This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 21!

See attached form for additional information.

Interagency Report Control No.: SH

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. CERTIFICATE NUMBER: 14-R-0144
CUSTOMER NUMBER: 1799

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

Revised 2009 Annual Report
Subitted 12/21/2009

Charles River Laboratories, Inc.
251 Ballardvale St
Wilmington, MA 01887

DEC 2 3 2009

Telephone: (508) -658-6000

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Atached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS Form 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasc such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs	32	1421	706	13	2140
5. Cats	–	–	–	–	–
6. Guinea Pigs	17	959	4562	2	5523
7. Hamsters	–	988	224	–	1212
8. Rabbits	492	2753	517	215	3485
9. Non-human Primates	5006	4652	473	2	5127
10. Sheep	–	–	–	–	–
11. Pigs	7	316	52	–	368
12. Other Farm Animals	–	–	–	–	–
13. Other Animals					
Peromyscus Mice	–	34	–	–	34
Vole	–	1	–	–	1
Gerbils	–	18	8	–	26

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anestetic, analgesic, and tranquilizing drugs, prior to, during, and following actual rese teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and ap Institutional Animal Care and Use Committee (IACUC). A summary of all such exceptions is attached to this annual report. In addition to identifying the IACUC-approved exceptions, this summary inc brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)

SIGNATURE OF C.E.O. OR INSTITUTIONAL OFFICIAL	NAME & TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL (Type or Print)	DATE SIGNED
(b)(6), (b)(7)c		12/21/2009

APHIS FORM 7023 (Replaces VS FORM 18-23 (OCT 88), which is obsolete.)
(AUG 91)

NP
12/28/2009

Charles River Laboratories
Customer #: 1799
USDA Research Registration #14-R-0144

Attachment #1

DEC 2 3 2009

Site #	Location Description
002	
005	
013	
014	
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017	(b)(2)High, (b)(7)f
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Preface:

Animals placed in Column "E" in this report were enrolled in studies undertaken for product registration purposes based on regulatory guidelines of the FDA 21 CFR 312.23 for pharmacology and toxicology studies and the Red Book. Guidance for study design and conduct also conformed with recommendations by the International Conference on Harmonization Guidelines. This guidance includes Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on non-clinical safety studies for the conduct of human clinical trial for pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997.

As per the ICH Guideline M3(R1) regulatory citation, *" The goals of the non-clinical safety evaluation include a characterization of toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility. This information is important for estimation of an initial safe starting dose for the human clinical trials and the identification of parameters for clinical monitoring for potential adverse effects. The non-clinical safety studies...should be adequate to characterize potential toxic effects under the conditions of the supported clinical trial."*

During the conduct of an animal toxicology study that is required by regulatory agencies, it is possible that some of the clinical signs of toxicity may result in more than momentary pain and/or distress. However, if one does not allow these signs of toxicity to develop, then the primary scientific goal of characterizing the toxic effects of the test article will not be achieved (and the study would be considered invalid by the regulatory authorities). Results of toxicology studies become part of the safety assessment of the potential new human drug that will result in the determination of an initial exposure of human subjects and the identification of parameters for clinical monitoring for potential adverse effects of the drug on people. During the conduct of an animal toxicology study, each drug-related effect is evaluated by the attending veterinary staff and the study director to determine if treatment to alleviate more than momentary distress/pain could interfere with the regulatory purpose/scientific goal (conduct) of the study. Treatments that could interfere with the purpose of conduct of the study are prohibited by FDA Good Laboratory Practice regulations [§ 58.90 (c)] and are withheld to assure that toxic effects can be evaluated.

Depending upon the nature of the compound, certain other regulations and guidelines promulgated by the FDA, EPA, TSCA, FIFRA and the OECD also apply and are listed in the Applicable Guidelines/Regulations section below.

