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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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Certifier	LATUNNA CHAIWEE

[Docket No. 00N-1609]

Digoxin Products for Oral Use; Reaffirmation of New Drug Status and Conditions for Marketing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is reaffirming its determination that digoxin products for oral use (tablets and elixir) are new drugs and announcing the conditions for marketing the products. Manufacturers who wish to begin to market or to continue marketing digoxin products for oral use must submit new drug applications (NDA's) or abbreviated new drug applications (ANDA's). Elsewhere in this issue of the **Federal Register**, FDA is publishing a proposed rule to revoke the regulations that establishes conditions for marketing digoxin products for oral use.

DATES: This notice is effective [*insert date of publication in the Federal Register*].

ADDRESSES: All communications in response to this notice should be identified with Docket No. 00N-1609 and directed to the appropriate office listed as follows:

Applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(j)): Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., rm. E150, Rockville, MD 20855.

Applications under section 505(b) of the act: Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852.

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Requests for an opinion on the applicability of this notice to a specific product: Division of Prescription Drug Compliance and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT: Mary E. Catchings, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

Digoxin is a member of a group of drugs known as cardiac glycosides. The cardiac or digitalis glycosides are a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in several plants and animals. The term digitalis is used to designate the whole group.

Since ancient times, squill (*Urginea (Scilla) maritima*) and foxglove (*Digitalis purpurea*) and other natural sources of cardiac glycosides have been used for their effects on the heart. Digoxin, which is extracted from the leaves of *Digitalis lanata*, was reportedly discovered and developed in 1930 at the Wellcome Chemical Works at Dartford. According to Burroughs Wellcome (now Glaxo Wellcome), the company has manufactured and marketed a digoxin product in the United States since 1934.

Digoxin has been used in the treatment of certain cardiac disorders for many years and labeled for use in heart failure, atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia. Digoxin is available for oral and intravenous administration.

Digoxin products for parenteral use and digoxin solution in capsules have previously been classified as new drugs (July 27, 1972, and July 26, 1982, respectively) and are subjects of approved applications. This notice addresses digoxin tablets and elixir.

Because of bioavailability problems found to exist with digoxin tablets, FDA has sought, over the years, to provide a systematic regulatory approach to ensure the uniformity of all marketed,

oral digoxin products. Since 1968, digoxin tablets (and related drugs) have been covered by a number of compliance programs.

In April 1970, FDA began a program to systematically test marketed lots of digoxin tablets. FDA took this action after the agency became aware of an apparent potency problem with this cardiac glycoside. As a result of this testing program, from April to November 1970, there were 79 recalls of digoxin products. In October 1970, FDA instituted a voluntary certification program in which participating manufacturers agreed not to release new lots of digoxin tablets until samples of the lots were tested by FDA and found to meet the United States Pharmacopeia (USP) requirements for potency and content uniformity.

Later, studies showed evidence of clinically significant differences in bioavailability between some batches of digoxin tablets made by different manufacturers, and even between some batches made by the same manufacturer. Because of these problems and because available data showed a general correlation between bioavailability and dissolution, the USP monograph for digoxin tablets was revised to include a requirement for dissolution.

In the **Federal Register** of January 22, 1974 (39 FR 2471), FDA issued a regulation (21 CFR 130.51; now § 310.500 (21 CFR 310.500)) establishing conditions for marketing digoxin products for oral use (tablets and elixir). The regulation: (1) Declared all digoxin products for oral use (tablets and elixir) to be new drugs, (2) required submission of ANDA's and bioavailability tests for all oral digoxin products, (3) required a mandatory FDA certification program for digoxin tablets based on dissolution testing by the National Center for Drug Analysis, (4) required a recall of any previously marketed batch of digoxin tablets found to fail USP dissolution specifications, and (5) set forth a labeling requirement for all oral digoxin products. The regulation announced the agency's intentions to initiate procedures to monitor digoxin product formulations to ensure that products requiring reformulations complied with in vitro test requirements and possessed uniform batch-to-batch bioavailability.

Because of the narrow margin between therapeutic and toxic levels of digoxin and the potential for serious risk to cardiac patients using digoxin products that may vary in bioavailability, the agency determined that immediate implementation of the corrective procedures detailed in the regulation was necessary and made § 310.500 effective on the date of publication in the **Federal Register**. Even though the regulation was effective immediately, FDA accepted comments on § 310.500 for 30 days, until February 21, 1974.

As a result of the comments submitted, FDA published notices in the **Federal Register** of March 8, 1974 (39 FR 9184 and 9219), that stayed the time for submission of ANDA's, stayed the requirement that labeling of digoxin products conform to § 310.500(e), and announced a public meeting to discuss the labeling of digoxin. The notices stated that the stay for submission of ANDA's would be lifted 30 days after a final decision on labeling revisions had been reached.

The submitted comments concerning the labeling requirements were reviewed by the agency's Cardiovascular and Renal Advisory Committee and discussed at a public meeting. Later, FDA published a proposed regulation in the **Federal Register** of April 28, 1976 (41 FR 17755), to revise the labeling for digoxin products set out in § 310.500(e). FDA also proposed to lift the stay only insofar as it affected the labeling requirement. The agency believed that revised labeling was necessary because the labeling then being used for digoxin tablets contained dosage information suitable for the older, less bioavailable formulations that the agency had removed from the market through the digoxin certification program. Continued use of such older labeling constituted a potential health hazard. The agency concluded that revision of the labeling was necessary as soon as practicable to protect the public health. Revisions were needed to correct dosage and other recommendations for use and warn against the use of such products in the treatment of obesity.

