VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

144

Guidance for Industry

Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food-Producing Animals with Respect to Antimicrobial Resistance

VICH GL27

FINAL GUIDANCE

This guidance document is an initial step in developing harmonized technical guidance for approval of therapeutic antimicrobial veterinary medicinal products intended for use in food-producing animals with regard to characterization of antimicrobial resistance selection in bacteria of human health concern in the European Union, Japan, and the United States.

Comments and suggestions regarding this document should be submitted to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov/. All comments should be identified with the Docket Number 2003D-0051.

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GUIDANCE ON PRE-APPROVAL INFORMATION FOR REGISTRATION OF NEW VETERINARY MEDICINAL PRODUCTS FOR FOOD PRODUCING ANIMALS WITH RESPECT TO ANTIMICROBIAL RESISTANCE

Recommended for Implementation
at Step 7 of the VICH Process
on 15 December 2004
by the VICH Steering Committee

Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food-producing Animals with Respect to Antimicrobial Resistance

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Introduction

The use of antimicrobial agents is likely to lead to selection of resistance whether administered to humans, animals or plants. Zoonotic organisms such as non-typhoid Salmonellae, *Campylobacter spp*. and enterohaemorrhagic *E. coli* (e.g. O157) can, by definition, be transferred to humans from animals. Therefore, it stands to reason that resistant zoonotic organisms can also be transferred to humans. The transfer of antimicrobial-resistant non-zoonotic bacteria or their genetic material from animals to humans via the food chain is also possible. However, data demonstrating the magnitude and importance of such transfer and whether such transfer occurs via consumption of contaminated meat or via contamination of water or vegetables by animal excreta are limited.[1,2,3] Humans are also a potential reservoir of antimicrobial-resistant microorganisms. [4,5]

The extent to which food-producing animals contribute to human exposure to antimicrobial-resistant microorganisms is difficult to quantify. However, when evaluating the safety of antimicrobial products for use in food-producing animals, regulatory authorities should consider the potential for such products to select for resistant bacteria. Therefore, guidance is needed for drug sponsors on the type of information that should be provided to the regulatory authorities. This information should help to characterize the potential for the use of the product to select for antimicrobial-resistant bacteria of human health concern. The information provided should be used as part of an overall assessment of the potential impact of the product on human health.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

Objectives

The objective of this document is to provide harmonized technical guidance in the E.U., Japan and the U.S. for registration of antimicrobial veterinary medicinal products intended for use in food-producing animals with regard to characterization of the potential for a given antimicrobial agent to select for resistant bacteria of human health concern.

For clarification, this guidance outlines the types of studies and data which are recommended to characterize the potential resistance development as it might occur in the food-producing animal under the proposed conditions of use of the product. This includes information which describes attributes of the drug substance, the drug product, the nature of the resistance, and the potential exposure of the gut flora in the target animal species. It does not account for post-slaughter factors such as processing of food products or kitchen hygiene that affect the potential human health impact.

Pathogen load studies, ecotoxicity studies, the process of risk assessment, the establishment of Acceptable Daily Intakes (ADIs), and consideration of residues of antimicrobial agents are not included in this guidance.

Special considerations may be appropriate for aquaculture products, because of fundamental differences in production systems, bacterial populations present, and potential zoonotic public health threats.

Data recommendations

Information in the subsequent sections has been designated as ‘basic’ or ‘additional’ data. Where information is designated as ‘basic’, it is recommended that sponsors provide such information.

Where information is designated as ‘additional’, sponsors may choose to include some or all of those data. The proposed use conditions of the product, the potential exposure of animal gut flora to the antimicrobial agent, the potential exposure of humans to resistant bacteria or their resistance genes, and the perceived importance of the drug (or related drugs) to human medicine may be factors on which the sponsor provides ‘additional’ data.

1. Basic information

1.1 Antimicrobial class

This information can be based on the drug substance's chemical structure, patent information, and information that is contained in subsequent sections. For example, the common name, chemical name, CAS (Chemical Abstract Services) registry number, chemical structure, and manufacturer’s code number and/or synonyms are recommended.

1.2 Mechanism and type of antimicrobial action

This information may be inferred from literature studies, patent information, or specific mechanism of action studies undertaken by the sponsor. Characterization as to bacteriostatic vs. bactericidal action should be included in this section.

1.3 Antimicrobial spectrum of activity

1.3.1 General data

Information on the antimicrobial agent should be provided by the sponsor including data from MIC (minimum inhibitory concentration) tests against a wide variety of microorganisms or from literature studies, in order to determine the overall spectrum of activity. Where MICs are determined by the sponsor, the source of the isolates may be from culture collections, diagnostic laboratories, or other repositories.

Where possible, MIC values should be determined with a validated and controlled method, such as those described in National Committee on Clinical Laboratory Standards (NCCLS) documents (e.g., M31-A2, Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria isolated from Animals; Approved Standard).

1.3.2 MICs of target animal pathogens (as per product label claim)

These data are considered supportive for the purposes of this guidance. Information on target animal pathogen MICs may be obtained from data within the Efficacy section of the dossier.

1.3.3 MICs of food-borne pathogens and commensal organisms

Data should be presented to show MICs of food-borne pathogens and commensal organisms. This information may be based on published data or on studies done by the sponsor. Depending on the spectrum of activity, appropriate organisms may include:

Food-borne pathogens:

- *Salmonella enterica*
- *Campylobacter* spp.

Food-borne commensal organisms such as:

- *Escherichia coli*
- *Enterococcus* spp.