Animals are placed in Category "E" following retrospective analysis. Retrospective categorization of pain or distress was made by the Attending Veterinarian (or their designee, also a laboratory animal veterinarian) in conjunction with the Study Director. Professional judgment calls, particularly with regard to the diagnosis of distress, were purposely conservative with a default of category E if there was any doubt.

The following are applicable guidelines and regulations covering the conduct of studies at all Charles River Laboratory Preclinical Services facilities (listed below).

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003.
- PART VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, No. 227, Nov 25, 1997
- EPA Health Effects Test Guidelines OPPTS 870.3050, 28-Day Oral Toxicity in Rodents, July 2000
- EPA Health Effects Test Guidelines OPPTS 870.3150, 90-Day Oral Toxicity in Non-Rodents, August 1998
- EPA Health Effects Test Guidelines OPPTS 870.3100, 90-Day Oral Toxicity in Rodents, August 1998
- EPA Health Effects Test Guidelines OPPTS 870.4100, Chronic Toxicity, August 1998

- EPA Health Effects Test Guidelines OPPTS 870.3500, Preliminary Developmental Toxicology Screen, March 1994
- EPA Health Effects Test Guidelines OPPTS 870.3600, Inhalational Developmental toxicity Study March 1994
- EPA Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study, August 1995
- EPA Health Effects Test Guidelines OPPTS 870.3800, Reproduction and Fertility Effects, August 1995
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 90-day Oral Toxicity Studies in Non-Rodents, 409, September 1998
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 90-day Oral Toxicity Studies in Rodents, 408, September 1998
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 28-day Oral Toxicity Studies in Rodents, 407, July 1995
- U.S. Food and Drug Administration (1994). International Conference on Harmonization; Guideline on detection of toxicity to reproduction for medicinal products. *Federal Register*, September 22, 1994, Vol. 59, No. 183.
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- Japanese Ministry of Health, Labour and Welfare (1997). Good Laboratory Practice Standard for Safety Studies on Drugs, MHW Ordinance Number 21, March 26, 1997.
- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97) 186/Final].
- U.S. Food and Drug Administration (2003). *Guidance for Industry - Photosafety Testing,* Center for Drug Evaluation and Research (DCER), May 2003
- Organisation for Economic Co-operation and Development (1987). *Guidelines for Testing of Chemicals.* Section 4, No. 402: Acute Dermal Toxicity, pp. 1-7
- Organisation for Economic Co-operation and Development (1992). *Guidelines for Testing of Chemicals.* Section 4, No. 406: Skin Sensitization, pp. 1-9.
- *Drug Registration Requirements in Japan,* 4th Edition (19910. Yakuji Nippo, Ltd., Tokyo, pp. 61-64.
- U.S. Food and Drug Administration (2005) Investigational New Drug Application, Title 21, Part 321.23, 8.ii.a
- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [ENV/MC/CHEM(98)17]
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry; detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare, GLP standard ordinance for non-clinical laboratory studies on safety of drugs, MHW Ordinance No. 21; March 26, 1997. Japan.
- OECD Environment Directorate. OECD Principles of Good Laboratory Practices, [C(97) 186/Final] (1998); Environmental Health and Safety Division
- U.S. Food and Drug Administration (1993). Points to consider in the characterization of cell lines used to produce biologicals.
- European Pharmacopoeia Monograph 5.2.3, Cell substrates for production of vaccines for human use. 01/2005:50203
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry; toxicokinetics: the assessment of systemic exposure in toxicity studies, ICHS3A; March, 1995, Rockville (MD).
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, MD(R1) Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

The following studies have been listed in Category "E" based upon the guidelines stated in the preface at the beginning of this report. The study designs that resulted in certain animals being placed retrospectively into Category "E" were required by federal regulations and guidelines listed in the applicable regulations/guidelines section below. For the purpose of this report studies have been given a unique number that corresponds to the actual study number. For reasons of confidentiality, actual study numbers are not presented but are available to the USDA for on-site inspection or report follow-up. Category "E" explanations/details are listed separately for each study.

