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Certifier	LAJUANA D. CALDWELL

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 310**

[Docket No. 00N-1610]

**RIN 0910-AC12**

**Digoxin Products for Oral Use; Revocation of Conditions for Marketing**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to revoke the regulation that establishes conditions for marketing digoxin products for oral use. This regulation is no longer necessary because the products, which are new drugs, can be regulated under the approval process for new drug applications (NDA's) and abbreviated new drug applications (ANDA's) as set forth in the Federal Food, Drug, and Cosmetic Act (the act). Elsewhere in this issue of the **Federal Register** FDA is publishing a notice with the agency's conclusions regarding the approval of the Lanoxin NDA and the conditions for marketing oral digoxin products.

**DATES:** Submit written comments by *[insert date 90 days after date of publication in the Federal Register]*. See section II of this document for the proposed effective date of a final rule based on this document.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**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.

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**SUPPLEMENTARY INFORMATION:****I. Background**

The regulation that the agency is proposing to revoke, § 310.500 (21 CFR 310.500), was published in the **Federal Register** of January 22, 1974 (39 FR 2471) (the January 1974 regulation), as amended March 8, 1974 (39 FR 9184), and September 30, 1976 (41 FR 43135). The regulation announced FDA's determination that digoxin products for oral use are new drugs within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and set forth conditions for marketing the products. FDA established the regulation to provide a systematic regulatory approach to ensure uniformity of marketed oral digoxin products. Studies had shown clinically significant differences in bioavailability of certain oral digoxin products. This variability was a major concern because of the drug's narrow therapeutic range and the potential risk presented to patients using digoxin products of varying bioavailability.

The conditions for marketing set forth in § 310.500 include requirements for submission of ANDA's and bioavailability tests for all oral digoxin products, a mandatory FDA certification program for digoxin tablets based on dissolution testing by the National Center for Drug Analysis, and labeling requirements for all oral digoxin products. The requirements for labeling and submission of ANDA's were stayed (39 FR 9184 and 9219, March 8, 1974); FDA later lifted the stay as it applied to the labeling requirements and issued revised labeling requirements (41 FR 43135, September 30, 1976). The requirement for submission of ANDA's, however, was stayed indefinitely (41 FR 43135). Thus, until recently, FDA has regulated all digoxin products for oral use under the labeling requirements set forth in § 310.500 with digoxin tablets also subject to the certification procedure set forth in § 310.500.

Since publication of § 310.500, the following actions have occurred that render the regulation unnecessary.

In September 1993, Glaxo Wellcome (then Burroughs Wellcome) submitted to the agency an NDA (NDA 20-405) under section 505(b) of the act (21 U.S.C. 355(b)) for Lanoxin (digoxin)

Tablets. 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 agency's Cardiovascular and Renal Drugs Advisory Committee (the 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 advisory 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 advisory 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 advisory 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 with the recommendations of the 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, premarket approval of digoxin products under batch certification is no longer warranted. FDA's conclusions regarding the approval of the Lanoxin NDA and the conditions for marketing oral digoxin products are published in a notice elsewhere in this issue of the **Federal Register**. In that **Federal Register** notice, FDA is reaffirming its determination that digoxin products for oral use are new drugs and requiring approved applications for marketing.

In addition, the dissolution requirements (i.e., the dissolution rates and methods of measuring digoxin tablet dissolution) specified in § 310.500 are no longer used as standards in the certification program. The current official United States Pharmacopeia (USP) includes a monograph, including dissolution requirements, for digoxin tablets that FDA considers suitable. Therefore, the dissolution requirements specified in § 310.500 for digoxin tablets are now obsolete.

Accordingly, FDA proposes to revoke § 310.500. This regulation is no longer necessary because the products, which are new drugs, can be regulated under the approval process for NDA's and ANDA's as set forth in section 505 of the act.

## **II. Proposed Effective Date**

FDA proposes that any final rule that may issue based on this proposal become effective 30 days after publication of the final rule.

## **III. Environmental Impact**

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## **IV. Analysis of Impacts**

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize the benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize any significant impact of a rule on small entities.

