NEW FOOD SAFETY INITIATIVES IN THE FOOD AND DRUG ADMINISTRATION

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ABSTRACT

Concern over the presence of veterinary drug residues in food has been increasing worldwide. Because of this concern, the Food and Drug Administration's Center for Veterinary Medicine (CVM) has been involved on an international basis in efforts to develop food safety standards for veterinary drugs. The major thrust of the Codex Committee on Residues of Veterinary Drugs in Foods (CC/RVDF) has been to achieve international agreement on veterinary drugs issues. CVM is an active participant on this committee. The CC/RVDF has established a list of priority veterinary drugs that are, or that have the potential to cause trade problems as the result of public health concerns. Included in this list are anabolic hormones, chloramphenicol, sulfonamides, nitrofurans, nitroimidazoles, somatotropins, benzimidazoles and trypanocides. In the upcoming years, the CC/RVDF will work toward developing international maximum residue levels for these compounds. The evaluation of the toxicity of veterinary drug-bound residues is another area of international concern. In conjunction with the Bureau of Veterinary Medicine, Health and Welfare Canada, CVM is developing guidelines on biological models to demonstrate the safety of veterinary drug-bound residues. In working with veterinary drug regulators from other countries, CVM has new solutions to human food safety problems.

(Key Words: Food Legislation, Drug Residues, Food, Drugs.)


Introduction

Enhancing productivity in animal husbandry often involves the use of substances that are physiologically, pharmacologically and toxicologically very potent. In countries with large-scale animal production, many animals are exposed to chemicals that may leave residues in the carcass at the time of slaughter.

In recent years, the presence of these veterinary drug residues in food has become an issue of intense international concern and debate. This concern is not limited to the scientific community. Consumers all over the world, through various means, have expressed their sincere desire for a drug-free meat supply.

Human Food Safety Requirements For Veterinary Drugs

Recently, the Center for Veterinary Medicine (CVM) published a series of guidelines describing how the Food and Drug Administration (FDA) evaluates the safety of veterinary drug residues in meat. These guidelines, entitled "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals" outlines the studies that FDA believes will provide an acceptable basis for determining the human food safety of a compound used in food-producing animals (FDA, 1987).

As discussed in these human food safety guidelines, drug manufacturers are asked to develop information on the amount, persistence and chemical nature of the total residue...
of a veterinary drug in the edible tissues of the treated target animals. CVM defines total residue as parent compound, free metabolites and metabolites that are covalently bound to endogenous molecules. The drug manufacturers also are asked to develop information on the metabolism of the compound in the species of laboratory animals used for toxicological testing.

Other countries also have outlined their approaches to evaluating the safety of veterinary drug residues. Most developed countries require studies similar to those requested in the U.S. Differences between countries occur in the interpretation of the data submitted on a particular compound and in the establishment of tolerances and withdrawal periods for veterinary products.

Differences in the use of veterinary drugs can present difficulties in international trade. For example, when one country allows the use of a drug that country may not export its products to other countries that prohibit the use of that drug if the products contain detectable residues. The use of increasingly more sensitive methods of analysis can inhibit trade to those countries that impose a zero tolerance for certain residues.

The U.S. has had a serious controversy with the European Economic Community (EEC) over the use of anabolic hormones for growth promotion in cattle. The EEC has prohibited the domestic use of these compounds for growth promotion in all food-producing animals. The EEC also has banned the importation of meat from any country that uses these compounds unless the country can certify that the animals never received hormone treatment.

The EEC has used consumer safety concerns for residues of anabolic hormones in treated meat as the basis for its ban on these compounds. However, the EEC has not cited any scientific evidence to support its concerns. The FDA has stated that consumers are not at risk from eating meat from implanted cattle because the amount left as a residue is extremely small and far below the level required to produce any toxic effect.

Thus, the FDA believes that the EEC ban on anabolic hormones has no scientific basis and, therefore, constitutes a non-tariff trade barrier. Because the two countries were unable to reach a compromise on this issue a trade war began.

International Consensus on Veterinary Drug Standards

Conflicts such as the one regarding anabolic hormones have highlighted the importance of developing international standards for drug residues in foods. However, until very recently, there has been little international cooperation on problems associated with veterinary drugs.

In 1984, the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) co-sponsored an Expert Consultation on Residues of Veterinary Drugs in Foods (FAO, 1985). At this meeting, government leaders in the veterinary drug world considered the importance of focusing on food safety issues from a global perspective. Because of the world-wide significance of the problem of veterinary drug residues, the Consultation recommended that the assessment of the safety of these compounds should be carried out internationally by an FAO/WHO body of veterinary drug experts. This committee, called the Joint FAO/WHO Expert Consultation on Food Additives (JECFA), would meet on an ad hoc basis to determine acceptable daily intakes (ADI) and maximum residue levels (MRL) for veterinary drug residues. The JECFA would report these MRL to a Codex Committee to use in elaborating international standards for veterinary drugs.

Based on the recommendation of this Consultation, the Codex Committee on Residues of Veterinary Drugs in Foods (CC/RVDF) was established in 1985.

Codex Committee on Residues of Veterinary Drugs in Foods

The CC/RVDF is one of the subsidiary bodies of the Codex Alimentarius Commission. This Commission was established in 1962 and currently has approximately 130 member nations. The major purpose of this organization is to elaborate international food standards in order to protect the health of consumers and to ensure fair trade practices. It is supported by WHO and FAO as part of their Joint FAO/WHO Food Standards Program.

Most of the work of the Commission is accomplished by subsidiary committees. There are three types of subsidiary committees: worldwide commodity committees, such as the Codex Committee on Cereals, Pulses, and Legumes; regional coordinating committees such as the Regional Co-ordinating Committee
for Africa; and worldwide general subject committees that deal with pesticide residues, food additive and contaminants, and the CC/RVDF.

