

The regulation of aquatic veterinary medicines has intensified during the last 35 years. This longer period of regulatory overview in the USA is reflected in the poorer availability of such products in comparison with Europe. Increased scrutiny of chemicals by CVM and EPA has decreased the availability of fish medicines, but the potential for a major increase in the number of aquaculture drugs available exists through federal, state, and private partnerships. Indeed, all current fish toxicants and drugs have been registered or approved as a result of partnerships.

The Federal and state fish hatchery systems are a major producer of fish for restocking and need aquaculture medicines as much as commercial aquaculture. Thus when the USFDA notified the U.S. Fish and Wildlife Service (USFWS) in 1964 that chemicals used at federal, state and private aquaculture facilities must be approved for specific applications against designated species under defined conditions that agency developed an action plan. As in Europe the cost of meeting full regulatory requirements was too great for potential drug sponsors, the USFWS set up a co-operative partnership to attempt to gain approval for several. The process has proved extremely slow and difficult, but such co-operative programmes continue to this day and have been the only route by which any aquaculture medicines have been properly approved in the USA. An overview of the history of these developments is given by Schnick (1999).

5.1 Veterinary Drug Approvals System

As in Europe, the USFDA requires animal drug manufacturers to prove that a new animal veterinary medicine is safe and effective for its intended use before it is approved for marketing. To ensure consumer safety the USFDA sets a tolerance (=MRL a meaning different to the EU use of the term tolerance) and withdrawal time for the product based on data supplied by the manufacturer. For veterinary medicines for use in food-producing animals, additional toxicology residue and metabolism studies are required. Manufacturers also must submit a reliable assay method for detecting drug residues in edible tissues of

food animals at slaughter.

The USFDA responsibility is for the safety to consumers of residues that remain in the edible tissue of the animal after drug treatment. As in Europe for fish, the edible tissue is considered to be muscle with adhering skin, except for those fish such as catfish where the skin is not consumed. The methods by which tolerances in these tissues are established in the USA are similar to those employed by the CVMP in Europe, via the ADI and appropriate safety factors. The tolerance for each approved drug is listed in Code of Federal Regulations, 21 CFR 556 (U.S. OFR, 1998).

5.2 Residue Monitoring and Surveillance

The FSIS is responsible for the safety of meat, poultry, and egg products to the American consumers to include presence of drug and chemical residues that violate Federal law (under authority of the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act). Imported meat, poultry, or eggs can only come from countries that have equivalent inspection systems as USDA; in 1999, 32 countries meet those requirements. The USFDA's Center for Food Safety and Applied Nutrition (CFSAN) is charged with protecting American consumers against impure, unsafe, and fraudulently labelled food other than in areas regulated by FSIS. No food or feed items may be marketed legally in the USA if it contains a food additive or drug residue not permitted by CFSAN or if the residue is in excess of an established tolerance. All imported products are required to meet the same standards as domestic goods. CFSAN regulates all seafood.

In general routine testing of national food animal production is carried out to provide information on the occurrence of residue violations annually. The focus of monitoring is on violations and only compounds with established safe limits, tolerances, or action levels are monitored. Sampling is random from healthy appearing animals.

Tolerances and action levels represent the maximum residue concentrations safe for daily consumption over a lifetime. As in Europe, unless violation is deliberate the focus is on prevention of re-occurrence.

Pro-active surveillance as opposed to routine monitoring is also undertaken when a suspicion that violation may be occurring, follow-up investigations are undertaken. FSIS and CFSAN can detain future shipments from the affected producer while tissue samples are analysed. USFDA follow-up investigation may lead to enforcement action when appropriate or necessary.

A final residue monitoring type is termed Exploratory. These projects generally fall within the two areas of occurrence of residues for which no safe limits (i.e., tolerances or action levels) have been established or in a species not approved for use of a particular drug.

