DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date January 16, 2001

From FDA GeneTox Network, Rosalie K. Elespuru, Ph.D., CDRH, Chair RKE
Through: Bernard A. Schwetz, D.V.M., Ph.D., Acting Deputy Commissioner BAS

Subject Docket No. 00D-1631 - Guidance For Industry. Safety Studies for Veterinary Drug Residues in Human Food: Genotoxicity Studies. VICH GL23. Draft Guidance.

To Dockets Management Branch (HFA-305)
Food and Drug Administration
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The FDA GeneTox Network is an FDA-wide group of genetic toxicologists with the objective of fostering communication and coordination of scientific issues related to genetic toxicology both within FDA and in the greater scientific community.

We believe that harmonization of regulatory guidelines across geographic regions and product classes is an important goal. The proposed VICH genetic toxicology testing guidance is not in harmony with existing guidances relating to foods, drugs and medical devices. These include guidance on genetic toxicology testing of food ingredients (Toxicological Principles for the Safety of food ingredients: Redbook 2000; http://vm.cfsan.fda.gov/~redbook/red-toca.html); guidance for genetic toxicology testing of human pharmaceuticals (ICH S2A, Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals, April 1996; and ICH S2B, A Standard Battery of Genotoxicity Testing of Pharmaceuticals, July, 1997; http://www.ifpma.org/ich5s.html); and the guidance for testing of medical devices (ISO 10993-3, The Biological Evaluation of Medical Devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity; http://www.aami.org/standards/standards.pubs.html#bioevaluation).

Our primary concern involves the lack of the Mouse Lymphoma Assay (MLA) as an integral part of the standard test battery (VICH GL23.2 Standard Battery of Tests). The MLA is unique in its capability of detecting a broad spectrum of genetic damage, including both gene (point) mutations as well as viable chromosomal mutations (e.g., deletions, translocations, gene conversion/mitotic recombination, and/or aneuploidy). All of these genotoxic events have been linked to cancer and other genetically-based human diseases. The proposed VICH standard three-test battery focuses on a more limited spectrum of genetic damage, and risks missing some types of cancer-causing agents. In order to cover the broadest spectrum of genetic damage, it is vital to retain the MLA assay as an optional alternative to in vitro chromosomal aberration testing within the standard framework of the genetic testing guidance.

This could be done quite easily by integrating the paragraph referring to the MLA found in Section 4 (Conduct of Assays) into Section 2, except for the sentence in Section 4 referring to the MLA that states "If it shall become internationally accepted for use, it may provide a useful alternative to the in vitro cytogenetic assay." On the contrary, international acceptance already exists, and we recommend that this sentence be deleted. International acceptance of MLA is

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shown by the presence of this assay in the standard genetic toxicology testing battery of the two international guidances referred to above, the ICH and the ISO. These guidances were signed by appropriate representatives of government and industry from the European Community, Japan and the United States. The latest discussion of the MLA in this context is the report from the International Workshop on Genotoxocity Test Procedures (IWGTP) working group on MLA, found in *Environmental & Molecular Mutagenesis* (2000) 35:185-190.

Veterinary drugs resemble both pharmaceuticals (in structure and action) and food additives (in low levels and route of human exposure). Since genetic toxicology testing is standardized (and harmonized) for both pharmaceuticals and food additives, there is no rationale for evaluating these products outside of existing internationally harmonized frameworks.

The FDA GeneTox Network

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