When possible, the strains included should be selected according to the following recommendations:

- Strains of relevant bacterial species/serotypes should be isolated from the proposed target animal species. When the product is intended for a broad range of animal species, the strains should be from the main food-producing species (e.g. cattle, pigs, and poultry).
- Preferably, the strain collection should include recent isolates.

Information on the tested strains should include:

- Identification at least to the species level.
- Origin, source and date of isolation.

1.4 Antimicrobial resistance mechanisms and genetics

Where possible, information on the resistance mechanism(s) and information on the molecular genetic basis of resistance to the antimicrobial agent should be provided. This information may come from literature or from studies done by the sponsor. Information from analogues may be provided in the absence of data on the drug substance.

1.5 Occurrence and rate of transfer of antimicrobial resistance genes

Information on the occurrence, or absence, of transfer and rate of transfer of resistance genes should be provided. This information may come from literature or from studies done by the sponsor. Specific studies to evaluate the occurrence of genetic transfer may follow a protocol such as found in Antibiotics in Laboratory Medicine, 4th ed., V. Lorian, ed. 1996. Williams and Wilkins, Baltimore, Maryland.

The sponsor may consider including data on target animal pathogens, relevant food-borne pathogens, and relevant commensal organisms. Information from analogues may be provided in the absence of data on the antimicrobial agent.

1.6 Occurrence of cross-resistance

Information on cross-resistance to the antimicrobial agent should be provided. This information may come from literature or studies done by the sponsor. This should include a phenotypic description and, if available, a genotypic description.

1.7 Occurrence of co-resistance

Information on co-resistance of the antimicrobial agent in question with other antimicrobial agents should be provided by literature information or studies done by the sponsor. This should include a phenotypic description and, if available, a genotypic description.

1.8 Pharmacokinetic data

Pharmacokinetic data may be obtained from other sections of the dossier in order to predict the antimicrobial activity in the intestinal tract. Data may include the following:

- Serum / plasma concentrations versus time data
- Maximum concentration (Cmax)
- Time of maximum concentration (Tmax)
- Volume of distribution (VD)
- Clearance (Cl)
- Area under the concentration-time curve (AUC)
- Bioavailability
- Protein binding

2. Additional information

Sponsors may also choose to include some or all of the following:

2.1 *In vitro* mutation frequency studies

In vitro mutation frequency studies involving test organisms may follow a protocol such as found in Antibiotics in Laboratory Medicine, 4th ed., V. Lorian, ed. 1996. Williams and Wilkins, Baltimore, Maryland.

2.2 Antimicrobial agent activity in intestinal tract

Where available, details may be provided on the concentrations of microbiologically-active compound within the intestinal tract contents or the feces when the antimicrobial product is administered according to the proposed conditions of use. The activity in question may be due to the parent antimicrobial agent, or to active metabolites.

Where such data are not available, details may be provided by metabolism studies relevant to the intestinal tract. Data from metabolism studies may be obtained from other sections of the dossier.

2.3 Other animal studies

The sponsor may choose to include information from other animal studies conducted to help characterize the rate and extent of resistance development associated with the proposed use of the antimicrobial product. This may include data from clinical studies conducted in support of other sections of the dossier.

The predictive value of the results of such studies is yet to be established with regards to resistance development. Therefore, the results of such studies should be interpreted in the context of all other pre-approval information described in this document.

2.4 Supporting information

When available and relevant, supporting information from literature or studies on previously approved uses of the drug product or related products may be provided.

3. Discussion

The sponsor should characterize the potential for the use of the product to select for antimicrobial-resistant bacteria of human health concern. To accomplish this, the sponsor should discuss the information provided in the previous sections in terms of the exposure of food-borne pathogens and commensal organisms to microbiologically active substance in the target animal after administration of the veterinary medicinal product under the proposed conditions of use.

Glossary

Antimicrobial agent or antimicrobial(s): naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of other micro-organisms).

Food-producing animals: Cattle, poultry and pigs are considered as food-producing animals. Because of regional differences, in some countries other animal species may be considered as food-producing animals.

Target animal pathogen: pathogenic bacterial species causing infection in the target animals for which the veterinary antimicrobial medicinal product is indicated to be used for, as claimed on the label.

Food-borne pathogens: zoonotic organisms, of which animals could be carriers in the intestinal content, that could be transmitted to humans by the food chain and subsequently cause food-borne infections in humans.

Food-borne commensal organisms: non-zoonotic bacterial species, living in the intestinal content of animals, that could be transmitted to humans by the food chain and that normally do not cause food-borne infections in humans.

References

1. Ministry of Agriculture Fisheries and Food. A Review of Antimicrobial resistance in the Food Chain: A Technical Report for MAFF. July 1998. http://archive.food.gov.uk/maff/pdf/resist.pdf.

2. European Commission. Opinion of the Scientific Steering Committee on Antimicrobial Resistance. May 1999. http://ec.europa.eu/food/fs/sc/ssc/out50_en.pdf.

3. Commonwealth Department of Health ad Aged Care and the Commonwealth Department of Agriculture, Fisheries and Forestry-Australia. The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR). September 1999. http://www.health.gov.au/internet/main/publishing.nsf/content/2A8435C711929352CA256F180057901E/$File/jetacar.pdf.

4. H. Kinde, et.al. Sewage Effluent: Likely Source of Salmonella enteritidis, Phage Type 4 Infection in a Commercial Chicken Layer Flock in Southern California. Avian Diseases 40:672-679, 1996.

5. H. Kinde, et.al. Prevalence of Salmonella in Municipal Sewage Treatment Plant Effluents in Southern California. Avian Diseases 41:392-398, 1997.