In summary, USFDA and FSIS approve residue detection methods and FSIS monitors meat, poultry, and eggs for tissue residues of drugs, pesticides, and environmental contaminants and CFSAN monitors the remaining food substances (including seafood) for the same residues.

Animals with illegal residues will be condemned by FSIS or CFSAN. Producers of these animals may be subject to detention of future shipments until they can prove their animals are in compliance with applicable tolerances. Repeated residue incidents may lead to legal sanctions.

Illegal residues detected by FSIS or CFSAN are reported to USFDA, the livestock producer, or other responsible individual, and, where appropriate, state authorities.

If the evidence shows a deliberate violation of the law, criminal charges may be filed against the producer. Information on residue monitoring and action against violations are published in the FDA Veterinarian Newsletter available on the USFDA web site (http://www.fda.gov/cvm/default.htm).

A good overview of the full procedure is available from the USFA web site as CVM Memo CVMM-19.

5.3 Veterinary Medicine Availability

The above information refers to monitoring for veterinary medicine residues in food animal species. The USA has only two antimicrobials approved for use in fish, the potentiated sulphonamide Romet® and oxytetracycline and few other approved products for fish which, in US terms, are all minor species.

Recognising this problem a number of US Federal initiatives have been undertaken, in particular the NRSP-7 minor use animal drug programme (http://www.nrsp-7.org/_vti_bin/shtml.dll/default.htm). As in Europe the market is insufficient to justify costly research expenditures by a pharmaceutical firm to obtain USFDA approval. NRSP-7 is designed to address the shortage of minor use animal drugs by funding and overseeing the efficacy, animal safety, and human food safety research and environmental assessment required for drug approval. The programme brings together aquaculture producers, pharmaceutical companies, the USDA (CVM), USDA and other bodies. [Note: Make this a separate paragraph.]

The position of the National Aquaculture New Animal Drugs Co-ordinator (NADA) was created by the Joint Subcommittee on Aquaculture to facilitate the approval of aquaculture medicines in the USA. Currently, more than 20 drugs are under development through various partnerships in the USA. One particular project, the Federal-State Aquaculture Drug Approval Partnership has six drugs with 11 label claims that will have all the data packages into CVM for approval by September 2003 (R. Schnick, personal communication).

The Animal Drug Availability Act of 1996 required the USFDA to provide Congress with a report, describing administrative and legislative proposals to improve and enhance the animal drug approval process for Minor Uses and Minor Species (MUMS) of new animal drugs. This report laid out nine proposals, eight of which require statutory changes. In response an industry coalition of aquaculture groups was formed in 1999 and expanded to include numerous other minor species groups. Strong support across a wide range of bodies led to the proposal for a Minor Use and Minor Animal Species Health Enhancement Act in 2001. Now, in April 2002, it is called the Minor Use Minor Species

Animal Health Act and will be amended to a bioterrorism bill that has already passed the US House of Representatives and the US Senate although in slightly different versions (R. Schnick, personal communication).

5.4 Imports

The fact that few aquaculture veterinary medicines are approved in the USA means that there are few tolerances (MRLs) set that are applicable for aquatic food species. This in its turn has a potential for conflict in that drugs such as oxolinic acid that have MRLs set either by international bodies such as Codex Alimentarius or by large markets such as the EU, but for which there are no tolerances for such products in the American market. Technically a fish or prawn with a residue of oxolinic acid below international limits would be illegal if imported into the USA if no valid tolerance in fish tissues had been set. Equally if substances such as chloramphenicol which is regarded as prohibited (Annex IV) by the EU did not have an action level set for violation in the USA, if it were not for the provisions under AMDUCA (see below), the residue might not have been regarded as being illegal.

