UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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Office of Pollution Prevention and Toxics
Risk Assessment Division
Science Support Branch

January 12, 2001

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, rm. 1601
Rockville MD 20852

Re: [Docket No. 00D-1631; FR Doc. 00-32113]

Sir:

Attached are comments on the draft guidance for genotoxicity studies for residues of veterinary drugs in human food, as requested in FEDERAL REGISTER 65, No. 243, pp 79106-79107, December 18, 2000.

These comments address the VICH proposal "Safety Studies for Veterinary Drug Residues in Human Food: Genotoxicity Studies" (VICH GL23).

These comments constitute the scientific opinions of the undersigned scientists. These comments do NOT constitute an official response of the U.S. Environmental Protection Agency.

Sincerely,

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Office of Research and Development

Attachment

00D-1631

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Comments on VICH proposal
"Safety Studies for Veterinary Drug Residues in Human Food: Genotoxicity Studies" (VICH GL23)

Michael C. Cimino, Ph.D., and Kerry L. Dearfield, Ph.D.

January 12, 2001

As scientists who have worked in government for decades, we submit comments on the draft guidance for genotoxicity studies for residues of veterinary drugs in human food, as requested in the FEDERAL REGISTER (1). The VICH proposal ("Safety Studies for Veterinary Drug Residues in Human Food: Genotoxicity Studies"; VICH GL23) is not consistent with the rest of the international regulatory community and, indeed, stands out as a conspicuous exception to harmonization. We strongly urge that the VICH guidance be reconsidered, with input from genetic toxicologists who have served in past harmonization efforts, so that it is consistent with the harmonized genotoxicity test scheme to which the rest of the world has agreed, and toward which other Centers of the Food and Drug Administration (FDA) have expended much effort. If adopted, the VICH guidance establishes a discrepancy that could prove embarrassing to the FDA, invite confusion or criticism, or cause erosion in the harmonization process.

Other FDA Centers require the mouse lymphoma assay (MLA) as part of their batteries for genotoxicity testing. This is established in the CFSAN Redbook, ICH guidances and ISO guidances, to which not only the U.S., but the European Community and Japan are signatories. In this requirement the FDA is also in harmony with the genotoxicity testing battery required by the U.S. Environmental Protection Agency (EPA) for pesticides and toxic substances. The EPA requires the MLA as one of the three tests in the battery for pesticides (2,3,4), and recommends its use (a mammalian cell mutation assay, with the MLA usually recommended) for toxic substances (3,4). Again, there is no reason for one Center of the FDA to employ a testing scheme at variance not only with those of all the other Centers, but also with other U.S. and international regulatory bodies.

The MLA tests for gene mutations in a viable, mammalian cell system, which provides a primary qualification for inclusion in screening genotoxicity testing batteries (3). Also, when performed with analysis for small colony formation (e.g., OECD

guideline 476; EPA OPPTS 870.5300), the MLA provides data collection for two endpoints for genotoxicity, i.e., gene mutation and chromosome mutation. The dual endpoint nature of the MLA is acknowledged in Section 4.2, ¶2 of the VICH proposal, which notes that "measurements of both small and large colonies has been proposed as an alternative method to detect clastogens [as well as gene mutations]." It continues that, if the MLA "shall become internationally accepted for use, it may provide a useful alternative to the in vitro cytogenetics assay." We submit that such international acceptance already exists. This is a major justification for including the MLA in the test schemes of the other FDA centers and of the EPA pesticide and toxic substances programs.

Efforts at international regulatory harmonization of the test battery for genotoxicity have been a long but very successful process. Since the VICH proposal deals with veterinary drug residues in human food, i.e., possible human exposure, there is no significant difference from direct human exposure to pharmaceuticals and food additives, which are currently tested via genotoxicity batteries that contain the MLA. There is no compelling scientific or regulatory rationale presented by the VICH proposal or elsewhere to abandon existing harmonized batteries.

On a different issue, the proposal appears to equate the terms "aneuploidy" and "polyploidy" in Section 4.2, ¶1, where it states that the assay for *in vitro* chromosomal effects may be used to determine changes in "ploidy." While the term "aneuploidy" refers to changes in numbers, it is usually reserved for changes in numbers of single or a few individual chromosomes, i.e., monosomies and trisomies. Changes in entire chromosome sets are referred to either as "polyploidy" or"haploidy." All deviations from the normal number of chromosomes are captured under the umbrella term "heteroploidy" (5).

REFERENCES:

(1) International Cooperation on Harmonisation of Technical Requirements for Approval of Veterinary Medicinal Products (VICH); Draft Guidance for Industry on "Safety Studies for Veterinary Drug Residues in Human Food: Genotoxicity Studies" (VICH GL23); Availability; Request for Comments. (Docket No. 00D-1631; FR Doc. 00-32113). Food and Drug Administration, Rockville, MD. Federal Register 65, No. 243, pp 79106-79107, December 18, 2000.

(2) Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 84, Mutagenicity, Addendum 9. U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. EPA Publication No. 540/09-91-122, 1991

(3) Dearfield KD, AE Auletta, MC Cimino, MM Moore. Considerations in the U. S. Environmental Protection Agency's testing approach for mutagenicity. Mutat. Res. 258: 259-283, 1991.

(4) AE Auletta AE, KL Dearfield, MC Cimino. Mutagenicity test schemes and guidelines: US EPA Office of Pollution Prevention and Toxics and Office of Pesticide Programs. Environ. Molec. Mutagen. 21: 38-45, 1993.

(5) EB Hook. The impact of aneuploidy upon public health: Mortality and morbidity associated with human chromosome abnormalities. In Aneuploidy: Etiology and Mechanisms, VL Dellarco and PE Voytek (eds), Basic Life Sciences Volume 36, Plenum Press, NY: pp 7-33, 1985.

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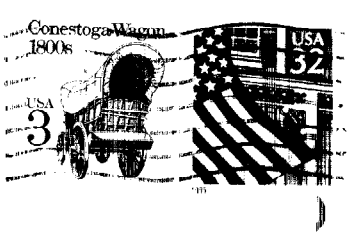

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