Approval Date: October 20, 1995

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

ANADA 200-109

B. Sponsor

Fort Dodge Laboratories
800 5th Street N.W.
Fort Dodge, Iowa 50501

C. Proprietary Name

Velenium™ (SELENIUM, VITAMIN E)

D. Established Name

vitamin E/selenium injection

II. BIOEQUIVALENCY STUDY

Bioequivalence was determined on the selenium component of the combination product. Vitamin E and selenium are synergistic in their therapeutic effects. The Vitamin E level in the product is relatively low in relation to nutritional requirements and is not readily quantifiable in the blood. Because Vitamin E and selenium are synergistic in their therapeutic effects, the Agency concluded that the bioequivalence of the combination product could be determined based on the blood level bioequivalence of the selenium component alone. A description of the bioequivalency study in selenium follows.

A. Investigators:

Fort Dodge Laboratories was the Sponsor of this study and the Study Director/Investigator was Dr. Robert Pollet of Fort Dodge Laboratories, 800 5th Street N.W., Fort Dodge, Iowa 50501.

The analytical determination of selenium in serum samples was conducted by Hazleton Laboratories, 3301 Kinsman Boulevard, Madison, Wisconsin 53704.

B. General Design of Investigation:

1. **Purpose of Study:** The purpose of the study was to assess the in vivo bioequivalency of two (2) injectable formulations of a Vitamin E/Selenium product in cattle. These two (2) products are the pioneer product and the generic product, which is the subject of this application.

2. **Test Animals:** A total of twenty (20) healthy cross-bred beef feeder calves (15 males and 5 females) were used. The weight of the calves was between 435 to 700 pounds.

3. **Study Design:** The study was conducted as a cross-over design; each formulation was given to an equal number of animals during two separate periods. During each treatment period, ten (10) calves received the pioneer (FDA approved) product and ten (10) calves received the test product. After the first treatment there was a 14-day washout period before administration of the second treatment. During the second dosing period, the treatments were crossed-over, such that each calf received both the pioneer (MuSe®) and the Fort Dodge Laboratories products.

4. **Route of Administration:** The pioneer product is labeled to be administered by subcutaneous or intramuscular injection. In this bioequivalency study all animals were treated by intramuscular injection.

5. **Dosage Used:** The recommended dosage for the pioneer product is 1 mL/200 pound body weight. This same dosage was used for the pioneer product and the generic product.

6. **Test Duration:** The test period consisted of a 14-day pre-treatment quarantine period to confirm the health of the test animals. The first treatment was given and serum samples were taken up through 54 hours post-treatment. A fourteen (14) day washout period was provided between the first treatment and the administration of the second treatment of this cross-over. After the second treatment, serum samples were taken up through 54 hours post-treatment.

7. **Pertinent Parameters:** The parameter measured in this bioequivalency study was the serum level of selenium following intramuscular administration of the pioneer product and the generic product.

C. Statistical Analysis:

CMAX and AUC values were analyzed for deviations from normality. Based upon the combined results obtained with normal probability plots, the Shapiro-Wilk's test ($p > 0.1$) and a Box-Cox analysis ($p>0.1$ using chi square distribution), it was determined that the untransformed data were normally distributed. Consequently, all data analysis was conducted on the original (linear) scale. These data were subsequently evaluated (without baseline correction) for treatment effects using a traditional analysis of variance (ANOVA) and an analysis of covariance (ANCOVA). The models used for these statistical procedures were as follows:

	LSMEAN REF	**LSMEAN TEST**	**RATIO T/R**	**CONFIDENCE LOW LIM**	**INTERVAL UPPER LIM**
AUC 0-46 (ng*hr/ml)**	1426	1453	1.02	87	116
CMAX* (ng/ml)	332	323	0.97	85	110
TMAX* (hr)	0.35	0.30	0.86	-	-

* statistical analysis based upon the following ANOVA model: overall mean + effects attributable to: sequence + subject nested within sequence + period + treatment + random error.

** statistical analysis based upon the following ANOVA model: overall mean + effects attributable to: sequence + subject nested within sequence + period + treatment + random error + baseline.

D. Conclusion:

A single IM dose (1 mL per 200 lbs.), 2 period cross-over study was conducted in 20 calves to compare the bioavailability of a pioneer product (i.e., reference drug) Mu-Se® with a Fort Dodge Laboratories test Vitamin E/Selenium formulation. The bioequivalence of these two Vitamin E/Selenium formulations was assessed by serum analysis for selenium levels. It can be concluded from the data collected that the two products are bioequivalent.

III. HUMAN FOOD SAFETY

Withdrawal Time
To be used only as directed in weanling calves and breeding beef cows. Discontinue use 30 days before the treated cattle are slaughtered for human consumption. This withdrawal period is the same as the pioneer's.

IV. AGENCY CONCLUSIONS

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirement of section 512(n) of the act and demonstrates that Velenium(TM) (SELENIUM, VITAMIN E) when used under the proposed conditions of use, is safe and effective for its labeled indications.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.