To address this the USFDA issued an advance notice of proposed rulemaking (ANPRM) that appeared in the August 10, 2001, Federal Register. The ANPRM stated that FDA intends to propose a regulation for establishing import tolerances, and solicited comments on issues related to the implementation of the import tolerances provision in section 4 of the Animal Drug Availability Act of 1996 (ADAA). The ADAA authorises FDA to establish drug residue tolerances (import tolerances) for imported food products of animal origin for drugs that are used in other countries, but that are unapproved new animal drugs in the U.S. Food products of animal origin that are in compliance with the proposed import tolerance will not be considered adulterated under the Federal Food, Drug, and Cosmetic Act and may be imported into the United States. This proposal was still open for comment until March 10, 2002.

CVM awarded a contract on the risk assessment of drugs and chemicals used in foreign aquaculture on September 28, 2001. The objectives of this contract are to create a database containing information on drug and chemical use in foreign aquaculture and perform a human food safety risk assessment for each drug and chemical listed in the database. FDA will use the results of this contract to prioritise the monitoring of drug and chemical residues in the edible tissue of imported aquaculture products, prioritise the development of methods to be used in the monitoring program, and provide a basis for promoting discussion with foreign countries regarding the hazard concerns identified by the risk assessment (R. Schnick, personal communication).

5.5 Extra-label Use of New Animal Drugs in Food-Producing Animals

The US equivalent of the EU veterinary medicines “cascade” principal is "Extra-label use" and is defined as "actual use or intended use of a drug in an animal in a manner that is not in accordance with the purpose approved on the label.” Under the provisions of the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), veterinarians are permitted to prescribe the use of medicines for purposes beyond those approved in a situation in which the veterinarian has professional responsibility for the animals concerned and when the health of an animal is threatened, or suffering or death may result

from failure to treat. Extra-label use of medicated feed in aquaculture is limited to medicated feed products approved for use in aquatic species (i.e., currently, only manufactured salmonid or catfish medicated feeds are allowed) (USFDA 2001). Much the same provisions for prescriber responsibility exist in this off label use as exist for the European prescription cascade system. Since no tolerance is set for off label use, adequate withdrawal times must be met so that no illegal drug residues occur in any food-producing animal subjected to extra-label treatment. This provision is in effect the equivalent of the Annex IV provisions of European Union Regulation 2377/90/EC.

5.6 Prohibitions Against Specific Off-label Use Under AMDUCA

Under AMDUCA provisions exist to allow USFDA to specifically prohibit the extra-label use of specific drugs in food-producing animals. Reasons for prohibition include lack of adequate analytical methods or if the extra-label use of the drug or class of drugs presents a risk to the public health.

Currently the following drugs are prohibited for extra-label animal and human drug uses in food-producing animals (only those relevant to aquaculture interests are listed here):

- Chloramphenicol
- Dimetridazole
- Furazolidone (except for approved topical use)
- Nitrofurazone (except for approved topical use)
- Fluoroquinolones

5.7 Investigational Use Of Unapproved Drugs

Unless prohibited under AMDUCA unapproved drugs can be used for investigational purposes in fish. A sponsor can apply for an investigational new animal drug (INAD) exemption that permits the use and interstate shipment of the unapproved drug. For food animals, an authorization is assigned to allow the slaughter of those animals treated with the drug under specified conditions of use and appropriate withdrawal time periods. Each fish farm that is using unapproved drugs operates under an INAD (has a specific number) and keeps treatment and withdrawal time records.

Since there are so few drugs approved for aquaculture and there were so many requests for investigational use of unapproved drugs, CVM started the compassionate INAD program since it was recognized that there is a need to permit the regulated use of drugs that are not yet approved. Through compassionate INADs, the producer has access to drugs for diseased fish while data are being collected to support the approval of the drug.

6 VICH, Codex Alimentarius Commission and Harmonisation

The European and USA regulatory procedures for approvals of veterinary medicines outlined above are specific to their own markets. In addition there are two international bodies moving towards the definition of internationally approved standards.

