Boehringer Ingelheim
Roxane Laboratories

October 1, 2001

4149 '01 OCT -2 P1:20

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 requesting that the Commissioner of the Food and Drug Administration make a determination that the drug product, Digoxin Elixir, 0.05 mg/mL, is suitable for consideration in an abbreviated new drug application (ANDA).

A. Actions Requested

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that the drug product, Digoxin Elixir, 0.05 mg/mL, is suitable for submission as an ANDA based upon a bioavailability study relative to the reference listed drug product. The reference listed drug product (RLD) upon which this petition is based is Lanoxin® (Digoxin) Tablets, 0.25 mg (GlaxoSmithKline) [1]. The petitioner is thus seeking a change in dosage form — from a tablet to an elixir — and a change in strength — from 0.25 mg per tablet to 0.05 mg/mL — from that of the RLD.

The petitioner is also requesting a waiver of the requirement to conduct pediatric studies in accordance with the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drug and Biological Products in Pediatric Patients; Final Rule (Pediatric Rule) (63 FR 66632) published December 2, 1998, and the requirements set forth in 21 CFR 314.55.

B. Statement of Grounds

B.1 Change in Dosage Form and Strength

The RLD is a tablet form of digoxin. The proposed drug product is a currently marketed elixir dosage form of digoxin that FDA has permitted to be marketed for years without

OIP-0449

CP 1

the requirement for a marketing application. It contains the same active ingredient as the RLD. Although the strength and formulation differ from those of the RLD, the absolute bioavailability of digoxin from the tablet (60% → 80%) and elixir (70% → 85%) are comparable and the recommended doses are the same [2, 3]. Recommended doses of digoxin are individualized for each patient. The difference in strength and dosage form merely means that the total dose of the elixir will be based on a specified volume of drug product rather than a fixed dose as provided by the tablet dosage form.

In support of the change in dosage form requested by this petition, the petitioner would like to point out that the agency has previously approved numerous ANDA suitability petitions allowing for a change in dosage form and strength. There are no proposed changes in labeling with the exception of the obvious change in dosage form and strength. Proposed Draft labeling for the elixir is included in Attachment 1. A copy of the labeling of the RLD is included in Attachment 2.

The dosing recommendations of the proposed product will be consistent with that of the RLD (Attachment 2). The proposed oral solution (elixir) dosage form will benefit those elderly or infirmed patients who because of preference or their disease state may not be able to swallow tablets. The product will be particularly useful for pediatric patients who may not be able to swallow tablets or who, based on their age and weight, must have a carefully measured dosage below that currently available in an FDA approved tablet product.

The proposed ANDA would provide an approved marketing application for an elixir dosage form of digoxin that has been marketed for years with acceptable efficacy and safety profiles.

B.2 Waiver of the Requirement to Conduct Pediatric Studies

In accordance with the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drug and Biological Products in Pediatric Patients; Final Rule (Pediatric Rule) (63 FR 66632) published December 2, 1998, and the requirements set forth in 21 CFR 314.55, the petitioner is requesting a waiver of the requirement to conduct pediatric studies. These regulations require information to assess the safety and effectiveness of the drug product for the claimed indications in all relevant subpopulations, and to support dosing and administration in each subpopulation for which the drug is safe and effective.

The RLD to which this petition refers provides dosing recommendations for the treatment of newborns and in addition provides instructions for dosing of premature infants. [2] In that regard, the petitioner requests a waiver under 21 CFR 201.23 for the need to conduct pediatric studies because even though the product represents a formulation that can be used in pediatric patients, the labeling for the RLD already adequately supports the use of

the proposed product in all pediatric subgroups. The waiver is requested in accordance with the citation reference above but because of the unusual circumstances surrounding this request (labeling already contains adequate directions for use in the pediatric population) the waiver is being sought. The reference product labeling contains the appropriate dosing recommendations for the entire range of pediatric age groups for which the product is indicated. It is the petitioner's belief that the introduction of an approved liquid dosage form will not create any additional usage in the existing pediatric population for whom the product is already recommended in the approved labeling for digoxin tablets, and based on the labeled warnings there is no additional pediatric sub age group of patients that would or could reasonably be contemplated. The use of the liquid product will simply provide a more convenient, easier to use and more accurately measurable product for those patients for whom it is currently labeled that includes both adults and all pediatric age groups.

Any approval of the elixir based on this petition would therefore not:

A. Represent a meaningful therapeutic benefit over existing therapies for pediatric patients in the age group not covered in existing labeling.

B. Increase usage of Digoxin Elixir in the pediatric population as it is already marketed although not the subject of an approved application.

In pediatric patients, digoxin has been used to treat congenital or acquired acute cardiac disease. [4] Although there are no specific references to pediatric patients in the Indications section of the labeling of the RLD, it does include the following recommendations in the Dosage and Administration section for dosing in children: [2]

> Children: In general, divided daily dosing is recommended for infants and young children (under age 10). In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults. Daily maintenance doses for each age group are given in Table 6 and should provide therapeutic effects with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. These recommendations assume the presence of normal renal function.

