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Comments
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INTERNATIONAL HARMONISATION OF ANTIBACTERIAL AGENT APPROVALS AND SUSCEPTIBILITY TESTING

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Objectives

The objectives of this workshop were to provide updates on the progress toward international harmonisation of antibacterial agent approvals and susceptibility testing.

International Harmonisation of Antibacterial Agent Approvals

In the first part of the workshop, two presentations centered on addressing issues and existing programs related to gaining approvals for antibacterial agents in the United States and Europe that have developed since 1997. Issues addressed that relate to international antibacterial agent approvals included antimicrobial resistance, environmental safety, import tolerances, and maximum residue levels. These issues had been identified at the European Association of Fish Pathologists (EAFP) conference in Edinburgh, Scotland in September 1997. Existing programs discussed that relate to the international harmonisation of aquaculture drug approvals included crop grouping research, data sharing among countries, individual drug company efforts to obtain approvals in many countries, and national or regional aquaculture drug approval research programs that could help gain approvals in other countries.

In the United States, the Federal-State Aquaculture Drug Approval Partnership through a major effort has made great progress toward approvals since 1997 for oral (florfenicol and extensions for oxytetracycline) and external antibacterials (chloramine-T, copper sulfate, hydrogen peroxide, and potassium permanganate). Researchers have submitted all the data required for approval of copper sulfate to the Center for Veterinary Medicine and all the other drugs listed above have had major submissions. As part of this Partnership, researchers are conducting crop-grouping research to develop compartmental and physiologically based pharmacokinetic models, residue chemistry profiles, and risk assessment of florfenicol as a model drug so that data requirements can be reduced for multiple species and other drugs. The crop grouping research will be completed in 2002. In addition, the following oral and external antibacterials are being pursued by other partnerships for approval: amoxicillin, erythromycin, and Pyceze™.

The U.S. aquaculture industry is working with other minor species groups to increase the availability of approved drugs through new legislation known as "The Minor Animal Species Health and Welfare Act of 2000. Amendments are being proposed to the Food, Drug, and Cosmetic Act that include (1) extended marketing periods for minor use animal drugs, (2) conditional drug approval for minor uses with no human food safety concerns, (3) drug index for minor species with no human food safety concerns, (4) establishment of an Office of Minor Use Animal Drugs in the Center for Veterinary Medicine, and (5) research grants. Proposals are being considered to amend the Internal Revenue Code and enhance existing programs. Another initiative by the Joint Subcommittee on Aquaculture, Working Group on Quality Assurance in Aquaculture Production is a "White paper" to address antimicrobial resistance issues. Prior to the Animal Drug Availability Act of 1996 (ADAA), it was unlawful to import any animal that contained residues of a drug not approved in the U.S. for use on that animal. After ADAA, exporting countries can establish safe import tolerances using criteria similar to those for U.S. drug approval requirements.

Since January 1, 1998, Member States (15 nations at present) in the European Union (EU) can no longer proceed with independent licensing decisions without consensus from the other members, forcing them to harmonise the approval of drugs between nations. New applications are required for (1) changes in the active ingredient, (2) addition or change of indication or target species, (3) change of maximum residue levels (MRLs), and (4) change of withdrawal period. EU legislation centres on two main areas—marketing authorisation (MA) and MRLs. EU directives are pieces of community law that Member States must convert into national legislation within 90 days. Both an MA and MRL are needed in each Member State for a drug to be used legally.

Each drug is placed in certain category in the EU that determines what is required for a MRL. These categories include Annex I (full MRL set; e.g., amoxicillin, sarafloxacin), Annex II (no MRL required; e.g., bronopol), Annex III (provisional MRL set for maximum of five years; e.g., oxolinic acid), Annex IV (no safe MRL can be set; e.g., chloramphenicol), and Annex V (lists the data required to establish an MRL). Since January 1, 1997, no drug may be used in food animals unless an MRL has been set. Because the workload has been so great, few drugs have obtained Annex I or II status; thus, oxolinic acid has an extended Annex III status until January 1, 2001. Malachite green is in limbo because no company has submitted an application for a market authorisation and, without an application, no MRL is requested or established. Malachite green use in food species is not permitted but equally it is not prohibited because of the lack of application.