Study: #1

Animals: 1 Rabbit

Type of Study: Intravenous Dosage-Range Development Toxicity Study of [redacted] in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **1Rabbit** from a developmental toxicity study.
#7951 (III; 0.05 MKD) was euthanized by recommendation during veterinary re-examination on gestation day 11 because the rabbit's condition had not improved during the course of the day. Signs began after dosing and the rabbit was regularly monitored by the vet staff until euthanasia later the same day. Clinical signs included intermittent ataxia, decreased activity, and dypsnea. This animal is being categorized as an E because the ataxia and dyspnea may have resulted in more than momentary distress. It was necessary to observe the animal post-dosing to determine if the clinical signs of toxicity were transient or not.

Study: #2
Animals: 12 Rabbits
Type of Study: A Pilot Embryo0Fetal Development and Toxicokinetic Study of [redacted] Administered Orally (Gavage) in New Zealand White Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **12 Rabbits** from a dosage range-finding developmental toxicity study.
#7811-7815 (V; 1000 MKD) and #7829 (V; 1000 MKD) experienced intermittent signs including ataxia, tachypnea, dypsnea, excess salivation, loss of righting reflex and brief convulsions beginning approximately one hour after dosage on GD8. The rabbits were monitored by the vet staff until euthanasia the same day (with the exception of #7829 who died while being monitored). These animals are being placed in category E because some of the intermittent clinical signs may have resulted in more than momentary distress. It was necessary to observe the animals post-dosing to determine if the clinical signs of toxicity were transient or not.

#7823 (IV; 300 MKD) was found dead. Necropsy results were consistent with gavage error. It is assumed that there was more than momentary distress/pain, therefore categorized as E.

#7821-7822 (IV; 300 MKD), #7824-7825 (IV; 300 MKD) and #7828 (IV; 300 MKD) experienced body weight loss (18.1-21.3% over 7 days) and reduced feed intake. Clinical signs included reduced fecal output, ungroomed coat and decreased activity. These rabbits were euthanized. It is possible that the inappetance and weight loss might have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #3
Animals: 1 Rabbit
Type of Study: Dose Range-finding Developmental Embry-Fetal Toxicity and Toxicokinetic Study with [redacted] via Subcutaneous Injection in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **1 Rabbit** from this dosage range-finding study.
#7516 (III; 90 MKD) experienced 17% body weight loss and reduction in feed consumption for seven days. The only clinical observation was reduced fecal output. This rabbit was euthanized. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #4
Animals: 5 Rabbits
Type of Study: Subcutaneous Dosage-Range Developmental Toxicity Study
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **5 Rabbits** of a dosage range finding developmental toxicity study.
#8216 (IV;20 MKD), #8217 (IV; 20 MKD), #8220 (IV; 20 MKD), #8222 (V; 40 MKD) and 38224 (V; 40 MKD) experienced body weight loss (6-19%) with a reduction in feed consumption and reduced fecal output over 5 to 8 days. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #5
Animals: 4 Rabbits
Type of Study: A Multiple-Dose Toxicokinetic Study of [redacted] Administered Orally (Gavage) in New Zealand White Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register,

September 22, 1994, Vol. 59, No. 183.
Diagnosis: **4 Rabbits** in the high dosage group of this multiple-dose toxicokinetic study.
#7845 (300 MKD), #7846 (300 MKD), #7847 (300 MKD) and #7848 (300 MKD) experienced body weight loss (8.1-17% over 3 to 5 days), reduced feed intake and reduced fecal output. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #6
Animals: 9 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of [redacted] in Rabbits

Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **9 Rabbits** from a developmental toxicity study.
#7792 (III;750 MKD), #7794 (III;750 MKD), #7759 (IV;1000 MKD), #7761 (IV;1000 MKD), #7769 (IV;1000 MKD), #7772 (IV;1000 MKD), #7773 (IV; 1000 MKD) and #7775 (IV; 1000 MKD) experienced body weight loss (8-14%) and a reduction in feed consumption over 4-6 days during the dosage period. Reduced fecal output and respiratory abnormalities were observed. Supportive care was provided prior to animals either being found dead or euthanized. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

#7790 ((III;750 MKD) was found dead approximately 24 hours after the first dose. Necropsy findings were consistent with gavage error. Prior to death, no clinical signs were present and the rabbit was observed frequently. While there were no clinical signs that could be interpreted as premonitory of death and no intent to withhold relief in the form of euthanasia, it is assumed that there may have been more than momentary distress/pain prior to the unobserved death, therefore categorized as E.

Study: #7
Animals: 4 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of [redacted] in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **4 Rabbits** from a dosage range finding reproductive toxicity study.
During the dosage period, **#7626 (500 MKD on GD 6-19), #7636 (500 MKD on GD 6-28), #7641 (750 MKD on GD 6-28) and # 7643 (750 MKD on GD 6-28)** lost body weight (14-25%) over 11 to 16 days and had reduced feed intake. Clinical observations included reduced fecal output, slight dehydration and thin body condition. Each rabbit remained active, bright, alert and responsive. Animals received supportive care. While animals appeared bright, active and alert, it is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #8
Animals: 5 Rabbits
Type of Study: A Subcutaneous Developmental toxicity Study o[redacted] in rabbits, Including a Toxicokinetic Evaluation

Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **5 Rabbits** from a developmental toxicity study.
#8389 (30 MKD), #8355 (30 MKD), #8363 (45 MKD), #8365 (45 MKD) and #8366 (45 MKD) experienced a reduction in feed intake along with 5-14% body weight loss accompanied by one or more of the following intermittent clinical signs: paleness, hematuria, decreased activity, ptosis, reduced fecal output, mass at injection site, or thin body condition. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #9
Animals: 17 Rabbits
Type of Study: Am embryo-fetal Development and Toxicokinetic Study of [redacted] Administered Orally (Gavage) in New Zealand White Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **17 Rabbits** from a developmental and toxicokinetic study.
#8429 (II; 20 MKD), #8461-8463 (IV; 200 MKD), #8465-8471 (IV; 200 MKD), #8473 (IV; 200 MKD), #8475-8476 (IV; 200 MKD), #8479 (IV; 200 MKD), #8493 (IV; 200 MKD) and #8495 (IV; 200 MKD) experienced body weight loss during the dosage period (7- 17% over 3 to 5 days) and reduced feed intake. Reduced fecal output, soft feces and ungroomed fur were observed. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #10
Animals: 6 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of [redacted] in Rabbits, Including a Preliminary Evaluation in Nonpregnant Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **6 Rabbits** on a dosage range-finding developmental toxicity study.
#7667-7669 (1000 MKD) and **#7670-7672 (2000 MKD)** experienced body weight loss (8-14%) and a reduction in feed consumption during each day of the day dosage period. The rabbits did not eat the supplemental food items that were offered as part of supportive care. Clinical signs included reduced fecal output, soft feces and ungroomed fur. It is possible that the

inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #11
Animals: 6 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of [redacted] in Rabbits, Including a Preliminary Evaluation in Nonpregnant Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **6 Rabbits** from a dosage range-finding developmental toxicity study.
#8243-8244 (250 MKD), #8246-8247 (500 MKD) and #8249-8250 (500 MKD) experienced body weight loss (13-25% over 6 to 13 days) and a reduction in feed consumption during the dosage period. Clinical signs included intermittent reduced fecal output, liquid feces, decreased activity, ungroomed fur and #8244 had a brief seizure on gestation day 13. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #12
Animals: 3 Rabbits
Type of Study: Developmental toxicity Study of [redacted] Administered Intravenously to Pregnant Female New Zealand White Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **3 Rabbits** from this developmental toxicity study.
#8623 (II;10 MKD), #8624 (II; 10 MKD) and #8629 (II; 10 MKD) experienced body weight loss (9-26%) and a reduction in feed consumption over 5 to 15 days. Clinical signs included intermittent reduced fecal output, paleness, mild dehydration and reduced level of activity. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #13
Animals: 4 Rabbits
Type of Study: Oral (Stomach Tube) Preliminary Seven-Day Toxicity Study in Non-Pregnant Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section ; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
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Diagnosis: **4 Rabbits** from a general toxicity study.
#6053 (1000 MKD), #6054 (1000 MKD), #6055 (1000 MKD) and #841 (500 MKD) had fair to low feed intake over the entire dosage period and lost between 8 and 18% body weight over the same period. All animals remained bright, alert and active. Other clinical signs included scant and/or no fecal output. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #14
Animals: 18 Rabbits
Type of Study: [redacted] Subcutaneous Developmental Toxicity Study in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **18 Rabbits** from a developmental toxicity study.
#8524 (II; 6 MKD), #8541 (II; 6 MKD), #8545 (III; 12 MKD), #8551 (III; 12 MKD), #7652 (III; 12 MKD), #8557 (III; 12 MKD), #8567 (IV; 25 MKD), #8569-8570 (IV; 25 MKD), #8572-8573 (IV; 25 MKD), #8575 (IV; 25 MKD), #8577 (IV; 25 MKD), #8579 (IV; 25 MKD), #8581 (IV; 25 MKD), #8583-8584 (IV; 25 MKD) and #8586 (IV; 25 MKD) experienced body weight loss during the dosage period (6 to 20% over 5 to 15 days) and reduced feed intake. Intermittent clinical signs of reduced fecal output, soft feces, ungroomed fur, thin body condition and mild dehydration were observed. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #15
Animals: 10 Rabbits
Type of Study: Intravenous (Infusion) Dosage-Range Developmental Toxicity Study of [redacted] in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **10 Rabbits** from a dosage range-finding developmental toxicity study.

#9047(V; 18MKD) experienced 8% body weight loss, reduced feed intake and clinical signs including decreased activity beginning with the first dosage. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore this rabbit was categorized as E.

#9046 (V; 18 MKD) experienced 14% body weight loss, reduced feed intake and clinical signs including decreased activity, liquid feces, bradypnea and ptosis beginning with the first dosage. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore this rabbit was categorized as E.

#9049 (V; 18 MKD) experienced 10% body weight loss, reduced feed intake and clinical signs including decreased activity beginning with the first dosage. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore this rabbit was categorized as E.

#9039 – #9040 (III; 1.5 MKD) and #9041-#9045 (IV; 6 MKD) experienced body weight loss (6-14%), reduced feed intake and exhibited non-transient clinical signs during the dosage period. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #16
Animals: 5 Rabbits
Type of Study: Subcutaneous Dosage-Range Developmental toxicity Study of [redacted] in Rabbits, Including a Satellite Toxicokinetic Evaluation
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This

dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **5 Rabbits** from a dosage-range finding developmental toxicity study.
#7681 (5 mg/kg), #7685 (15 mg/kg), #7687 (50 mg/kg), and #7617-#7618 (50 mg/kg) experienced body weight loss (6-22%) and reduction in feed consumption during the dosage period. Intermittent clinical signs included reduced fecal output, soft feces, mucoid feces, and ungroomed fur. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #17
Animals: 5 Rabbits
Type of Study: [redacted] Oral (Stomach tube) Once Daily Embryo Fetal Development Study in the Dutch Belted Rabbit
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **5 Rabbits** from a developmental toxicity study.
#9423 (I; 0 MKD), #9480 (II; 4MKD), #9416 (III; 30 MKD), #9449 (IV;60 MKD) and #9456 (IV; 60 MKD) experience body weight loss (6-16 %) and reduction in feed consumption for four or more days during the dosage period. Clinical signs were reduced fecal output and/or soft feces. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #18
Animals: 9 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of [redacted] in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **9 Rabbits** from a developmental toxicity study
During the dosage period, **#8901(0 MKD), #8924 (750 MKD), #8926-#8928 (750 MKD), #8930 (750 MKD), #8933-#8934 (750 MKD) and #8961 (750 MKD)** lost body weight (5-30 %) over 6 to 18 days and feed intake was reduced. Clinical observations included reduced fecal output, slight dehydration and thin body condition. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #19
Animals: 11 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of [redacted] in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive

process.

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **11 Rabbits** from a developmental toxicity study.
#9563 (III; 150 MKD), #9565 (III; 150 MKD), #9576 (IV; 750 MKD), #9583 (IV; 750 MKD), #9585 (IV; 750 MKD), #9587-#9589 (IV; 750 MKD), #9596-#9597 (IV; 750 MKD) and #9599 (IV; 750 MKD) experienced body weight loss (4-15%) and a reduction in feed consumption over 5 to 14 days during the dosage period. Reduced fecal output was observed. Supportive care was provided. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #20
Animals: 27 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of [redacted] in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Twenty seven rabbits** from a developmental toxicity study.
#9634 (II; 100 MKD), #9636 (II; 100 MKD), #9642-9644 (III; 200 MKD), #9646 (III; 200 MKD), #9651(III; 200 MKD), #9657-9658 (III; 200 MKD), #9661-9662 (IV; 400 MKD), #9664 (IV; 400 MKD), #9666- 9672 (IV; 400 MKD), #9674-9675 (IV; 400 MKD), #9677-9678 (IV; 400 MKD), #9680 (IV; 400 MKD) and #9687-9689 (IV; 400 MKD) experienced body weight loss (5-31% over 6 to 20 days) and a reduction in feed consumption beginning during the dosage period. Reduced fecal output was noted in each of these animals and other intermittent clinical signs included mucoid or liquid feces, ptosis, perinasal discharge, slow respiration, decreased activity, ungroomed fur, thin body condition, dehydration, loss of righting reflex and jaundice. It is possible that the inappetance and weight loss as well as some of the other intermittent clinical signs may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #21
Animals: 2 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of [redacted] in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **2 Rabbits** from a developmental toxicity study.
#9870 (IV; 1 MKD) and #9873 (IV; 1 MKD) experienced body weight loss (14% and 7% respectively), reduced feed intake for 4 or more days and exhibited non-transient clinical signs during and/or after the dosage period. Clinical signs over one or more days included ptosis, scant fecal output, dehydration and decreased activity level. It is possible that the inappetance and weight loss as well as some of the other intermittent clinical signs may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #22
Animals: 18 Rabbits
Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of [redacted] in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum

tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **18 Rabbits** from a dose range-finding developmental toxicity.
#7201-7202 (vehicle), #7204-7205 (vehicle), #7207-7208 (1.0 MKD), #7210-7212 (1.0 MKD), #7213-7218 (3.0 MKD), #7219 (9.0 MKD) and #7223-7224 (9.0 MKD) were diagnosed by the veterinary staff with discomfort at the dosage injection site for one or more days during the dosage period. Mild to moderate localized swelling, increased warmth and redness were also noted in one or both ears. The feed consumption levels were not affected and no body weight was lost. Supportive care (cold compresses applied as needed) was provided. It is possible that some of the intermittent clinical signs may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #23
Animals: 9 Rabbits
Type of Study: [redacted] Dosage-Range Developmental Toxicity Study in Rabbits by Oral (Stomach tube) Route
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **9 Rabbits** on a dosage range-finding developmental toxicity study.
#8838-#8840 (II; 250 MKD) lost body weight daily (7-11% cumulative loss) and feed intake was reduced during the five day dosage period. Reduced fecal output, ungroomed fur and mydriasis were noted for one or more days prior to scheduled euthanasia at the end of the study. It is possible that the inappetance and weight loss as well as some of the other intermittent clinical signs may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

