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Expert Report: A PRENATAL DEVELOPMENTAL TOXICITY STUDY OF OK-5203 TECHNICAL GRADE IN RABBITS

Report Number WIL-292005

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Alan M. Hoberman, Ph.D. DABT, Fellow ATS

I. Expert Review and Opinion

A fully GLP compliant developmental toxicity study in rabbits with OK-5203 was conducted according to EPA OPP 83-4 guidelines. The protocol was designed to be in general accordance with the United States EPA Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study, August, 1998, the OECD Guidelines for Testing of Chemicals Guideline 414, Prenatal Developmental Toxicity Study, 22 January 2001 and the Japanese MAFF Guidelines, 12 NohSan No. 8 147, 24 November 2000.

This expert opinion evaluated the final report methods, results and conclusions in relation to the comments in the Classification Labeling Harmonization (CLH) report for the proposal for harmonized classification and labeling for Flutianil concerning a classification of developmental toxicant in rabbits based on the following:

> "In a guideline developmental toxicity study in rabbits, there was a slight increase in the foetal incidence of visceral hydrocephalus at the top dose of 1000 mg/kg bw/day (3 foetuses in 1 litter vs 0 in controls) in the absence of maternal toxicity. Although this increase marginally exceeds the historical control range (maximum of 2 foetuses in a single litter) and there is no difference in the total number of foetuses with any malformations between this dose group and the controls, relation to treatment of this malformation cannot be excluded.
>
> Overall, there is limited evidence that Flutianil is a developmental toxicant in rabbits."

This developmental toxicity study was conducted 19 Feb 2007 to 15 Mar 2007 (period of dosing).

It is my opinion and the opinion of the EU reviewers that the rabbit study was well conducted and GLP compliant. Based on the historical control data presented in the report and noted in the summary above, the incidence of hydrocephalus at the top dose of 1000 mg/kg/day was one fetus more in a single litter than observed in the historical control data presented in the report. Therefore the litter incidence which is the more appropriate unit for evaluation in developmental toxicity studies did not differ from the historical control data base of the Testing Facility.

The historical control data presented in the final report covers the period from Dec 2003 to June 2006 and this would be the only data available at the time the report was complied. This review being conducted in 2015 has the advantage of access to historical control data from the same source of rabbits as used in the reported study over the period prior to and after the conduct of the study.

The following information presents the fetal and litter incidence of hydrocephalus from Covance time-mated rabbits in GLP compliant developmental toxicity studies. NOTE: As the definition of hydrocephalus varies between Test Facility, fetuses listed below had to have either marked or extreme dilation of the lateral ventricles of the brain to be considered to have hydrocephalus. Fetuses with slight or slight to moderate dilation were not considered to have hydrocephalus as slight to moderate dilation is a reversible condition.

Years	Total Studies	Total Litters	Total Fetuses	Litters with hydrocephalus	Range	Fetuses with hydrocephalus	Range
2005 to 2006	91	1151	9721	8	0 to 1	12	0 to 4
2007 to 2009	49	936	7708	2	0 to 1	6	0 to 5
2010 - 2011	34	607	5219	1	0 to 1	1	0 to 1
2012 - 2013	37	632	5246	2	0 to 1	2	0 to 1

Based on this additional historical control information, it was clear that during the time this study was conducted the incidence of hydrocephalus had increased and has since come back to a lower level. Therefore, the slight increase in the fetal incidence but not litter incidence of hydrocephalus that occurred in the OK-5203 rabbit study occurred during the period 2007 to 2009 when a general increase in the fetal and litter incidence of hydrocephalus was occurring spontaneously the Covance NZW rabbit. Changes in spontaneous rates of any malformation are expected to fluctuate over time as the NZW rabbit is an out bred strain. Based on the evaluation by this expert reviewer, the relationship to treatment of the apparent increased incidence of hydrocephalus in the OK-5203 study is questionable.

II. Methodology Used for Developing *Expert Review and Opinion*

II.A. Information provided by Dr. Arce

Final Report
A Prenatal Developmental Toxicity Study of OK-5203 Technical Grade in Rabbits
Study Number: WIL-292005
Data Requirement: US EPA OPPTS 870.3700, OECD Guideline 414, JMAFF 12 NohSan No. 8147
Study Director: John F. Knapp, BS
Study Initiation Date: 8 December 2006
Study Completion Date: 29 June 2007

CLH Report: Proposal for Harmonised Classification and Labeling: Based on Regulation (EC) No 1272/2008 (CLP Regulation) Annex VI, Part 2
Substance Name: Flutianil

II.B. *Expert Reviewer*

Alan M. Hoberman, Ph.D., DABT, Fellow, ATS, has approximately 40 years of experience in conduct of non-clinical reproductive/developmental toxicity studies and in regulatory interaction with EPA and multiple international regulatory bodies. A summary of the reviewer's experience is provided as Appendix A (a full *curriculum vitae* is available upon request).

