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Aquaculture 196 (2001) 245–251

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**Aquaculture**

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www.elsevier.nl/locate/aqua-online

Review article

# Antimicrobial susceptibility data and new animal drug approval in the United States: a historical overview

Thomas A. Bell\*

*U.S. Food and Drug Administration, Center for Veterinary Medicine, Office of New Animal Drug Evaluation, 7500 Standish Place, Rockville, MD 20855, USA*

Received 22 May 2000; accepted 30 August 2000

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## Abstract

The requirements and procedures necessary to gain approval for a new animal drug in the United States are briefly reviewed with respect to the requirement and applicability of antimicrobial susceptibility testing data, in particular, as these relate to what is referred to as Professional Flexible Labeled (PFL) animal drugs. The history and process by which the National Committee for Clinical Laboratory Standards (NCCLS) has established internationally recognized and utilized antimicrobial susceptibility testing procedures is reviewed in the context of standardization of procedures used in the clinical veterinary setting. Both the NCCLS and the PFL topics are discussed relative to their applicability to antimicrobial resistance in aquatic species' isolates and their nexus to efforts to begin the process of developing and using standard procedures for aquatic isolates. Published by Elsevier Science B.V.

*Keywords:* U.S. animal drug approvals; NCCLS; Aquatic bacterial isolates; Antimicrobial resistance; Antimicrobial susceptibility testing; Aquaculture

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## 1. Background

The Food and Drug Administration's Center for Veterinary Medicine (FDA/CVM) is the United States' Federal agency responsible for the approval of drugs for use in all

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\* Current address: U.S. Fish and Wildlife Service, Division of the National Fish Hatchery System, 4401 North Fairfax Drive, Arlington, VA 22203, USA.

*E-mail address:* thomas\_a\_bell@fws.gov (T.A. Bell).

non-food and food animals. A new animal drug may only gain approval when evidence is supplied to CVM, in the form of a New Animal Drug Application (NADA) that adequately documents the effectiveness and safety of the drug when used in accordance with the directions supplied on the product label. The safety component of an NADA is further subdivided into evidence that supports safety to the animal being treated, safety to the environment, safety to people administering or manufacturing the drug, and safety to people who may be exposed to the animals after treatment.

The latter safety subcomponent is likewise subdivided into two areas of concern. First, the drug must be shown to be safe to people who consume products derived from the treated food animal, i.e., no harmful drug residues remaining in the edible tissues. Second, and that linked to the general topic of this workshop (Workshop on Minimum Inhibitory Concentrations Methodologies Used in Aquaculture, 24–27 November 1998, The Centre for Environment, Fisheries and Aquaculture Science, Weymouth Laboratory, Barrack Road, The Nothe, Weymouth, United Kingdom), the drug must be shown to be safe to people who are exposed to microbes whose antimicrobial resistance patterns have been modified directly or indirectly by the drug. The latter safety concern centers on people being exposed either by ingestion of food products from the treated animals or by direct or indirect exposure to treated animals.

In its role as the regulatory agency responsible for new animal drug approvals, the CVM must review various types of data, derived from numerous types of experimental procedures, which are submitted by pharmaceutical firms in support of their claims of effectiveness and safety. Historically, *in vitro* antimicrobial susceptibility data have not been an essential component of submitted NADAs. However, such data are now playing a greater role in NADAs, and it is believed that their importance will increase even further in the near future.

Antimicrobial susceptibility data are presently being submitted, in a few NADAs, as part of the data to support the effectiveness of the drug. It is anticipated that such data will also play an essential role in the demonstration of predicted or existing antimicrobial resistance patterns (or the lack thereof) for the new animal drugs as these relate to human safety. In the context of how antimicrobial susceptibility data may be used in NADAs, it should be noted that there presently exist no U.S. laws or regulations that neither require nor prohibit the inclusion of antimicrobial susceptibility data in an NADA. However, some changes have occurred to U.S. laws, regulations and policies that affect the importance of such data. These changes will be briefly discussed below.

