CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20405

ADMINISTRATIVE DOCUMENTS

SEP 30 1997

APPLICATION SUMMARY

NDA 20-405 Lanoxin (digoxin) Tablets (62.5, 125, 187.5, 250, 375, and 500 mcg)
Glaxo Wellcome Co.
Research Triangle Park, NC 27709
Date of Submission: September 30, 1993
Date of Labeling Submission: September 15, 1997

BACKGROUND

Please refer to the Application Summary dated 5/22/97 for a complete background of this application.

Medical

The labeling for this application was discussed with the firm in a meeting on July 28, 1997. At that time, most of the issues relating to the package insert were resolved. One issue, however, remained in question. The firm proposed to include a description of the results of the DIG trial in the clinical trials section of the labeling. Most of what the firm wanted to add were considered secondary endpoints of the trial. Since the primary endpoint of this trial was not statistically significant (mortality), Dr. Stockbridge did not believe that any results of the trial should be described in the labeling. The firm, however, thought that the information would be valuable to practitioners. It was decided at the meeting that a table should be created that would describe the results of the DIG trial. This table would be accompanied by appropriate disclaimers stating that the trial did not meet its primary objective.

The firm submitted a draft of their proposed table to Dr. Stockbridge. Initially, the firm only wanted to include data relating to hospitalizations due to CHF; Dr. Stockbridge thought that total hospitalizations was more appropriate. After consulting with Dr. Lipicky, it was decided that the data from both would be expressed in the table. Discussion was then initiated as to how the median time to event should be expressed. The firm thought that this information would be important to the practitioner, but the method of expressing this figure in the table could not be agreed upon. It was finally decided to delete all reference to median time to event and just include the hospitalization figures.

The labeling discussions were finalized on September 26, 1997. A clean draft of the labeling was created using the disc supplied by the firm. An approval on draft letter was prepared for Dr. Lipicky's signature.

Establishment Inspection

An acceptable establishment inspection was received on July 30, 1997.

Gary Buehler 9/30/97
Project Manager

Orig NDA
HFD-110
HFD-110 SBenton, HFD-110 GBuehler

OCT 26 1994

CSO OVERVIEW

NDA 20-405 · Lanoxin (digoxin) Tablets

Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Date of Submission: September 30, 1993

Date of Receipt: September 30, 1993

BACKGROUND

For background of this application, please refer to the application summary dated November 18, 1993.

MEDICAL - Dr. Rodin

Dr. Rodin recommended approval of the application on the basis of the results from the RADIANCE and PROVED trials. He did not believe that the firm should be awarded exclusivity for the add to ACE claim.

STATISTICAL - Dr. Nuri

Dr. Nuri stated he could not conclude that the patients receiving digoxin had statistically significant increases in exercise time over placebo. He did state, however, that the two major studies (RADIANCE and PROVED) resulted in significantly less treatment failures among the digoxin group than the placebo group.

PHARMACOLOGY - Dr. Resnick

No issues.

BIOPHARMACEUTICS - Dr. Fadiran

Dr. Fadiran thought that the pharmacokinetics section of the labeling should be revised. This was not done by the firm. Dr. Fadiran also made some recommended changes in the drafted labeling. These changes are listed in his review, but in light of the fact that Dr. Lipicky has decided not to change the labeling at this time, they may have to wait until the digoxin labeling is revised for inclusion.

Dr. Fadiran also recommended dissolution specifications. These will be included in the approvable letter.

CHEMISTRY - Ms. Cunningham

Chemistry deficiencies were faxed to the firm in March, 1994. To date, a response has not been received. Reference to the facsimile transmission will be included in the approvable letter.

ENVIRONMENTAL ASSESSMENT

Because this drug has been on the market for over 50 years, approval of this application will not affect the amount of digoxin introduced into the environment. An environmental assessment was not prepared for this application.

LABELING

Dr. Lipicky has decided that the labeling for this product need not be revised at this time. The application will be approved using the existing labeling. Changes will have to be made to the How Supplied section to incorporate the new tablets strengths that will be approved.

ESTABLISHMENT INSPECTION - METHODS VALIDATION

The establishment inspection has not been completed. Methods validation has also not been completed. These deficiencies will be added to the approvable letter.

DSI INSPECTIONS

The decision was made at the 45 day filing meeting that DSI inspections will not be required for this application. This decision was made jointly by Drs. Lipicky and Temple.

ACTION

An approvable letter will be drafted for Dr. Lipicky's signature. Existing deficiencies will be FPL including the new tablet strengths in the How Supplied section, Chemistry Deficiencies and Establishment Inspection.