The VICH which was launched in 1996 is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration. Its full title is the International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. The harmonisation initiative began the in 1983 when the first International Technical Consultation on Veterinary Drug Registration (ITCVDR) was held. Since then a series of government and industry initiatives have been developed, culminating in the formation of the VICH.

- The Codex Alimentarius Commission formed a Committee on Residues of Veterinary Drugs in Foods in 1985 (CCRVD).
- As described above, standard requirements for veterinary product registration across were introduced in Europe starting in 1981.
- In January 1993 a discussion document was published by FEDESA. It set out a programme for the international harmonisation of registration requirements for veterinary pharmaceuticals and biologicals.
- The Office International des Epizooties (OIE, the international veterinary organisation) set up an ad hoc group on harmonisation of veterinary medicinal products in 1994.

The objectives of the VICH are to provide a forum for dialogue between regulatory authorities and the veterinary medicinal products industry on the differences in the technical requirements for product registration in the EU, Japan and the USA. Also to identify areas where modifications of existing methods and standards could be achieved without affecting consumer safety leading to harmonisation of technical requirements and replace corresponding regional requirements. Currently VICH has concentrated on methodology for authorisation of veterinary medicines and has not considered food safety aspects.

The Codex Alimentarius Commission (CAC) is a joint FAO / WHO commission charged with developing standards for food safety with world wide application. Amongst the standards being developed by Codex are Maximum Residue Levels for residues of veterinary medicinal products in food of animal origin. To set these MRLs data is analysed by JECFA, the Joint FAO/WHO Expert Committee on Food Additives. The CAC MRLs so far developed are available on the CAC web site at http://apps.fao.org/CodexSystem/vetdrugs/vetd_ref/vetd-e.htm. No CAC MRLs relevant to aquaculture medicines currently exist.

7 Conclusions

The approvals systems for authorisation of veterinary medicines, including those for aquaculture medicines, in Europe and the USA have been elaborated separately, but in practical terms are very similar, particularly in regard to aspects of residues and consumer safety. Both have provisions for prohibiting any use of specific products in food animal species and the lists of prohibited products are essentially similar. Equally both extend these provisions to cover third countries.

Although moves are underway to create a standard set of authorisation and residue safety standards which can be applied world wide, these are still at a very early stage of development and do not yet have any application in the field of aquaculture medicines.

Monitoring programmes for detection of veterinary residues (both of actives and of metabolites) currently appear to be more active in Europe. This has led to detection of metabolites or residues of prohibited (Annex IV) substances in aquaculture products imported into Europe (choramphenicol and nitrofurans). Under European Directive 96/23 and Regulation 2377/90, any detection of such Annex IV substances in food animals at any time in the production cycle results in the imported aquaculture product being regarded as unsafe for human consumption by definition. This applies no matter how low the residue may be, or what the practical risks may or may not be. Any use of Annex IV substances in food animal species is prohibited in the EU and in animal products imported into the EU. It should be remembered that the policy of preventing residues of Annex IV substances in food products is applied equally to European and non European production and has a consumer safety basis.

Substances are placed in Annex IV because there is sufficient data to indicate a human health hazard from consumption, but insufficient data to determine safe levels for consumers. Regulation 2377/90 was introduced to replace national laws in the Member States, many of which were based on zero residues. Almost all-existing veterinary medicines were eventually allocated to one of the three Annexes that permit use or attempts to set an MRL were abandoned by the sponsors. Annex IV was designed for those few substances for which consumer health risk had been demonstrated and for safe levels could not be demonstrated.

It is not impossible that if adequate modern toxicological data were to be done, safe levels could be determined. Such work is however very expensive and in practice can only be carried out by or with the sponsorship of the pharmaceutical industry or government. Those compounds presently in Annex IV of EU Regulation 2377/90 did have some sponsorship of this type, but once data sufficient to indicate that likelihood of demonstrating consumer safety was generated, research support ceased. Thus chloramphenicol once had an Annex III allocation with a provisional MRL of 10ppb, but safe levels could not be demonstrated from the available data and it was transferred to Annex IV.