Table 6 Daily Maintenance Doses in Children with Normal Renal Function

Age	Daily Maintenance Dose (μg/kg)
2 to 5 years	10 to 15
5 to 10 years	7 to 10
Over 10 years	3 to 5

Although not specified in the current label for the RLD, recommendations for loading and maintenance doses for premature neonates, neonates, and children less than 2 years of age are available in the literature. [5-8]

The pharmacokinetics of digoxin after oral administration have been well studied in infants and children, as evidenced by the substantial body of literature dating back at least 30 years. The 1983 review by Bendayan and McKenzie [8] cites 73 references and that by Latifi, et al. [4] in 2000 cites 89. Neither review should be considered as a complete review of the available literature and serve only to illustrate the amount of information available on digoxin in this population.

The following is a brief overview of digoxin pharmacokinetics in pediatric patients including comparisons to adults:

> The absolute bioavailability of digoxin from the elixir formulation has been reported to be 52% → 79% [8], comparable to that in adults (70% → 85% [2, 3]). Digoxin distribution in adults [9] and children [10, 11] follows a biphasic or triphasic pattern. Digoxin is extensively distributed in patients of all ages although volumes of distribution in neonates and infants tend to exceed those reported in adults [10] while premature infants may have somewhat smaller volumes [11]. The elimination half-life of digoxin is longer in premature newborns (38 → 88 hours), most likely as a consequence of immature renal function [12] and ranges from 18 → 46 hours in full-term neonates, infants, and children. [8] These values are comparable to those in adults, which range from 36 → 48 hours [2, 9].

It is interesting to note that there is currently an unapproved marketed oral solution (elixir) dosage form in a 0.05 mg/mL (0.25 mg/5mL) strength that is cited in the labeling of the approved listed drug product. The labeling also includes general instructions for switching a patient between a tablet and oral solution dosage form. Approval of this petition will bring the oral solution under the FDA's regulatory umbrella and will not result in a change in labeling from that of the reference listed drug product.

C. Conclusion

The petitioner requests the Commissioner to find that a change in dosage form from a tablet to an elixir and a change in strength from 0.25 mg per tablet to 0.05 mg/mL for Digoxin Elixir raises no questions of safety or effectiveness and that the elixir is suitable for submission as an ANDA based upon a bioavailability study relative to the reference listed drug product. The petitioner further requests, based upon the information provided above, a waiver under 21 CFR 201.23 for the need to conduct pediatric studies.

The undersigned requests that the Commissioner grant this petition and authorize submission of an ANDA for a liquid for of Digoxin (elixir) 0.05 mg/mL (0.25 mg/5mL).

D. Environmental Impact

According to 21 CFR 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

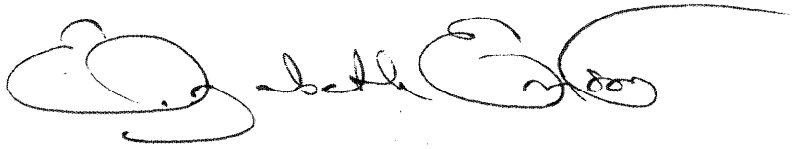
E. Economic Impact

According to 21 CFR 10.30(b), petitioner will, upon request by the Commissioner, submit economic impact information.

F. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



Elizabeth A. Ernst
Associate Director, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

G. References[1]

1. Electronic Orange Book (www.fda.gov/cder/ob).
2. Lanoxin® (digoxin) Tablets, USP. Product Information. GlaxoSmithKline (www.glaxowellcome.com).
3. Lanoxin® (digoxin) Elixir Pediatric. Product Information. GlaxoSmithKline (www.glaxowellcome.com).
4. Latifi S, Lidsky K, Blumer JL. Pharmacology of inotropic agents in infants and children. Prog Pediat. Cardiol. 2000;12:57-79.
5. Park MK. Use of digoxin in infants and children, with specific emphasis on dosage. J. Pediat. 1986;108:871-877.
6. Hastreiter AR, van der Horst RL, Voda C, Chow-Tung E. Maintenance digoxin dosage and steady-state plasma concentration in infants and children. J Pediat 1985;107:140-146.
7. Nyberg L, Wettrell G. Digoxin dosage schedules for neonates and infants based on pharmacokinetic considerations. Clin Pharmacokinet 1978;3:453-461.
8. Bendayan R, McKenzie MW. Digoxin pharmacokinetics and dosage requirements in pediatric patients. Clin Pharm 1983;2:224-235.
9. Kramer WG, Lewis RP, Cobb TC, Forester WF, Visconti JA, Wanke LA, Boxenbaum HG, Reuning RH. Pharmacokinetics of digoxin: Comparison of a two- and a three-compartment model in man. J Pharmacokinet Biopharm 1974;2:299-315.
10. Wettrell G. Distribution and elimination of digoxin in infants. Eur J Clin Pharmacol 1977; 11:329-335.
11. Hastreiter AR, Simonton RL, van der Horst RL, Benawra R, Mangurten H, Lam G, Chiou WL. Digoxin pharmacokinetics in premature infants. Pediat Pharmacol 1982;2:23-31.
12. Lang D, von Bernuth G. Serum concentration and serum half-life of digoxin in premature and mature newborns. Pediatrics 1977;59:902-906.

[1] Copies of all literature references are included in Attachment 3.