#8841-#8843 (III; 500 MKD) and #8844-#8846 (IV; 1000 MKD) had reduced feed intake, body weight loss of 8-13%, reduced fecal output, liquid feces, ungroomed fur and a non-transient reduction in activity level on one or more days during the five day dosage period. Two rabbits also exhibited intermittent hyperreactivity and ataxia. It is possible that the inappetance and weight loss as well as some of the other intermittent clinical signs may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #24
Animals: 2 Guinea Pigs
Type of Study: A 3-week Subcutaneous Toxicity and Tolerability Study with [redacted] in Male Hartley Guinea Pigs
Guidelines/Regulations:

- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section ; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **2 Guinea Pigs** from a toxicity and tolerability study.
Beginning on the first day of dosage, **#106 (II; 10 mg/kg/dose)** experienced reduced feed intake and body weight loss (18%) over 7 days. Supportive care included administration of subcutaneous fluids. Intermittent clinical signs included bradypnea, mild dehydration, decreased activity level and hunched posture. This animal was euthanized by the recommendation of the study director on study day 7. No gross abnormalities were observed at necropsy examination. It is possible that some of the intermittent clinical signs may have been consistent with more than momentary distress and therefore this animal was categorized as E.

On study days 3 and 4, **#114 (II; 10 mg/kg/dose)** exhibited reduced weight-bearing on one front limb. One side of the neck was also mildly swollen. It is likely that this was an inadvertent sequela to jugular blood collection a few hours before the

exam. Feed consumption was not reduced during this time. On study day 5, all clinical signs had resolved. It is possible that some of the intermittent clinical signs may have been consistent with more than momentary distress and therefore this animal was categorized as E.

Study: #25
Animals: 12 Rabbits
Type of Study: [redacted] Dosage-Range Developmental Study in Rabbits by Oral (Stomach Tube) Route
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **12 rabbits** from a dosage range-finding developmental toxicity study.
#106 (II; 50 MKD), #110 (II; 50 MKD), #112-#113 (III; 75 MKD), #117- #120 (IV; 125 MKD), #121-#123 (V; 200 MKD) and #125 (V; 200 MKD) lost body weight daily (6-23% cumulative loss) and feed intake was reduced for seven or more days during the dosage period. Reduced fecal output and ungroomed fur were noted. It is possible that the inappetance and weight loss may have been consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #26
Animals: 9 Dogs
Type of Study: Intravenous Toxicity study
Guidelines/Regulations:

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003
- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section ; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **9 Dogs** on a dose range finding toxicity study.
D3762/M, D3769/F, D3764/M, D3756/M, D3766/M, D3770/F, D3771/F, D3772/F and D3774/F – exhibited various intermittent clinical signs following dosing that may have been associated with more than momentary distress. Clinical signs included decreased activity, respiratory abnormalities, neurologic and gastrointestinal abnormalities. Animals were monitored closely. One of the objectives of the study was to determine if clinical signs are transient, so observation needed to continue until this determination could be made. Animals were euthanized once this end point had been achieved.

Study: #27
Animals: 1 Dog
Type of Study: Oral Toxicity Study
Guidelines/Regulations:

- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section ; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **1 Dog** – on an oral toxicity study.
D2322/Gr2/M: Necropsy results were consistent with gavage error. It is assumed that there was more than momentary distress/pain, therefore categorized as E.

Study: #28
Animals: 3 Dogs
Type of Study: Oral Toxicity Study

Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives
- OECD Environment Directorate. OECD Principles of Good Laboratory Practices, [C(97) 186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **3 Dogs** – on an oral toxicity study.

