Boehringer Ingelheim
Roxane Laboratories

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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Roxane Laboratories, Inc.

Re: Docket 00N-1610

Dear Sir or Madame:

February 16, 2001

Roxane Laboratories appreciates the opportunity to provide comments to the proposed rule, Digoxin Products for Oral Use; Revocation of Conditions for Marketing, dated November 24, 2000. This notice will require approved applications as a condition of marketing oral digoxin products 30 days after publication of the final rule. Roxane Laboratories requests that FDA extend the effective date for requiring approved marketing applications after publication of the final rule from 30 days to two years. Support for this request is provided below.

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Roxane Laboratories has been marketing Digoxin Elixir, USP pursuant to the provisions of 21 CFR 310.500 since 1988. Digoxin Elixir meets all requirements set forth in the USP to assure consistent drug product quality standards. Historically, FDA's primary concern has not been related to Digoxin Elixir but rather to the tablet forms of this drug. In 1970, FDA initially addressed its concern related to digoxin tablets by the establishment of a voluntary certification program that required that each lot of digoxin tablets be tested to assure compliance with USP requirements for potency and content uniformity. FDA later added a requirement for specified dissolution testing of digoxin tablets prior to release of a batch. The primary focus of the agency's concern and subsequent testing requirements related to variations in bioavailability of commercially available digoxin tablets. Specific testing requirements were imposed by regulation to minimize differences in bioavailability found in digoxin tablets. This regulation (21 CFR 310.500) outlined the conditions for marketing oral digoxin products which also included Digoxin Elixir.

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There has been no evidence of issues related to variability in the bioavailability of Roxane's Digoxin Elixir during the marketing history of the drug product. While it may be possible for oral solution formulations of digoxin to vary slightly in bioavailability, the likelihood of significant differences from batch to batch or between batches of different manufacturers of Digoxin Elixir is expected to be minimal and represent a low potential for a potential for a safety or efficacy issue. We believe that our long-standing marketing history with this product clearly demonstrates consistent drug product quality and an excellent safety and efficacy record.

In addition to the lack of evidence that currently marketed Digoxin Elixir products represents a safety concern for patients, removal of unapproved products from the marketplace thirty days after publication of the final rule may result in a shortage of this medically necessary product. Digoxin products are used for patients with serious cardiac conditions. Presently, there are only two manufacturers of Digoxin Elixir products. Roxane Laboratories currently provides approximately 50% of this product to the market. Sudden withdrawal of supply from the marketplace may result in a shortage of a medically necessary drug product. By extending the effective date of the final rule a shortage of this critical drug product can be avoided without compromising the overall public health objectives of the proposal. Absent any information suggesting a problem with currently marketed Digoxin Elixir products, a reasonable extension of the effective date accomplishes FDA's goal of requiring approved applications for marketing of the products without jeopardizing the continued availability of Digoxin Elixir to those seriously ill patients for which this product is essential.

Please note that Roxane Laboratories does not object to the Agency's proposal to require submission of NDAs or ANDAs for digoxin products. It does, however, request that FDA reconsider the timeline imposed by requiring all digoxin products to be subject to an approved application within thirty days of the publication of the final rule. Preparation for all aspects of a regulatory submission in accord with current FDA requirements for a NDA or ANDA represents substantial time and effort. Method development and validation, manufacturing of a batch(es) appropriate stability testing for the requisite number of batches, bioavailability testing, among other requirements, represent a significant amount of time to complete. Moreover, there is no listing of a Reference Listed Drug for Digoxin Elixir in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange book), therefore at this time there is no guidance from the Agency for a basis for submission.

Additionally, drug master files must be prepared and available for Agency review prior to submission of an application. In spite of the time required to prepare and submit an application for this drug product, FDA has proposed that all marketed digoxin products be regulated under the approval process for NDAs and ANDAs thirty days after publication of the final rule.

Because manufacturers cannot predict the publication of the final rule, it may be impossible to comply with the approval requirements within 30 days of date of the publication of the final rule. Even under the best of circumstances, it may take considerably longer to prepare and submit a marketing application and obtain approval to be in compliance within the proposed 30 day effective date. It is highly unlikely that an application could be submitted to FDA and approved in a timeframe of less than two years. Therefore, Roxane Laboratories respectfully requests that FDA extend the effective date of the proposed rule to be two years after the publication of the final rule. This extension will permit preparation and submission of quality applications and sufficient time for the FDA to complete the review of the application.

We are prepared to work with the Agency to resolve any questions or concerns regarding the status of our product. Correspondence concerning this response should be addressed to Ann M. Maloney, Director, Drug Regulatory Affairs – Approved Products. I can be contacted by telephone at (614) 241-4130 or by telefax at (614) 241-0321.

Sincerely,

Ann M. Maloney

Ann M. Maloney
Director, Drug Regulatory Affairs – Approved Products

FROM: Debbie Gray (614)276-4000
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