The agency has reviewed this proposed rule and has determined that it is consistent with the regulatory philosophy and principles identified in the Executive order and these two statutes. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of

costs and benefits for the proposed rule because the proposed rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation-adjusted statutory threshold is \$110 million. No further analysis is required under the Regulatory Flexibility Act because the agency has determined that this proposed rule will not have a significant effect on a substantial number of small entities.

Several studies have indicated a significant variation in the bioavailability of digoxin products for oral use. Concerned that this variation in bioavailability would adversely affect safety and effectiveness, FDA published the January 1974 regulation that established conditions for marketing digoxin products for oral use. This regulation included requirements for ANDA's and bioavailability test results for all oral digoxin products, a mandatory FDA batch certification program for digoxin tablets, and revised labeling for all oral digoxin products. On March 30, 1974, the requirements for labeling and ANDA submissions were stayed. On September 30, 1976, the agency lifted the stay for the labeling requirement. Digoxin tablets continue to be regulated under the certification procedure. On September 30, 1997, FDA approved an NDA for digoxin tablets. As a result, manufacturers of digoxin tablets are now eligible to obtain ANDA's. The agency is now publishing a notice reaffirming its determination that all oral digoxin products are new drugs and lifting the stay of the requirements for submitting ANDA's. Therefore, manufacturers of digoxin products will be required to obtain an approved marketing application to enter or remain on the market. As batch certifications are no longer considered necessary, this proposed rule would revoke the January 1974 regulation.

Presently, there are three manufacturers of digoxin tablets. Two of these companies have already obtained either an NDA or an ANDA. Once FDA requires these products to have approved applications for marketing, the remaining company will need to obtain an ANDA to remain on the market. In addition, FDA will require the two manufacturers of digoxin elixir to obtain approved applications. The agency estimates that it will take these companies up to 480 hours to complete the paperwork requirements associated with the submission of either an ANDA or a 505(b)(2)

application. Applying the 1999 labor rate of approximately \$41 per hour for a regulatory affairs specialist (with a 40 percent adjustment for benefits),<sup>1</sup> this one-time cost totals approximately \$60,000 (3 submissions x 480 hours x \$41/hour) for all current manufacturers, or \$20,000 (480 x \$41) per submission. FDA estimates that there were two market entrants over the past 10 years. Based on this data, the agency assumes that two manufacturers of digoxin products for oral use may enter the marketplace each decade, resulting in possible future submission costs for potential new manufacturers. Some additional annual costs may also be incurred over the life of the application. Although manufacturers may experience some savings from the removal of the batch certification requirement, this savings will be negligible.

According to the Small Business Administration, manufacturers of pharmaceutical preparations with 750 or fewer employees are considered small entities. Applying this definition, only one of the four current manufacturers that will incur submission costs is small. In addition, these costs are likely to represent less than 1 percent of gross revenue. Therefore, the agency certifies that this action will not have a significant economic effect on a substantial number of small entities.

#### **V. Paperwork Reduction Act of 1995**

This proposed rule does not require information collection subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (Public Law 104–13). The information collection consists of the submission of NDA's or ANDA's for digoxin products for oral use. The information collection requirements for the submission of NDA's and ANDA's are contained in 21 CFR part 314 and have been approved under OMB Control Number 0910–0001, which expires on November 30, 2001.

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<sup>1</sup> U.S. Department of Labor, Bureau of Labor Statistics, "1999 Occupational Earnings Data," Lawyer: <ftp://ftp.bls.gov/pub/special.requests/lf/aat39.txt>, 26 April 2000.

## VI. Requests for Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments regarding this proposal by [*insert date 90 days after date of publication in the Federal Register*]. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

### List of Subjects for 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 310 be amended as follows:

### **PART 310—NEW DRUGS**

1. The authority citation for 21 CFR part 310 continues to read as follows:

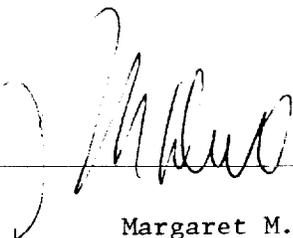
**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.

§ 310.500 [Removed]

2. Section 310.500 *Digoxin products for oral use; conditions for marketing* is removed.

Dated: 11-17-00

November 17, 2000



Margaret M. Dotzel  
Associate Commissioner for Policy

[FR Doc. 00-???? Filed ??-??-00; 8:45 am]

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