D2275/Gr4/M, D2288/Gr4/M and D2294/Gr4M: These dogs experienced intermittent non-weight bearing lameness, some muscle atrophy and abnormal posturing. All were euthanized. It is possible that some of the intermittent clinical signs may have been consistent with more than momentary distress and therefore these animals were categorized as E.

Study: #29
Animals: 12 Rabbits
Type of Study: A Single Dose Dermal Irritation Study in New Zealand White Rabbits with Two Formulations of Test Article
Guidelines/Regulations:

- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section ; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **12 Rabbits -**
All animals in Groups 7 and 8 (**12 total**) exhibited neurologic signs shortly after dosing. Clinical signs in group 7 were transient and all animals fully recovered. Animals in group 8 were euthanized when it was determined that clinical signs were not transient. Most had a self-limiting seizure or convulsion-type activity post-dosing. Treatment with anti-seizure medication would have interfered with goals of study. Seizures are considered to be painful by the USDA, therefore these animals were categorized as E.

Study: #30
Animals: 1 Non-human Primate
Type of Study: Toxicology Study
Guidelines/Regulations:

- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25, 1997. Maintenance of the ICH Guideline M3(R1) on Non-Clinical Safety Studies for Conduct of Human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **1 Non-human Primate** – on a toxicology study.
Necropsy results were consistent with gavage error. It is assumed that there was more than momentary distress/pain, therefore categorized as E.

Study: #31
Animals: 1 Non-human Primate
Type of Study: Toxicology Study
Guidelines/Regulations:

- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25, 1997. Maintenance of the ICH Guideline M3(R1) on Non-Clinical Safety Studies for Conduct of Human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: : **1 Non-human Primate** – on a toxicology study.
Necropsy results were consistent with gavage error. It is assumed that there was more than momentary distress/pain, therefore categorized as E.

IACUC-APPROVED EXCEPTIONS TO REGULATIONS AND STANDARDS

The IACUC must approve exemptions from non-human primate environmental enhancement plans and dog exercise activities. The animals were observed daily by the animal care and technical staff and the veterinary technician (or veterinarian). The following exceptions to standards/regulations were approved by the IACUC during this reporting period.

Species: Nonhuman Primate
Number: 184
All animals were on metabolism and pharmacokinetics studies and may have been used on more than one study. Pair housing, environmental enrichment devices inside the cage and/or dietary restrictions (no fruit peels or peanut shells) were withheld after dose administration for up to 15 days during sample collection. Environmental enrichment devices were allowed outside the cage. External stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided. There were no exemptions while being held on the colony between studies.

Species: Nonhuman Primate
Number: 692
Exemption: 499 nonhuman primates were exempted for up to 72 days; 145 were exempted for up to 156 days; 48 were exempted for 170-330 days.
All animals were on toxicology studies and were exempt from social housing. Environmental enrichment devices and external stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided.

Species: Nonhuman Primate
Number: 10
Animals were on surgical studies and were exempted from social housing for up to 72 days.

Species: Nonhuman Primate
Number: 41
Animals were on pharmacology studies and may have been used on more than one study. Social housing was exempted for up to 29 days during telemetry monitoring.

Species: Dog
Number: 57
All animals were on metabolism and pharmacokinetics studies and may have been used on more than one study. Pair housing and/or exercise was exempted after dose administration for up to 15 days during sample collection. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. There were no exemptions while being held on the colony between studies.

Species: Dog
Number: 425
Exemption: 295 dogs were exempted from exercise for up to 57 days; 94 dogs were exempted from exercise for up to 134 days; 36 dogs were exempted from exercise for up to 275 days. All animals were on toxicology studies. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage.

Species: Dog
Number: 21
All animals were on surgical studies and were exempted from social housing for up to 31 days.

Species: Dog
Number: 56
Animals were on pharmacology studies and may have been used on more than one study. Pair housing and/or exercise was exempted after dose administration for up to 15 days during sample collection and telemetry monitoring. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. There were no exemptions while being held on the colony between studies.