Date of Approval: April 27, 2005

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (ANADA)

ANADA 200-366

Carprofen Caplets
(carprofen)

25 mg, 75 mg, and 100 mg caplets

Dogs

For the relief of pain and inflammation associated with osteoarthritis

Sponsored by:

IMPAX Laboratories, Inc.

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number:	ANADA 200-366
b. Sponsor:	IMPAX Laboratories, Inc. 30831 Huntwood Ave. Hayward, CA 94544 Drug Labeler Code: 000115
c. Established Name:	Carprofen
d. Proprietary Name:	Carprofen Caplets
e. Dosage Form:	Scored caplet
f. How Supplied:	25 mg caplets: Bottles of 60, 100, and 180 75 mg and 100 mg caplets: Bottles of 60 and 180
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	25 mg, 75 mg, or 100 mg carprofen per caplet
i. Route of Administration:	Oral
j. Species/Class:	Dogs
k. Recommended Dosage:	The total daily dose may be administered as 2 mg/lb (4.4 mg/kg) of body weight once daily or divided and administered as 1 mg/lb (2.2 mg/kg) of body weight twice daily. Carprofen Caplets are scored and dosage should be calculated in half-caplet increments.
l. Pharmacological Category:	Anti-inflammatory/Analgesic
m. Indications:	For the relief of pain and inflammation associated with osteoarthritis in dogs.
n. Pioneer Product:	RIMADYL Caplets; carprofen; NADA 141-053; Pfizer, Inc.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

A. Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and pioneer formulations of carprofen caplets.

Protocol Title: A Randomized, Two-Way Crossover, Single-Dose, Open-Label Study to Evaluate the Relative Bioavailability of a Test Tablet Formulation of Carprofen (25 mg) Compared to an Equivalent Dose of a Commercially Available Reference Drug (RIMADYL Caplets, 25 mg, Pfizer, Inc.) in 36 Fasted, Healthy Dogs

Testing Facility: Southwest Bio-Labs, Inc.
401 North 17th St., Suite 11
Las Cruces, NM

Study Number: Southwest Bio-Labs, Inc.: 202-0624d
Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence of IMPAX Laboratories, Inc.'s 25 mg carprofen caplets and Pfizer, Inc.'s RIMADYL Caplets, 25 mg, in a 2 way crossover study in dogs.

Summary: Thirty-six beagle dogs (18 males (M) and 18 females (F) were randomly assigned to two treatment groups containing 18 animals (9M + 9F). Each group was given an oral dose of 25 mg of carprofen of either the IMPAX formulation or the Pfizer RIMADYL formulation in a 2-way crossover study. The dogs ranged in age from 1 to 4 years and weighed 22 $\pm$ 6 pounds. Phase I began on Study Day one with Group I animals receiving the IMPAX formulation and Group II animals receiving the Pfizer formulation. After a 7 day washout, Phase II began on Study Day 8 with the Group I animals receiving the Pfizer formulation and the Group 2 receiving the IMPAX formulation. For each phase of the study, pre-dose blood samples were taken and sampling continued with post-dose samples taken at 0.25, 0.50, 0.75, 1, 1.5, 2, 4, 6, 12, 24, 36, and 48 hours. All blood samples collected were processed, plasma harvested, and stored frozen until shipped to PHARMout Laboratories, Inc., Sunnyvale, CA for carprofen analysis using a fully validated analytical method.

Results: The following pharmacokinetic (PK) parameters were computed from the plasma concentration data using the actual sample collection times:

- $AUC_{0\text{-}LOQ}$: Area under the plasma concentration-time curve (ng-hr/mL) from time zero to the time of the last quantifiable concentration (t), calculated using the linear trapezoidal rule:

  $\Sigma_i(t_i-t_{i-1})(C_i+C_{i-1})/2$, i=1 to t, where C_i is the plasma concentration at time t_i.

- C_{max}: Maximum or peak concentration obtained by inspection (ng/mL).

- T_{max}: Time of maximum or peak concentration, obtained by inspection (hr).

C_{max} and $AUC_{0\text{-}LOQ}$ were analyzed using ln-transformed data, but their means presented below are geometric or back transformed least squares means of ln-transformed values. T_{max} was analyzed using untransformed data. The calculated values of C_{max}, $AUC_{0\text{-}LOQ}$, and T_{max} for the test and reference products are represented in Table 1.

Table 1: PK Parameters for Test and Reference Carprofen Products

PK Parameter	Carprofen Mean	RIMADYL Mean	% Ratio	90% Confidence Interval (expressed as a percentage)
C_{max}	31341.75*	30501.72*	102.75	-3.81, 9.77
$AUC_{0\text{-}LOQ}$	179879.32*	183880.22*	97.82	-8.75, 4.87
T_{max}	1.11**	1.12**	99.11	NA

*Geometric means listed are based on back transformed least squares means of ln-transformed values.
**Least square means are calculated from non-transformed data.