The first session of the CC/RVDF was held in Washington, DC, on October 27-31, 1986 and was attended by representatives from 34 countries and 10 international organizations. One of the major accomplishments of the first meeting was to establish criteria for selection of drugs to be reviewed by the JECFA.

In order to be placed on the priority list for evaluation by the JECFA and subsequent development of an MRL by the CC/RVDF, the veterinary drug, when used in accordance with good veterinary practices, should meet some, but not necessarily all, of the following criteria: 1) the drug results in residues in the food commodity; 2) the drug or its residues are a matter of public health concern; 3) the residues of the drug affect international trade to a significant degree; and 4) the drug is available for use as a commercial product. In addition 1) there must be a firm indication that relevant data will be made available for evaluation; and 2) CC/RVDF should take into account any work on residues of the drug undertaken or completed by other Codex Committees.

At its first session, the CC/RVDF elaborated a list of veterinary drugs that it decided met these criteria. The drugs selected by the Codex Committee as international priorities included anabolic hormones, chloramphenicol, sulfonamides, nitrofurans, nitroimidazoles, quinoloxaline-di-N-oxides and trypanocides (FAO/WHO, 1986).

In two subsequent meetings of the CC/RVDF, the priority list was expanded to include benzimidazoles, penicillin, tetracyclines, somatotropins and phenothiazines (FAO/WHO, 1987, 1988).

**Joint Expert Committee on Food Additives**

In June 1987, the first meeting of the JECFA for the evaluation of veterinary drug residues occurred. The JECFA evaluated the anabolic hormones and chloramphenicol (WHO, 1988). This committee recommended that chloramphenicol not be used in food-producing animals because it was not possible to give an assurance that residues of this drug would be safe for sensitive subjects who may develop aplastic anemia.

Additionally, JECFA stated that establishing a tolerance for a hormone that is produced endogenously at variable levels is unnecessary because the residues resulting from the use of these compounds as growth promoters in accordance with good veterinary and animal health practices would not pose a hazard to human health. The JECFA also calculated tolerance for residues of both zeranol and trenbolone acetate. The decisions by the JECFA established beyond any doubt that anabolic products as used today in a number of countries in the world are safe.

The second meeting of the JECFA for the evaluation of veterinary drug residues was held in Geneva in February 1989. The JECFA reviewed data on albendazole, sulfamethazine, sulfathiazole, nitroimidazoles, trypanocides and trenbolone acetate. An MRL was recommended for albendazole, trenbolone acetate and sulfamethazine. Additional data were requested on the other compounds before an MRL could be determined.

The JECFA also considered the biological impact of veterinary drug residues bound to cellular constituents in animal tissues (bound residues) at the February 1989 meeting.

**Veterinary Drug-Bound Residues**

Bound residues of veterinary drugs are nonextractable, covalently bound residues of the parent drug or its metabolites that are not the result of endogenous incorporation. The FDA requires drug manufacturers to demonstrate the safety of these residues.

If the parent compound is not a carcinogen, FDA will discount from the residue of toxicological concern that portion of the covalently bound residue that the drug manufacturer demonstrates is not bioavailable, using an appropriate animal model.

However, if the parent compound is a demonstrated carcinogen, FDA will not accept bioavailability data alone to discount the covalently bound residue from carcinogenic concern. The agency's reluctance to use the bioavailability approach under these circumstances is related to the potential for gastrointestinal bleeding and concern over gastrointestinal carcinogenesis. Thus, most companies have elected not to pursue the development of veterinary drugs that have sizeable amounts of bound residues because of the uncertainties and expenditures in time and money needed to
resolve questions regarding the safety of these compounds.

In discussions with the Canadian Bureau of Veterinary Drugs (BVD) it became apparent that both governments should examine the issue of bound residues and formulate, if possible, guidelines to the industry on what would constitute an adequate amount of testing to determine whether these compounds are safe. Scientists from both countries agreed that more broadly based scientific approaches were needed for addressing the toxicological potential of bound residues of carcinogenic animal drugs.

As a first step in this process, FDA, BVD and the U.S. and Canadian Animal Health Institutes co-sponsored an international symposium on Biological Models to Determine the Safety of Bound Residues in the Tissues of Food-Producing Animals. This symposium was held in Washington, DC in October 1988, just prior to the third session of the CC/RVDF. At this symposium a "mechanistic" approach to the evaluation of bound residues was proposed.

Knowledge of the mechanism by which drugs are activated to reactive and toxicity of covalently bound residues. As an example, mechanistic studies could identify the metabolic pathway leading to the covalent binding of metabolites to proteins. By the in vitro testing of model compounds having structures similar to the protein-bound adduct, one could evaluate the toxicological potential of the bound residue.

Based on the toxicity profile of the parent compound and the nature of the bound residue, a series of in vivo and in vitro tests could be performed to demonstrate that the bound residue no longer retains the biological activity of the parent drug.

The results of this symposium were presented at the 34th meeting of the JECFA, which was convened in Geneva in February 1989. The JECFA endorsed this mechanistic approach as being a scientifically sound alternative for demonstrating the safety of bound residues. Currently the U.S. and Canada are finalizing their guidelines for the safety assessment of bound residues. These guidelines will be discussed with our European colleagues at the next CC/RVDF meeting in October 1989.

Conclusion

The Center for veterinary Medicine has been involved in several international initiatives. In working with veterinary drug regulators from other countries, CVM has been able to find new solutions to problems. The development of international activities pertaining to veterinary drugs was long overdue and many exciting new initiatives in this area are expected.

Literature Cited