As of January 1998, a residue directive in the EU has been in place that control veterinary drug residues in food. This directive introduces fish meat, poultry meat, milk, and honey into the Member States monitoring programs and requires them to search for illegal or excessive drug residues in fish meat. Countries exporting products into the EU are also required to demonstrate that they are compliant with these regulations. One sample is required for any 100 tons of production. Analysis is required for residues of drugs in excess of the established MRL and of illegal drugs (those with no MRL in fish or Annex IV drugs).

Since 1997, EU guidance has been developed for environmental risk assessment for veterinary drugs. Ecotoxicity testing of drugs for use in fish farming is based on a tiered approach covering physico-chemical

parameters, environmental fate, and biological effects.

The EU has addressed antimicrobial resistance through a briefing paper that was presented in 1997 to the World Health Organisation. The basic findings were that human health was not likely to be affected by use of antibacterials in aquaculture. The aquaculture industry as a whole has done very well by reducing its usage of antibacterials in favor of vaccines. This is especially true in Norway and Scotland. Only the ornamental fish industry still uses many drugs.

International harmonisation can be enhanced through partnerships that were identified at the 1997 EAFP conference. Several international organisations have activities and missions that lend themselves to harmonisation. Workshops sponsored by the World Aquaculture Society and EAFP have contributed to better understanding of what co-operation is possible and what can be done to increase aquaculture drug approvals world-wide. Much work is still needed to obtain true harmonisation by these organisations. Better communications are needed to promote harmonisation. Websites and mail groups are needed that can help this cause. The international harmonisation workshops held as part of the World Aquaculture Society established a mail group that could be more active and the U.S. National Coordinator for Aquaculture New Animal Drug Applications has a new website that offers information on both national and international activities and issues.

International Harmonisation of Antibacterial Susceptibility Testing

In the second part of the workshop, presentations centered on the rationale, development, and testing of draft susceptibility testing protocols (disc diffusion, agar dilution, and broth dilution for both micro and macrodilution) that are intended to be standardised world-wide. These provisional protocols were developed at a workshop held in Weymouth, England in November 1998 by persons mainly from the EAFP membership. The purpose of these protocols is to develop internationally accepted standards that will allow aquatic diagnostic and research laboratories to (1) test disease-associated bacterial isolates for antimicrobial susceptibility patterns and (2) recommend appropriate therapy in a standard, internationally accepted manner. Added benefits include aiding the approval process for antibacterial agents and helping to determine the antimicrobial resistance of aquaculture pathogens world-wide. The draft protocols include standardised procedures for such components as media preparation, inocula, diffusion discs, and incubation.

The main reason for developing the protocols was that no one could communicate in a consistent manner about the clinical outcome of the disease therapy or the susceptibility of pathogens. The rationale used in the workshop included (1) obtaining the goodwill of 24 people to discard their own methods, (2) using acceptable limits based on quality assurance, (3) determining what the results meant, (4) setting of breakpoints, and (5) examining established breakpoints for their validity. These protocols must be useful and they are useful if they are useable. This effort will need some financial support. A proposal is in draft form for major funding from the EU.

The EAFP Work Group relied heavily on the documents of the National Committee for Clinical Laboratory Standards (NCCLS) in the formation of its provisional protocols. The NCCLS is an international, interdisciplinary, nonprofit, standards-making, and educational organisation that promotes the development and use of voluntary standards and guidelines within the human and animal healthcare communities. After the Workshop, the NCCLS Subcommittee on Veterinary Antimicrobial Susceptibility Testing (VAST) was approached to work co-operatively toward internationally standardised aquatic isolate protocols. VAST was impressed with the progress and commitment of the EAFP Work Group and recommended the formation of VAST Aquaculture Working Group (AqWG) to facilitate the development of official NCCLS protocols. A partial AqWG was formed in July 1999 and persons were added at the EAFP conference in Rhodes, Greece. The AqWG is comprised of members as follows: three from VAST, three from EU, eight from North America, one from Asia, and one from Australia.

Researchers worldwide had been invited to assess the protocols after testing them and to report on their results and critical reviews of these protocols at this workshop. Several researchers did indeed present results that demonstrated the difficulties and contradictions in the provisional protocols. All researchers were encouraged to summarize their results, place them on the website (www.nuigalway.ie/mic/eusus), and provide comments to Dr. Peter Smith at the University of Galway, Ireland (peter.smith@nuigalway.ie). It was hoped that significant progress could be reported in two years time at the next EAFP conference.