The criteria for calculating the confidence bounds for C_{max} and $AUC_{0\text{-}LOQ}$, as described in CVM's Bioequivalence Guidance, is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the log scale of each parameter and then take the anti-log of the confidence limits minus 1 multiplied by 100. The resulting bounds should be between -20.00% and +25.00% of the mean of the reference product. As seen in the table, the two pivotal pharmacokinetic parameters for determining product bioequivalence, $AUC_{0\text{-}LOQ}$ and C_{max}, fall within those bounds.

The PK parameter, $T_{max,}$ is interpreted by clinical judgment and the difference is not medically important. Therefore, the study objective to determine the bioequivalence of generic and pioneer carprofen products was achieved.

B. Dissolution Study

In vitro dissolution data were submitted in support of the request for waiver of *in vivo* bioequivalence study requirements for the 75 mg and 100 mg strength caplets. The *in vitro* dissolution data were generated in accordance with CVM's requests (900 mL freshly degassed phosphate buffer, pH 7.5, using Apparatus 2 at 50 rpm). The sponsor also provided information confirming that the inactive ingredients for the IMPAX product do not interfere with the UV spectrophotometric methods used for quantitating the amount of carprofen dissolved in the dissolution buffer (absorbance at 300 nm, tested against the standard solution).

To demonstrate comparable *in vitro* dissolution between the proposed IMPAX and RIMADYL products, the following criteria were required:

1) Twelve units of the test and reference products are used for each set of dissolution tests.
2) The relative standard deviation in percent dissolved less than 15% at the first sampling time and equal to or less than 105 at all other sampling times.
3) Comparability is based upon the model-free approach as defined in CDER's 8/97 guidance for industry titled "Dissolution Testing of Immediate Release Dosage Forms". The similarity factor (f_2) is calculated as follows:

$$f_2 = 50 * \log \{[1+(1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} * 100\}$$

where n = the number of time points, R_t is the mean dissolution value of the reference product at time t, and T_t is the mean dissolution value of the test product at time t. Comparability is defined by f_2 values that are equal to or greater than 50.

The *in vitro* dissolution data demonstrated that in each dissolution comparison the relative standard deviation was less than 10%. Thus, the f_2 criterion could be employed for comparing profiles.

A requirement for conducting the dissolution study was that if the 25 mg test and reference products were bioequivalent but presented with very different *in vitro* dissolution profiles, then the 75 mg and 100 mg test products could be compared to the lot of the 25 mg strength IMPAX product that underwent *in vivo* bioequivalence testing. The 25 mg IMPAX and RIMADYL caplets presented with markedly different *in vitro* profiles. Nevertheless, these two products were shown to be bioequivalent. Accordingly, the 75 mg and 100 mg strength IMPAX caplets were compared to the lot of the 25 mg IMPAX caplet that underwent *in vitro* testing. IMPAX conducted two sets of dissolution runs on the 25 mg caplets: one to cover the request for waiver of the 75 mg caplets and a second to cover the waiver request for the 100 mg caplets.

Calculations of f_2 using means based upon the exact percent dissolved reported for each caplet are presented in Table 2.

Table 2: Comparability of Carprofen Caplets
Similarity Factor (f_2) Calculations

Comparison	f_2
75 vs. 25	49.2
100 vs. 25	48.9

CVM concluded that slight deviations from 50 do not necessarily indicate that the two curves are different. In particular, considering that the very marked *in vitro* differences observed between the 25 mg strengths of RIMADYL and IMPAX caplets did not influence product performance, we have, with confidence, concluded that the very slight deviation between the 25 mg versus 75 mg and 100 mg caplet profiles will have no impact on *in vivo* product performance. Accordingly, a waiver of *in vivo* bioequivalence study requirements for 75 mg and 100 mg strength caplets was granted.

3. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

4. AGENCY CONCLUSIONS:

This Abbreviated New Animal Drug Application (ANADA) filed under section 512(b)(2) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that Carprofen Caplets, when used under its proposed conditions of use, is safe and effective for its labeled indications.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as follows:

Generic Labeling for ANADA 200-366: Carprofen Caplets
Container labels for 25 mg caplets in bottles of 60, 100, and 180
Container labels for 75 mg and 100 mg caplets in bottles of 60 and 180
Package Insert
Dog Owner Information Summary

Pioneer Labeling for NADA 141-053: RIMADYL Caplets
Container labels for 25 mg, 75 mg, and 100 mg caplets in bottles of 14, 60 and 180, and blister packs containing 4 caplets
Package Insert
Dog Owner Information Summary