One purpose of this contribution (synopsis) is to discuss the history and iterative dialogue, relative to antimicrobial susceptibility data, which has taken place both within CVM, and between CVM and those outside of the U.S. Federal government that are affected by our laws, regulations and policies. This article will be divided into three sections. First, the history of the “Professional Flexible Label” (or PFL) drug-approval concept in the context of NADAs and the use of antimicrobial susceptibility data to support such approvals of new animal drugs with a PFL. Second, a brief overview of the National Committee for Clinical Laboratory Standards’ (NCCLS) veterinary antimicrobial susceptibility data collection standards and CVM’s and international aquatic animal health professionals’ involvement in this process. Third, comments of how the latter two areas may impact on, or be impacted by, drug approvals for aquaculture species.

## 2. Professional flexible label (PFL) concept

A PFL is defined as the approved new animal drug label that is written broadly and flexibly enough (i.e., a broadened claim and/or a dosage range) to reduce the need for veterinarians to prescribe the drug for indications and/or a dosage beyond that stated on the approved product label (referred to as an extralabel use). A PFL may only be as broad and flexible as the supplied data permit. However, some of the types of data that may be used to support a PFL may be non-traditional in form, such as antimicrobial susceptibility data (when interpreted together with pharmacokinetic data and data generated in clinical trials).

Historically, the concept of PFLs began in the 1980s during formal meetings between the CVM and two key organizations in the U.S. animal health industry, the American Veterinary Medical Association (AVMA) and the Animal Health Institute (AHI). These discussions resulted in the joint submission to CVM, by AHI and AVMA, of a formal Citizen's Petition (CP) in 1991. The CP basically proposed to CVM that label claims (and the data to support such claims) for new animal drugs be broad and flexible enough to permit the veterinarian to prescribe the product for uses based on the label AND their professional judgment. The primary objective, as stated in the CP, was to reduce the tension between the veterinarian's legal and ethical responsibilities to their clients under the existing laws and regulations relating to approved new animal drugs, i.e., the veterinarian was legally obliged to prescribe the drug only for the indications defined on the label, while at the same time, the veterinarian was ethically obliged to eliminate or reduce the pain and suffering in the afflicted animals.

Discussion continued between the CVM, AHI, AVMA and other interested parties from the early to mid 1990s. These discussions formally culminated in a 1995 workshop sponsored jointly by the CVM, AHI, AVMA and the American Association of Veterinary Pharmacology and Therapeutics (AAVPT). The workshop was entitled: "Professional Flexible Labeling: An Interactive Workshop on First Principles". The proceedings and follow-up documents from the workshop were published in the *Journal of the American Veterinary Medical Association* in 1995 and 1996 (Farho, 1995; Gloyd, 1996; Papich, 1995; Sundlof, 1995).

The PFL-related activities noted above have resulted in changes to U.S. laws, regulations and other public documents that affect drug approvals. Two public documents of note are the U.S. Animal Drug Availability Act of 1996 (ADAA) and the CVM Guidance Document No. 66. The ADAA, which amends the U.S. Federal Food, Drug and Cosmetic Act, makes it clear that *in vitro* data may comprise a portion of the "...adequate and well-controlled studies..." required in an NADA to provide "...substantial evidence..." to demonstrate effectiveness of the drug. The CVM also responded to the previously noted activities by publishing a publicly available Guidance Document No. 66 in 1998. The latter document entitled: "Guidance to the Industry—Professional Flexible Labeling of Antimicrobial Drugs", (CVM, 1998) provided the pharmaceutical industry with CVM's current thinking on PFL concepts, by offering mutually non-binding suggestions as to how the pharmaceutical industry might generate PFL's for new animal drugs, in particular antimicrobials. A major topic of discussion within the guidance document was the use of *in vitro* antimicrobial susceptibility data to

support the approval of a new animal drug. A more recent FDA/CVM document, “Guidance to the Industry—Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals” (CVM, 1999), provides additional information on antimicrobial susceptibility testing and new animal drug approvals. All U.S. FDA/CVM documents are available at their website ([www.fda.gov](http://www.fda.gov)). Additionally, CVM maintains a complete section on their website ([www.fda.gov/cvm](http://www.fda.gov/cvm)) that provides all current documents and other information on antimicrobial resistance.

