I. GENERAL INFORMATION

A. File Number

NADA 138-955

B. Sponsor

Medico Industries, Inc.
P.O. Box 338
Elwood, Kansas 66024

C. Proprietary Name

Tylosin Injection, 50 mg/ml & 200 mg/ml

D. Established Name

tylosin injection

E. Dosage Form

Tylosin Injection 50 mg/ml is available in 100 ml vials; Tylosin Injection 200 mg/ml is available in 100 ml, 250 ml, and 500 ml vials.

F. Dispensing Status

Over the Counter (OTC)

G. Dosage Regimen

Beef cattle and nonlactating dairy cattle:

Inject intramuscularly 8 mg per pound of body weight once daily (1 ml of the 50 mg product per 6.25 pounds or 1 ml of the 200 mg product per 25 pounds). Treatment should be continued 24 hours after symptoms of the disease have stopped, not to exceed 5 days. Do not inject more than 10 ml per site. The 50 mg formulation is recommended for use in calves weighing less than 200 pounds.

Swine:

Inject intramuscularly 4 mg per pound of body weight (1 ml of the 50 mg product per 12.5 pounds or 1 ml of the 200 mg product per 50 pounds) twice daily. Treatment should be continued 24 hours after symptoms of the disease have stopped, not to exceed 3 days. Do not inject more than 5 ml per site. The 50 mg formulation is recommended for use in baby pigs weighing less than 25 pounds.

H. Route of Administration

For intramuscular use only.

I. Indication

Tylosin Injection is indicated for use in the treatment of bovine respiratory complex (shipping fever, pneumonia) usually associated with *Pasteurella multocida* and

Corynebacterium pyogenes; foot rot (necrotic pododermatitis) and calf diphtheria caused by *Fusobacterium necrophorum* and metritis caused by *Corynebacterium pyogenes* in beef cattle and nonlactating dairy cattle.

In swine, Tylosin Injection is indicated for use in the treatment of swine arthritis caused by *Mycoplasma hyosynoviae*; swine pneumonia caused by *Pasteurella* spp.; swine erysipelas caused by *Erysipelothrix rhusiopathiae*; acute swine dysentery associated with *Treponema hyodysenteriae* when followed by appropriate medication in the drinking water and/or feed

II. EFFECTIVENESS

The efficacy of tylosin has been established by the National Academy of Sciences and the National Research Council (NAS/NRC) which evaluated the drug to be probably effective in the treatment of infections in cattle and swine when such infections are caused by organisms susceptible to tylosin. The Food and Drug Administration concurred with the findings of the Academy which were published in the FEDERAL REGISTER on July 22, 1970. The regulations were subsequently amended to provide for revised labeling and an extension of the preslaughter withdrawal periods for cattle and swine effective October 2, 1981, at which time the NAS/NRC status of the drug was upgraded from probably effective to effective.

Accordingly, a bioequivalency study was conducted by the TechAmerica Research Center (TARC), formerly know as Elars Bioresearch Laboratories, 225 Commerce Drive, Fort Collins, CO 80524 to demonstrate bioequivalency of Medico's proposed Tylosin Injection with Elanco's NAS/NRC/DESI reviewed Tylan Injection.

The study was a crossover design utilizing twenty-four healthy, crossbred calves (12 males and 12 females) weighing approximately 400-700 pounds. After a two week acclimation period, the calves were randomly assigned to one of two groups consisting of six males and six females each. Group I received Medico's proposed product at the rate of 8 mg/ml body weight as a single intramuscular injection, while Group II received the same dosage of Elanco's Tylan. Following a 21 day washout period, the calves were weighed again and the procedure repeated with Group I receiving Elanco's Tylan and Group II receiving Medico's product. The animals were fasted for 18 and 24 hours prior to treatment and for 12 hours following treatment in each period. Venous blood samples were collected from each animal prior to treatment and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 9, 12, 16, 24, 36 and 48 hours after treatment for each period.

Results

The tylosin serum levels for both the Medico's product (Drug A) and the approved product (Drug B) are depicted graphically in figures 1-3. In the initial study, the curves generated to 16 hours are virtually superimposable. In the second study, the crossover, the curves do not appear identical at all points as the time to peak concentration is approximately 1.0 hour earlier for the Elanco preparation. However, when all of the data from both experiments are depicted graphically, the curves appear virtually superimposable.