The implication for producers in third countries that arise from detection of Annex IV substances in food animal product is potentially serious. The EU permits import only for countries that have approved monitoring programmes that the European Commission

believes to be as good as those in place in Europe as regards protecting European consumers. Detection of any Annex IV substances is likely to result in an immediate reassessment of the monitoring programmes and at least a temporary ban on imports until the situation is resolved. If suppliers are responsible for use of prohibited substances, the remedy is simple, stop use and demonstrate that product contamination has ceased. More difficult could be cases of contamination from outside of the producer's control, demonstrating the origin and preventing further contamination may be impossible.

As is frequently commented, the last ten years have been ones of major change in regulation of veterinary medicines, both in Europe and in the USA. Whilst it might be hoped that some stability might be achieved now that the initial processes associated with the open market within Europe, this will not be the case. The codification of medicines legislation under Directive 2001/82/EC is welcome, but further review is also planned. At the time of writing further major changes are underway with the creation of the European Food Safety Authority (EFSA) http://www.efsa.eu.int/ that will assume responsibility for consumer safety aspects of veterinary medicines residues. This will include the replacement of all or parts of the responsibilities of existing advisory committees. New advisory panels will be formed as follows:

- Panel on food additives, flavourings, processing aids and materials in contact with food;
- Panel on additives and products or substances used in animal feed;
- Panel on plant health, plant protection products and their residues; Panel on genetically modified organisms;
- Panel on dietetic products, nutrition and allergies;
- Panel on biological hazards (including TSE/BSE issues);
- Panel on contaminants in the food chain;
- Panel on animal health and welfare

These changes reflect increasing emphasis on consumer safety under the Health and Consumer Protection Directorate of the European Commission which, together with EFSA will increasingly responsible for these areas (http://europa.eu.int/comm/dgs/health_consumer/index_en.htm).

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8.2 Legislation: USA

The basic American legislation in the Form of the Code of Federal Regulations is accessible on the web at http://www.access.gpo.gov/su_docs/aces/aces140.html, and in addition the USFDA and USDA both have excellent web sites with extensive background and explanatory information about the use of medicines in aquaculture.

US Food and Drug Administration, Center for Veterinary Medicine: http://www.fda.gov/cvm/default.htm

US Dept of Agriculture: http://www.usda.gov/

Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) http://www.fda.gov/cvm/index/amducca/amducafr.htm

Animal Drug Availability Act of 1996 (ADAA) http://www.fda.gov/cvm/index/adaa/adaatoc.html

The Federal Food, Drug, and Cosmetic Act (as amended by the FDA Modernization Act of 1997) (FD&CA) http://www.fda.gov/cvm/index/ffdc_act/ffdcatoc.html

U.S. Office of the Federal Register, 1998, Tolerances for Residues of New Animal Drugs in Food. Code of Federal Regulations, Title 21, Part 556, U.S. Government Printing Office, Washington, D.C. http://www.fda.gov/cvm/guidance/guidedocs.htm

8.3 Legislation: European Union

All current European legislation cited here may be found in PDF or HTML format on the European Commission web site at http://europa.eu.int/eur-lex/en/search/search_lif.html. CVMP and EMEA documents may be found at the EMEA web site at http://www.emea.eu.int/. These web sites are extensive and are updated frequently, all addresses given here were valid in mid April 2002. Background and explanatory information is more easily found on the web sites of the responsible agencies and departments of the Member States (e.g. UK at http://www.vmd.gov.uk/ and http://www.foodstandards.gov.uk/)

Commission Decision 2001/487/EC modifying Decision 2000/159/EC on the provisional approval of residue plans of third countries according to Council Directive 96/23/EC *Official Journal of the European Communities,* No L167/68**.** http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_176/l_17620010629en00680074.pdf

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