II.C. Information Obtained by *Expert Reviewer*

Historical Control Data, Covance New Zealand White Rabbits, Denver PA, as compiled by Charles River Laboratories, PCS –PA 2005 to 2013

Appendix A Summary of Experience

Alan M. Hoberman, Ph.D., DABT, Fellow, ATS

Experience

Board-certified (D.A.B.T. 1988) toxicologist with 40 years in laboratory and senior management experience in preclinical aspects of drug discovery and development.

- Elected to Fellowship of Academy of Toxicological Sciences (2006).
- As president of Argus International, he directs the staff of scientists and other professionals providing scientific, technical and regulatory support to chemical and pharmaceutical companies, academia, government agencies, legal firms and others both in the USA and abroad.
- As Executive Director, for Charles River Preclinical Testing Services, PA (formerly Argus Research), he manages a CRO, which provides consulting services in regulatory affairs and safety testing of pharmaceutical, agrochemical, cosmetic, food and biotech health care products for OTC and professional uses.
- Former Editor in Chief of *Toxicology and Industrial Health*, Sage Publications, London, he was responsible for evaluation, processing and publication of original manuscripts dealing with current research in toxicology, submitted by American and international scientists. He coordinated an Editorial Board of 24 scientists who are experts in their fields.
- He has participated in the development of multiple products for skin care, including Retin-A®, Renova®, Botox® and Tarazoten®, as well many sunscreens, cosmetics and fragrances, in addition to anti-cancer agents, including Lenalidomide® and Taxol®, and bio-tech products, including Epo® and other pharmaceutical agents.
- He has participated in over 1000 safety studies of various agents, interacting with the more than 400 pharmaceutical, chemical and consortium organizations supporting these activities, including Merck, Johnson and Johnson, Wyeth, Sumitomo, BASF, Glaxo Smith Kline and the Cosmetics, Toiletries and Fragrance Association, as well as with the U.S. FDA and EPA.
- As an executive of a CRO (Charles River Laboratories, formerly Argus Research Laboratories) that provides preclinical testing and a consulting group (Argus International) he has extensive experience and expertise in the following areas:
    - Preparation of regulatory submission for NCEs from pre-IND/CTS through NDA/MAA
    - Design, conduct, monitoring and reporting of pre-clinical, Phase 1 and Phase 2 IND studies in preparation for regulatory submission
    - Preparation of CTD technical and summary sections
    - Oversight for project management of entire submission process
- Extensive regulatory affairs experience including:
    - Interaction with EPA and FDA
    - Conduct of inspections (actual and mock)
    - Pre-submission meetings with FDA with Sponsors to organize approach
    - Submission meetings with FDA and Sponsors regarding strategy, compliance and presentation

- Extensive knowledge of US and international regulatory requirements and strategies
    - Participation in development of ICH guidelines
    - Author of several papers and book chapters regarding US agency guidelines and compliance
    - Presentations at universities, scientific meetings and conferences regarding regulatory requirements

Publications and Professional Activities (see Curriculum Vitae for details)

- Editor in Chief of *Toxicology and Industrial Health* (2010-2013)
- Serves on the editorial boards of the *International Journal of Toxicology* and *Toxicology and Industrial Health.*
- Invited lecturer at numerous meetings and symposia in the United States, Europe and Japan.
- Co-editor of reference/textbook: Hoberman, A.M. and Lewis, E.M, editors (2012) *Pediatric Nonclinical Drug Testing: Principles, Requirements and Practices.* John Wiley & Sons: Hoboken, NJ
- He has over 80 publications, several book chapters, and over 100 presentations of abstracts and lectures in the field on many aspects of toxicology, including reproductive and developmental toxicology, neurotoxicology, photobiology and carcinogenicity as well as related topics on computerized data gathering and reporting and regulatory issues in the laboratory environment.
- Active member of over 12 national and international professional societies and organization and has served as an officer or committee member on many of these. He currently serves on the Board of the Pennsylvania Society for Biomedical Research and the Council of the European Teratology Society.

Education

Pacific Western University: Ph.D., Toxicology, 1982
University of Arkansas: M.S., Interdisciplinary Toxicology, 1979
University of Virginia: Anatomy, Major, 1975 to 1976
Drexel University: B.S., Biology, 1975

Additional Certification

Diplomate, American Board of Toxicology, 1988
Recertification: 1994 to 1998, 1999 to 2003, 2004 to 2008, 2009 to 2013
Fellow, Academy of Toxicological Sciences, 2006
Recertification: 2011

Corporate Affiliations (see Curriculum Vitae for details)

- Argus International, Inc. Horsham, Pennsylvania, 1981 - Present
- Charles River Laboratories (Formerly Argus Research Laboratories) 1981 - Present
- Hazleton Laboratories America, Inc. Vienna, Virginia. October 1979 - 1981
- University of Arkansas for Medical Sciences at Little Rock and at the National Center for Toxicological Research 1976 to 1979
- McNeil Laboratories, Inc. 1971-1975