There have been several new animal drugs approved within the past four years that have included substantial antimicrobial susceptibility data in support of a PFL. The PFL products that have been approved to date have all been for non-food companion animals, e.g., orbifloxacin (Orbax<sup>®</sup>) for dogs and cats. The broad claim and dosage range in the Orbax<sup>®</sup> approval was supported by a multifaceted database, which included clinical field trial, target animal safety, pharmacokinetic and minimum inhibitory concentration (MIC) data. This database was instrumental in permitting the label indications for this particular drug to be as broad and flexible as possible, i.e., “... for the management of diseases associated with bacteria susceptible to orbifloxacin...”

### **3. The national committee for clinical laboratory standards process**

The National Committee for Clinical Laboratory Standards (or NCCLS—940 Valley Road, Suite 1400, Wayne, PA 19087, USA) is an independent, private organization that has functioned to standardize procedures for *in vitro* testing of human and veterinary bacterial pathogens. The NCCLS standardized procedures have been rigorously tested and are commonly accepted and used by diagnostic laboratories and pharmaceutical firms throughout the U.S. and in other countries. More complete information on NCCLS and their available procedures, guidelines and documents can be found at their website ([www.nccls.org](http://www.nccls.org)).

Current versions of their procedures for human pathogens were published during the period 1993–1997 and may be found at their website. These publications comprise descriptions of standardized methods, protocol guides, and the testing-criteria development and performance standards for *in vitro* testing.

In parallel with their human pathogen standards, NCCLS also has established veterinary pathogen standards. Historically, this work began in 1992 with the formation of the NCCLS Veterinary Antimicrobial Susceptibility Testing Subcommittee (VAST). The VAST comprises members from academia, the pharmaceutical industry and Federal regulatory agencies. A CVM scientist is a current member. In addition to the permanent members, the VAST also routinely consults with numerous experts in several topical areas associated with veterinary microbiology and medicine.

The current veterinary standards have been incorporated in two primary NCCLS publications. The first is the “Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals”, Publication No. M31-A (NCCLS, 1999). All NCCLS published standards, as they are modified and refined, may be purchased in one of three chronologically ordered versions—the first

available is the proposed (P), followed by the tentative (T) and finally the approved (A) version. Publication M31 is presently available in the approved version. This publication is intended to provide the standards by which veterinary diagnostic laboratories conduct antimicrobial susceptibility tests on veterinary isolates. The second publication (M37), entitled “Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents: Approved Guidelines”, Publication No. M37-A (NCCLS, 1998), was also recently published as an approved version. As the title would suggest, this latter publication is intended to provide standardized procedures to be used by pharmaceutical firms during the research and development of new products.

Although both NCCLS veterinary publications are quite inclusive relative to applicability to isolates of animal origin, neither publication addresses isolates from aquatic species. The NCCLS VAST was aware of aquaculture and diseases of aquatic species during the formulation of their publications, but they were unable to incorporate procedures unique to aquatic isolates into the standards developed for terrestrial animal isolates. The NCCLS has expressed interest in the documents planned for development at the Workshop on Minimum Inhibitory Concentrations Methodologies Used in Aquaculture (24–27 November 1998, The Centre for Environment, Fisheries and Aquaculture Science, Weymouth Laboratory, Barrack Road, The Nothe, Weymouth, United Kingdom). The NCCLS VAST has been apprised of the Weymouth workshop activities, including generated documents, and has committed to assist in this endeavor. It is hoped that the Weymouth workshop efforts will assist the international aquatic diseases community in their endeavor to standardize and simplify antimicrobial susceptibility procedures for aquatic isolates.