Gary Buehler, CSO

Orig NDA
HFD-110
HFD-110 GBuehler

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG 8 1990

FROM: Director, Office of Drug Evaluation I
Director, Office of Drug Evaluation II

SUBJECT: Drug Studies in Pediatric Patients

TO: ODE I and II Directors, Deputy Directors, and Supervisory CSO's

The attached checklist, "Drug Studies in Pediatric Patients" (the "pediatric page"), has been drafted as part of our ongoing effort to heighten awareness of the need for information on the use of drugs in pediatric patients and transfer of that knowledge to product labeling. The checklist should be completed in the division and included in the action package for every new chemical entity recommended for approval. Although the checklist, as completed, will show the status of pediatric information at the time of preparation of the NDA action letter, completing it will require prior thought and action on the part of the reviewing division. In particular, for drugs that should be studied in pediatric patients after approval, the division will need to actively encourage the firm to conduct studies and to document the results of those discussions.

Robert Temple

Robert Temple, M.D.

James Bilstad

James Bilstad, M.D.

Attachment

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-405 Trade (generic) names Lanoxin (digoxin) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

X 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

This drug has been on the market for many years. The labeling contains very complete instructions for dosing in children. These instructions are probably not based on controlled clinical trials, but do come from years of experience using this drug in children.

Gary Buehler
Signature of Preparer

9/29/97
Date

cc: Orig NDA
HFD-__/Div File
NDA Action Package

Merrell

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**

Memorandum

DATE : OCT 26 1994

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 20-405, Digoxin (Trade Name, Lanoxin), Burroughs Wellcome

TO : NDA 20-405 File

Although digoxin is approved in the form of digoxin solution in a capsule (trade name, Lanoxicaps, approval in 1982) this tablet formulation of digoxin (trade name, Lanoxin), which is not bioequivalent to Lanoxicaps is not approved. Since it is not bioequivalent to Lanoxicaps, empirical proof of efficacy was required for its approval. Of interest is the fact that although digoxin (frequently used in the form of Lanoxin) is considered (along with diuretics) the mainstay of therapy for congestive heart failure (ACE inhibitors or other inotrope/vasodilator therapy is usually added to a regimen of digitalis (usually digoxin) and diuretics), yet data from major controlled clinical trials that show digoxin improves exercise tolerance and/or symptoms of congestive heart failure only became available recently (the most recent being publication of the data from the RADIANCE trial, in 1993). Until recently, using today's standards, Lanoxin could not have received a data dependant approval.

The data supplied by Burroughs Wellcome in NDA 20-405 consists of the results of 2 randomized, parallel group, placebo-controlled, withdrawal trials (RADIANCE and PROVED) that they sponsored, in which Lanoxin was used, and for which they had Case Report Forms. They also submitted reprints of 10 other published (the number of 10 includes one abstract, so, there were 9 full length publications), controlled, clinical trials (only one of these 9 publications (Lee, et. al., NEJM 306:699, 1982) was submitted previously in support of the Lanoxicaps NDA). The principal evidence for efficacy is derived from RADIANCE and PROVED; the published studies (one study, the milrinone-digoxin study, publication by DiBianco, NEJM 320: 677-683, 1989, stands out among them) offer good supporting data but the published studies alone, by today's standards, would have made an approval/non-approval decision a difficult judgement. It is notable, and in keeping with the historical use of digitalis in the treatment of congestive heart failure, that every placebo comparison (digoxin vs placebo) was essentially a digitalis withdrawal study (with the probable exception of the Lee publication (NEJM 306: 699-705, 1982) where diuretic therapy was the only mentioned background therapy as patients entered the

study. All other trials enrolled patients who had at least a 3 month history of digitalis usage, and digitalis therapy was stabilized and then withdrawn.

The doses of digoxin used in each of the trials, where it is listed in Dr. Rodin's review, varied between 0.125 to 0.5 mg/day. The digoxin dose was titrated to that which was considered, by the trial physicians, to be optimal but was monitored by measurement of serum concentration which was kept between 0.7 (2 trials), 0.9 (2 trials), 1.0 (1 trial), 1.5 (1 trial) and 1.7 (1 trial), 2.0 (2 trials), 2.5 ng/ml (3 trials). So the range of optimally titrated doses of digoxin was 0.125 to 0.5 mg/day and the resultant serum concentration had a range from 0.7 to 2.5 nanograms/ml. The mean digoxin dose in the RADIANCE and PROVED study was 0.38 mg/day and in the Milrinone-Digoxin study was 0.21 mg/day.