FDA published a final regulation in the **Federal Register** of September 30, 1976 (41 FR 43135), that amended § 310.500(e) by revising the required labeling for digoxin products for oral use. The rule lifted the stay for revised labeling. The requirement for submission of ANDA's was stayed pending resolution of the agency's ANDA policy.

This notice reaffirms FDA's determination of new drug status for digoxin products for oral use and announces the conditions for marketing the products.

II. Legal Status

Digoxin products for oral use, as set forth in § 310.500, are new drugs as defined in section 201(p) of the act (21 U.S.C. 321(p)), and subject to the requirements of section 505 of the act. As discussed above, FDA based its determination of new drug status on new information that emerged about the bioavailability of digoxin products for oral use. Studies had shown significant variation in bioavailability of the products that occurred in batches from a single manufacturer as well as in batches produced by different manufacturers. Because variations in bioavailability can adversely affect the safety and effectiveness of the products, FDA concluded that the products could not be considered generally recognized as safe and effective and are new drugs requiring approved applications for marketing.

At the time that § 310.500 was published, FDA had not approved any NDA's for digoxin products for oral use. Since FDA stayed the requirement in § 310.500 for submission of ANDA's, FDA has regulated digoxin products for oral use under the remaining requirements in § 310.500.

In September 1993, Glaxo Wellcome (then Burroughs Wellcome) submitted to the agency an NDA (NDA 20-405) for Lanoxin (digoxin) Tablets under section 505(b) of the act. The submission included safety and effectiveness data on the drug product. In addition to published studies from the literature, the submission included two original studies sponsored by Glaxo Wellcome. These were double-blind, placebo-controlled studies of Lanoxin Tablets in treating congestive heart failure patients taking angiotensin converting enzyme (ACE) inhibitors and/or diuretics.

Based on its review of NDA 20-405 for Lanoxin Tablets, FDA concluded that the application was approvable. The agency determined that the issue of labeling, including appropriate indications, for the drug product should be presented to the Cardiovascular and Renal Drugs Advisory

Committee. During this time, the agency began a systematic review of the labeling for cardiac drugs in general.

In May 1996, the advisory committee addressed the issue of labeling for Lanoxin (digoxin) Tablets. The committee recommended that digoxin be indicated for resting and ambulatory heart rate control in atrial fibrillation and that use in atrial flutter be excluded. The committee recommended that the indication for heart failure should state that most clinical trial data came from trials where digoxin was used in combination with diuretics and ACE inhibitors. The committee also considered preliminary results of The Digitalis Investigation Group (DIG) clinical trial conducted by the National Heart, Lung, and Blood Institute of the National Institutes of Health and the Department of Veterans Affairs Cooperative Studies Program. The DIG trial was a randomized, double-blind, placebo-controlled multicenter trial to evaluate the effects of digoxin (Lanoxin) on mortality from any cause and on hospitalization for heart failure over a 3- to 5-year period in patients with heart failure and normal sinus rhythm. The committee recommended that the final results of the DIG trial be submitted to the Lanoxin Tablets NDA and be incorporated into the labeling.

Glaxo Wellcome submitted the results of the DIG trial to the agency in April 1997. The results of the trial showed that digoxin did not affect mortality adversely.

Based on the review of NDA 20-405 for Lanoxin Tablets and the recommendations of the Cardiovascular and Renal Drugs Advisory Committee, FDA approved NDA 20-405 for the following indications:

Heart Failure: LANOXIN is indicated for the treatment of mild to moderate heart failure. LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, LANOXIN should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified. [Glaxo Wellcome received 3 years of exclusivity for this indication.]

Atrial Fibrillation: LANOXIN is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

Because of the approval of NDA 20-405, digoxin tablets are now eligible for ANDA's under section 505 of the act. Therefore, by this notice, FDA is lifting the stay for submitting ANDA's for digoxin products for oral use.

This notice reaffirms FDA's previous determination that digoxin products for oral use are new drugs requiring approved applications for marketing. Because the new drug status of digoxin has already been established by notice-and-comment rulemaking, the agency is not providing a formal procedure for the submission of claims that a particular digoxin product for oral use is not subject to the new drug provision of the act. (Cf. 62 FR 43535, August 14, 1997 (oral levothyroxine sodium; determination of new drug status).)

III. Conditions for Approval and Marketing

On September 30, 1997, FDA approved NDA 20-405 for Lanoxin Tablets (62.5, 125, 187.5, 250, 375, and 500 micrograms) held by Glaxo Wellcome Inc. for the indications listed above.

Approval of an NDA under section 505(b) of the act and § 314.50 (21 CFR 314.50) or an ANDA under section 505(j) of the act and § 314.94 (21 CFR 314.94) is required as a condition for marketing all digoxin products for oral use. Such an ANDA should use Glaxo's NDA 20-405 as the reference listed drug.

Elsewhere in this issue of the **Federal Register**, FDA is publishing a proposed rule to revoke § 310.500, thus eliminating the conditions for marketing digoxin products for oral use established by that regulation.

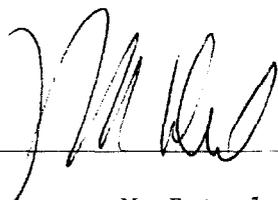
Inquiries regarding procedures for obtaining approval of NDA's should be directed to the Division of Cardio-Renal Drug Products (HFD-110), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857, 301-594-5300.

Inquiries regarding procedures for obtaining approval of ANDA's should be directed to the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, Maryland 20855, 301-827-5845.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505 (21 U.S.C. 352, 355)).

Dated: 11-15-00

November 15, 2000



Margaret M. Dotzel,
Associate Commissioner for Policy.

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