DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 80-936

AUG 24 1972

Barr Laboratories, Inc.
Attention: Mr. Stanley Benerofe
165 Livingston Street
Northvale, New Jersey 07647

Gentlemen:

Reference is made to your abbreviated new drug application dated February 29, 1972, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isoniazid Tablets, 100 mg.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved.

The periodic reporting requirements of Section 130.13(b)(4) of the new drug regulations are waived in regard to this application as published in the Federal Register of September 26, 1969.

Any significant change in the conditions outlined in this abbreviated new drug application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 130.9 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

The requirement for adequate data to assure the biologic availability is being deferred at the present time. However, our action in approving this application is based upon an understanding that if this requirement is reinstated you will perform the appropriate procedures.

The enclosures summarize the conditions relating to the approval of this application.

At the time of the next printing, however, revise the ADVERSE REACTIONS section as requested in our letter of May 22, 1972.

Please submit twelve copies of the revised package insert when available.

Sincerely yours,

Paul A. Bryan, M.D.
Director
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

Enclosures:
Conditions of Approval of a New Drug Application
Records and Reports Requirement

RECORDS AND REPORTS REQUIREMENT
(21 CFR 130.13)

130.13 Records and reports concerning experience on drugs for which an approval is in effect.

(a) On receiving notification that an application for a new drug is approved, the applicant shall establish and maintain records and make reports that are necessary to facilitate a determination whether there may be grounds for invoking section 505(e) of the Act to suspend or withdraw approval of the application, including adequately organized and indexed files containing full reports or any of the following kinds of information, pertinent to the safety or effectiveness of the drug or the adequacy of the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug to assure and preserve its identity, strength, quality, and purity, that has not previously been submitted as part of his application for the drug and which is received or otherwise obtained by him from any source:

(1) Unpublished reports of clinical experience, studies, investigations, and tests conducted by the applicant or reported to him by any person involving the drug that is the subject of the application and related drugs, and reports in the scientific literature involving the drug that is the subject of the application. An adequate summary and bibliography of reports in the scientific literature will ordinarily suffice. (The applicant must identify at the time of each report submission each drug he considers related to the subject drug.)

(2) Unpublished reports of animal experience, studies, investigations, and tests conducted by the applicant or reported to him by any person involving the drug that is the subject of the application and related drugs, and reports in the scientific literature involving the drug that is the subject of the application. An adequate summary and bibliography of reports in the scientific literature will ordinarily suffice. (The applicant must identify at the time of each report submission each drug he considers related to the subject drug.)

(3) Experience, investigation, studies, or test involving the chemical or physical properties or any other properties of the drug; such as, its behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug.

(4) The information required by this section shall include, when known, adequate identification of its source, including the name and post office address of the person who furnished such information.

(5) Copies of all mailing pieces and other labeling, and if it is a prescription drug all advertising, other than that contained in the application, used in promoting the drug;and copies of the currently used package labeling that gives full information for use of the drug, whether or not such labeling is contained in the application.

(6) Information concerning the quantity of the drug distributed, in a manner and form that facilitates estimates of the incidence of any adverse effects reported to be associated with the use of the drug. This does not require disclosure of financial or pricing data.

(7) Information concerning any previously unreported changes from the conditions described in an application, including changes conforming to the conditions of § 130.9(a)(5).

(b) The applicant shall submit to the Food and Drug Administration copies of the records and reports described in paragraph (a) of this section (except routine assay and control records) appropriately identified with the new-drug application(s) to which they relate, as follows. Such copies, including form FD-1639, shall be submitted in duplicate, except that other individual patient case reports may be submitted in single copy. In lieu of Form FD-1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion and if forwarded with the same number of copies as specified for Form FD-1639; all formats proposed for such use will require initial review and approval by the Food and Drug Administration. Each report for human-use drugs that forwards an advertisement or promotional labeling pursuant to subparagraph (3) of this paragraph or a periodic report pursuant to subparagraph (4) of this paragraph shall be accompanied by a completed transmittal form FD 2253 (Transmittal of Advertisements and Promotional labeling for Drugs for Human Use) or FD 2252 (Transmittal of Periodic Reports for Drugs for Human Use), respectively. Forms are obtainable from the Food and Drug Administration, Department of Health, Education, and Welfare, 200 C Street N.W., Washington, D. C. 20204.

(1) Immediately upon receipt by the applicant, complete records or reports covering information of the following kinds:

(i) Information concerning any mixup in the drug or its labeling with another article.

(ii) Information concerning any bacteriological, or any significant chemical, physical, or other change or deterioration in the drug, or any failure of one or more distributed batches of the drug to meet the specifications established for it in the new-drug application.