The univariate analyses were done on the areas under the cruve, the peak blood serum level, and the time-to-peak blood serum level. The analysis showed no

significant (at alpha = .05 or less) treatment effects for the univariate measures. However, the analysis did show, for time-to-peak serum levels moderately significant (alpha between .05 and .10) treatment effects. Also, the method showed significant period effects for all three measures. In comparing Period 1 and Period 2, the second period for both Medico and Elanco, showed less area under the curve, had a lower peak serum level, and took longer to reach the peak serum level. For both periods, the Medico product showed a larger area under the curve and a longer time-to-peak serum level than did the Elanco product. However, the peak serum level measure showed Medico's values higher for Period 1 and Elanco's values higher for Period 2.

The proposed bioequivalency guidelines suggest that one should have an 80% chance of detecting a 20% difference in the means of the two drugs. A value above 20% indicates that the study was not large enough to detect meaningful differences if they occurred. The percent difference detectable for each measure studied is given in Figure 4. The only measure that does not meet the guidelines' specifications is time-to-peak. However, time-to-peak is not a continuous variable and has only a limited number of unique potential values. The two products are considered to be bioequivalent.

Figure 4. Smallest Mean Percent Difference that is Detectable with 80% Power

Measures	**Percent Mean Difference for Tylosin**
Overall serum level	19%
Area under the curve	7%
Peak Serum Level	11%
Time-to-peak	29%

Means of Univariate Measures by Period and Total

	Means – Period 1	**Means – Period 2**	**Means – Total**
Area Under the Curve – Medico	30.00	23.83	26.92
Area Under the Curve – Elanco	28.83	23.34	26.09
Peak Serum Level – Medico	4.66	3.05	3.86
Peak Serum Level – Elanco	4.61	3.30	3.96
Time-to-Peak Serum Level – Medico	1.33	1.83	1.58
Time-to-Peak Serum Level – Elanco	1.25	1.42	1.34

III. TARGET ANIMAL SAFETY

Tylosin Injection was evaluated by the National Academy of Sciences and the National Research Council (NAS/NRC) and found to be probably effective and safe for use in

cattle, swine, dogs and cats. The findings of the Academy were published in the FEDERAL REGISTER Vol. 35, No. 141, July 22, 1970.

IV. HUMAN FOOD SAFETY

The Food and Drug Administration has established a tolerance of 0.2 ppm for negligible residues of tylosin in the uncooked fat, muscle, liver and kidney of swine and cattle (21 CFR 556.740).

Nearly superimposable blood level curves obtained from the bioavailablity study (which demonstrated bioequivalency of the proposed Medico Tylosin Injection with Elanco's NAS/NRC reviewed Tylan) were submitted in lieu of residue depletion studies (refer to Figure 1, 2, 3, and 4). In accordance with the current CVM Bioequivalency Study Guidelines (December, 1982), this allows the sponsor of the proposed product to use the same preslaughter withdrawal times found on the approved new animal drug product, Elanco's Tylan . An amendment to the regulations was published in the October 2, 1981 Federal Register which not only upgraded the NAS/NRC status from probably effective to effective but also provided for revised labeling and extended preslaughter withdrawal times. Accordingly, the Medico label bears the FDA recognized withdrawal times of 21 days for cattle and 14 days for swine.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of 512 of the Act and demonstrate that Tylosin Injection, when used under its proposed conditions of use, is safe and effective for the labeled indications.

Approval of the application poses no increased human risk from exposure to residues of tylosin because the number of food-producing animals receiving medication will not significantly increase and because the drug is already regulated at the requested use level. Accordingly, this approval does not require a complete reevaluation of human safety data supporting the drug's use.

Thus, all new animal drug applications for NAS/NRC/DESI reviewed compounds are eligible for approval based upon demonstration of bioequivalence at the same withdrawal time as the NAS/NRC/DESI accepted preparation (unless the withdrawal time is based on a new tolerance for the drug which was independently requested by the sponsor or a new withdrawal time was established because the sponsor submitted unrequested additional evidence in support of a shorter withdrawal time).

VI. ATTACHMENTS

1. Tylosin Injection intermediate carton label
2. Tylosin Injection container label
3. Tylosin Injection package insert

Copies of these labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.