Of the 3 largest trials (RADIANCE, PROVED, Digoxin-Milrinone) where background therapy for the placebo group was only a diuretic, 377 (178 in RADIANCE, 88 in PROVED and 111 in Digoxin-Milrinone) patients with congestive heart failure on a stable dose of digoxin were randomized. Each, compared to placebo, had a statistically significant ($p = 0.05$, 0.003 and 0.003, for RADIANCE, Proved and Digoxin-Milrinone) better duration of maximal exercise in the digoxin group (45.5, 100.5 and 60 sec., respectively). In RADIANCE the distance walked in 6 minutes improved significantly (p 0.002, 0.045 and 0.021, for weeks 4, 8 and 10, respectively), trended in the right direction in PROVED but was not significant (only 88 patients randomized) and was not measured in the Digoxin-Milrinone study.

In the Captopril-Digoxin trial, compared to placebo, there was no difference in maximal exercise tolerance. However, this should not be viewed as a discrepant finding since the placebo group was receiving concomitant diuretics and captopril (not diuretics alone). It is known that captopril will increase maximal exercise tolerance and is consistent with (in fact led to labeling for captopril) the notion that ACE inhibitors do not depend upon the presence of digoxin to manifest their effects on exercise tolerance.

The results from the other published studies, most of them cross-over in design in randomized populations varying from 15 to 35 patients, were consistent with maximal exercise tolerance (when measured) being improved by digoxin but not always statistically significant.

Patients feeling better (symptoms, NYHA class, quality of life) were measured in various ways and in each of the studies, including publications, either trended in the right direction or were statistically significant with p values in the 0.003 range. That patients feel better when on digoxin is clear from the crudest of measures. For example in RADIANCE, 37% of patients randomized to placebo dropped out for

therapeutic failure vs 14% for patients randomized to digoxin. In PROVED dropouts for therapeutic failure were 46% for placebo vs 24% for digoxin. Kaplan-Meier estimates for the probability of treatment failure showed considerable superiority for digoxin, compared to placebo with p values of 0.003 and 0.04 for RADIANCE and PROVED, respectively.

In RADIANCE and PROVED, the LVEF deteriorated less in the digoxin groups and the Left Ventricular End Diastolic Volume increased less in the digoxin groups. Compared to placebo these changes had p values of between 0.001 and 0.04 except for the LVED in PROVED which had a p of 0.34 but was in the correct direction.

The Lee study is worthy of comment since it plays a unique role in this NDA consideration. Although the data are convincing that digoxin can be differentiated from placebo in a randomized withdrawal trial, one could, perhaps, not be willing to conclude that digoxin could be differentiated from placebo in a population with congestive heart failure but naive to digoxin. Or in other words, to what degree should one think that the results seen in the accumulated data are dependent in some adverse "rebound" effect of withdrawal. Would it be important to keep patients currently receiving digoxin on digoxin but never to start digoxin therapy for a patient who is not on digoxin (i.e., not running the risk of making the patient dependent upon digoxin)? The Lee trial addresses this question, since the patients enrolled in that trial were apparently naive to digoxin.

The Lee trial was small, only randomized 35 patients (with 10 of the 35 withdrawn, so it was really on 25 patients and 6 were receiving vasodilators) and not completely reported. The mean dose of digoxin was 0.435 mg/day. Nonetheless, the mean congestive heart failure score significantly ($p = 0.05$) favored digoxin and the LVED volume was decreased by digoxin ($p = 0.003$). It is of some importance that the Lee trial reported the mean dose of digoxin administered to be 0.435 mg per day; a larger mean dose than 0.38 mg/day (RADIANCE and PROVED) or the 0.21 mg/day (Milrinone-Digoxin study). This reflects the way in which the dose of digoxin has been decreasing over the years since the Lanoxicaps NDA was approved.

Since there is no data that would suggest that some form of withdrawal phenomenon is associated with withdrawal of digoxin, the reservation about accepting withdrawal data as definitive proof of efficacy is more a probabilistic reservation as opposed to a data-driven reservation. That combined with the Lee study are sufficient, I think, to allow acceptance of the withdrawal trial data to be considered substantially convincing that digoxin, in the form of Lanoxin is an effective therapy of congestive heart failure.

CONCLUSION and ACTIONS

Lanoxin should be approved and the RADIANCE as well as the PROVED trial should be considered as necessary for this action to be taken. That digoxin in the form of liquid in gelatin capsules (Lanoxicaps) was approved in 1982 should not influence thinking related to the necessity of RADIANCE and PROVED in 1994 for approval of a distinctly different dosage form of digoxin (this NDA, Lanoxin, NDA 20-405). For example, even though captopril was approved in 1988 (6 years after the Lanoxicaps approval) for the treatment of congestive heart failure on the basis of a single, placebo-controlled, exercise tolerance trial of 3 months duration, it would be impossible for another drug, even of the same pharmacological class, to be approved on the basis of a single trial even if it were as convincing as the captopril trial was. In 1982 ventricular premature beat suppression alone was considered sufficient for the approval of an antiarrhythmic agent, but now such evidence alone would be grossly insufficient (except under unusual circumstances).