(2) As soon as possible, and in any event within 15 working days of its receipt by the applicant, complete records and reports concerning any information of the following kinds:

(i) Information concerning any unexpected side effect, injury, toxicity, or sensitivity reaction or any unexpected incidence or severity thereof associated with clinical uses, studies, investigations, or tests, whether or not determined to be attributable to the drug, except that this requirement shall not apply to the submission of information described in a written communication to the applicant from the Food and Drug Administration as types of information that may be submitted at other designated intervals. "Unexpected" as used in this subdivision refers to conditions or developments not previously submitted as part of the new-drug application or not encountered during clinical trials of the drug, or conditions or developments occurring at a rate higher than shown by information previously submitted as part of the new-drug application, or than encountered during such clinical trials.

(ii) Information concerning any unusual failure of the drug to exhibit its expected pharmacological activity.

(3) When mailing pieces, any other labeling, and advertising are devised for promotion of the drug, specimens shall be submitted at the time of initial dissemination of such labeling and at the time of initial publication of any advertisement for a prescription drug. Mailing pieces and labeling that are designed to contain samples of a drug shall be complete except for omission of the drug.

(4) All the kinds of information described in paragraph (a) of this section, other than that submitted under the provisions of subparagraph (1), (2), and (3) of this paragraph, shall be submitted at the following intervals, unless otherwise ordered in a written communication from the Commissioner:

(i) If the drug is intended for administration to man, within intervals of 3 months beginning with the date of approval of the application during the first year following such date; within intervals of 6 months during the second year following such date; and at yearly intervals thereafter.

(ii) If the drug is intended solely for administration to animals, at intervals within 6-months beginning with the date of approval of the application during the first year following such date, and at yearly intervals thereafter: Provided, however, that such reports are not required from applicants to the extent that the reporting obligation is based on their manufacture of complete medicated feed.

(iii) Whenever an applicant is required to submit reports under the provisions of subdivision (i) or (ii) of this subparagraph with respect to more than one approved application for preparations containing the same drug so that the same item(s) of information is (are) required to be reported for more than one application, he may elect to submit as part of the report for one such application all the information common to such applications in lieu of reporting separately and repetitively on each. The applicant shall state when this is done and identify all the applications for which the reports are submitted.

(iv) The submitted copies of records and reports shall include all the required information that was received or otherwise obtained by the applicant during the designated intervals.

(5) On written order of the Commissioner, within the time stated in such order or agreed to by the applicant and the Commissioner, any designated records or reports containing the kind of information described in this section.

(c) The reports submitted under the provisions of this section are not required to furnish the names and addresses of individual patients unless the applicant is notified in writing by the Food and Drug Administration that individual patient identification is required with respect to designated reports in order to permit further investigation or because there is reason to believe that such reports do not represent actual results obtained.

(d) The applicant shall upon request of any properly authorized officer or employee of the Department, at reasonable times, permit such officers to have access to and copy and verify any records and reports established and maintained under the provisions of this section.

(e) If the Food and Drug Administration finds that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with the provisions of this section, or that the applicant has refused to permit access to, or copying or verification of such records or reports, the Commissioner shall give the applicant due notice and opportunity for a hearing on the question of whether to withdraw the approval of the application, as provided in section 130.14 and 130.27.

(f) Upon written request of the applicant, stating reasonable grounds therefor, the Commissioner will make available any information in possesion of the Food and Drug Administration of the kinds the applicant is required to maintain under the provisions of this section, except information readily available to the applicant from other sources or information which the Commissioner concludes must be considered confidential.

(g) The "applicant" required to establish and maintain records and make reports required by this section and under the regulations in section 130.35 includes any person whose name appears on the labeling of the drug as its manufacturer, packer, or distributor under an approval or who is engaged in the manufacturing, processing, packing, or labeling of the drug under an approval of the application or any supplement to it; Provided, however, that in order to avoid unnecessary duplication in the submission of reports any such applicant's obligation to submit a report may be met by its submission on his behalf, designated as such, by another person responsible for reporting.

Conditions of Approval of a New Drug Application

The signing of the new drug application form is regarded as a commitment on your part that:

> All representations in the application apply to the drug produced until an approved supplement to the application provides for a change or a change is made in conformance with other provisions of § 130.9 of the new-drug regulations.
>
> The labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contra-indications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with § 1,106(b) (21 CFR 1,106(b)).

Section 505(e) of the Federal Food, Drug, and Cosmetic Act provides for approval of the application to be withdrawn if: clinical or other experience, tests, or other scientific data show that the drug is unsafe or not shown to be safe for use; further information indicates there is a lack of substantial evidence that the drug will have the effect it is represented to have; the application contains an untrue statement of material fact; the applicant fails to establish or maintain required records or make required reports; new information shows that the methods, facilities, or controls used in the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;or the labeling of the drug is false and misleading.

The drug may not be labeled with another distributor's name, or repacked, or relabeled by another person unless provided for in the approved application or in conformance with § 130.9 of the new drug regulations.

Section 301(l) of the Act prohibits the use in the labeling, or in any advertising, of any representation or suggestion that an application with respect to the drug is approved under section 505, or that the drug complies with the provisions of that section.

The approval of this application under section 505 in no way relieves you of the responsibility for complying with all other provisions of the Act.