#### **4. The PFL and NCCLS process and their relationship to antimicrobials in aquaculture**

Antimicrobial susceptibility data have the potential to serve two very important functions in the regulatory arena of U.S. new animal drug approvals. First, and not necessarily in order of importance, antimicrobial susceptibility data, when submitted as part of an NADA, may permit new antimicrobial animal drugs to be approved with broad and flexible labels (PFLs). New animal drugs with such PFLs may represent: (a) a cost and time savings to the pharmaceutical firms, when compared to the normal procedure of legally amending an NADA for expanded label claims, (b) a means by which veterinarians will be less often forced to prescribe drugs in an extralabel manner in order to reduce pain and suffering or to save the life of an animal, and (c) a means by which the growth of new animal husbandry industries (new compared to beef, swine and poultry) are facilitated through efficient and safe disease management. A prime example of the latter would be the aquaculture industry in the U.S. There presently exist only two antibiotics (oxytetracycline and sulfadimethoxine + ormetoprim) approved for use on fish in the U.S., and in these cases, the approved labels are restricted to a very limited number of species and diseases.

Second, and of increasing importance, antimicrobial susceptibility data will probably play a significant role in the determination of how safe a new animal drug is relative to

its impact on the development of antimicrobial resistance. The CVM has recently acknowledged, publicly, the importance of such potential resistance development via the use of antibiotic in animals, and the potential for the transfer of such resistance to human pathogens. In an effort to develop laws, regulations and policies to properly address this issue, the CVM has solicited public comments on when to require, and how to generate, antimicrobial resistance information to support a prospective NADA or to maintain an existing NADA.

In both of the aforementioned uses of antimicrobial susceptibility data, the CVM strongly supports (and may ultimately require) standardized, verifiable antimicrobial susceptibility data generation procedures. It is understood that a process similar to that of NCCLS, and the other national standards, will be required to establish such conventions. The work begun at the Weymouth workshop is an essential step in this endeavor.

## 5. Conclusions and future directions

Minor-species industries (those animals other than cattle, swine, chickens, horses, dogs and cats), and in particular aquaculture, may be most likely to utilize antimicrobial susceptibility data, in their pursuit of NADAs. Given aquaculture's inherent diversity of species and culture conditions, there appears to be even greater opportunity to use antimicrobial susceptibility data as a major subcomponent of the data required to document a new animal drug's effectiveness. Antimicrobial susceptibility data are likely to be necessary to permit extrapolation to drug labels covering a large number of species and/or indications.

In spite of a relatively clear recognition of the importance of antimicrobial susceptibility data in our understanding of antimicrobial resistance, at this point it is not apparent as to the exact procedures by which these data will be used. Regardless of the latter point, there is no question that antimicrobial susceptibility data, when used, will have to be generated by a standardized, verifiable protocol to be of value.

The work that has begun at the Weymouth workshop is the all-important first step in international standardization of antimicrobial susceptibility testing. Its value is exceptionally far-reaching, extending well beyond the regulatory arena. The potential to realize a significantly improved melding of laboratory and clinical information will be immeasurable in the arena of animal disease management.

## References

- CVM, 1998. Guidance for Industry—Professional Flexible Labeling of Antimicrobial Drugs; Guidance Document No. 66. U.S. Food and Drug Administration, Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855, USA.
- CVM, 1999. Guidance for Industry—Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals, Guidance Document No. 78. U.S. Food and Drug Administration, Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855, USA.

- Farho, C.J., 1995. Review of the first interactive workshop on professional flexible labeling; an Animal Health Institute perspective. *Journal of the American Veterinary Medical Association* 207 (7), 869–871.
- Gloyd, J.S., 1996. A step closer to reality: professional flexible labeling for animal drugs. *Journal of the American Veterinary Medical Association* 208 (4), 457–459.
- NCCLS, 1998. Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents; Approved Guideline. NCCLS Document M37-A (ISBN 1-56238-369-8). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.
- NCCLS, 1999. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard. NCCLS Document M31-A (ISBN 1-56238-377-9). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.
- Papich, M.G., 1995. Review of the first interactive workshop on professional flexible labeling; an American Veterinary Medical Association perspective. *Journal of the American Veterinary Medical Association* 207 (7), 871–874.
- Sundlof, S.F., 1995. Review of the first interactive workshop on professional flexible labeling; the Center for Veterinary Medicine perspective. *Journal of the American Veterinary Medical Association* 207 (7), 867–868.