It was mentioned above that the dose of digoxin, admittedly largely on a semi-anecdotal basis resulting from consideration of the notable adverse effects of digoxin, has gradually been decreasing over the last 20 years from the range of 0.25 to 0.5 mg/day (as was the practice that produced data resulting in the 1982 Lanoxicaps approval and the mean dose of 0.435 mg/day in the Lee study) to the current 0.125 to 0.25 mg/day (e.g., the mean dose of 0.21 mg/day in the Milrinone-Digoxin study). So the data submitted in this NDA (NDA 20-405) establish the efficacy of the currently used digoxin doses (the data in the Lanoxicaps NDA were at greater doses).

Over the last decade we have learned that short-term studies in congestive heart failure can lead to erroneous conclusions. The 3- to 6-month studies contained in NDA 20-405 are sufficiently long, although in fact borderline with respect to length, to qualify according to 1994 standards.

The 573 patients randomized in RADIANCE, PROVED, Digoxin-Milrinone and Captopril-Digoxin, give sufficient numbers to feel confident that digoxin does not adversely affect survival (survival actually being part of the combined end-point for RADIANCE and PROVED). Of course these studies have insufficient power to conclude that there is a favorable effect upon survival, but current standards simply require sufficient evidence to rule out obvious adverse effects upon survival of an agent for use in congestive heart failure that has positive inotropic properties. It is comforting also to know (not from data contained in this NDA) that regimens of other drugs (that include digoxin) are well known to have favorable effects upon survival.

So, in contrast to the 1982 approval of Lanoxicaps, the current NDA (with heavy reliance of RADIANCE and PROVED) allows one to conclude that Lanoxin, at doses that are currently prescribed has clinically relevant effects (decrease hospitalizations and mortality) as well as makes patients feel better (decrease symptoms and improve exercise tolerance). One could not have arrived at those conclusions from the data contained in the Lanoxicaps NDA; although one could, from that NDA, have surmised that digoxin improves exercise tolerance and symptoms at doses used 2 decades ago.

From a regulatory point of view, this approval establishes a standard (namely, Lanoxin from Burroughs Wellcome) that all other marketed formulations should use to establish bioequivalence, using current radio-immuno-assay techniques.

Raymond J. Lipicky, M.D.

cc
Orig.
HFD-110
HFD-110/CSO
HFD-110/RLipicky
sb/7/7/94;ef:8/10/94

EXCLUSIVITY SUMMARY for NDA # 20-405 **SUPPL #** _____

Trade Name Lanoxin **Generic Name** DIGOXIN
Applicant Name Glaxo Wellcome **HFD-** 110

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /+/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 9330 Lanoxin Inj

NDA # 18-118 Lanoxicaps

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) **Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?**

YES /X/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # -437

Investigation #2, Study # 436

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _ -437

Investigation #__, Study # _ -436

Investigation #__, Study # _____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /X/ Explain _____ NO /___/ Explain _____

May 5, 1997 req for exclusivity states studies were sponsored by Glaxo Wellcome (Burroughs Well.)

Investigation #2

YES /X/ Explain Same as #1

NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /X/ NO /X/

If yes, explain: The applicant should be awarded exclusivity for the CHF indication. No new studies were submitted for the ventricular rate control. They should not be given exclusivity for that indication.

Gary J. Buehler
Signature
Title: Reg Health Proj. Manager

5/20/97
Date

Ray Lipicky
Signature of Division Director

5/29/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

8/8/95

NDA 20–405 LANOXIN® (digoxin) Tablets

Item 13

Patent Information On Any Patent Which Claims the Drug (21 U.S.C. 355 (b) or (c))

Patent Information on Product of Burroughs Wellcome Co. Research Triangle Park, NC 27709

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

1. **Active Ingredient(s):** Digoxin
2. **Strength(s):** 62.5, 125, 187.5, 250, 375, and 500 µg
3. **Trade Name:** LANOXIN
4. **Dosage Form:** Tablets
5. **NDA Number:** 20–405
6. **Approval Date:** (not yet approved)
7. **Applicable Patent Numbers and Expiration Date:**

   No applicable patents govern our application for LANOXIN (digoxin) Tablets.