Rx Drug Study Bulletin #231

DATE: November 4, 1977

TO: All REGIONAL FOOD & DRUG DIRECTORS
AND DISTRICT DIRECTORS
ATTN: NAS/NRC COORDINATORS
COMPLIANCE BRANCH CHIEFS

FROM Prescription Drug Compliance Branch, HFD-313
Division of Drug Labeling Compliance

SUBJECT Drug Products Containing Dipyrone

Re: Federal Register of June 17, 1977

On November 4, 1977, a Regulatory Letter was issued to firnns believed to be manufacturers, repackers, or distributors of drug products for human use containing dipyrone as a follow-up to the Federal Register notice of June 17, 1977. The letter requested the firms' intentions regarding discontinuance of marketing and removal of outstanding stocks from the market.

BACKGROUND:

Prompted by an increasing number of reports (between 1962 and 1964) of fatal agranulocytosis associated with aminopyrine and dipyrone (a sodium sulfonate derivative of aminopyrine) containing drugs, the Commissioner of Food and Drugs convened an ad hoc committee to study these drugs. As a result of their findings, the Commissioner concluded that these drugs were unsafe and were regarded as misbranded under Section 502 of the Federal Food, Drug, and Cosmetic Act when labeled or advertised for routine use as antipyretics or analgesics, and that such preparations were new drugs and might be approved as safe and effective for marketing on the basis of New Drug Applications containing restricted labeling and indications for use. Their use was to be restricted to their antipyretic effect in serious life where salicylates or similar drugs were known to be ineffective, contraindicated, or not tolerated. This resulted in promulgation of Part 201.311 of the CFR which declared all of these drugs to be new drugs and provided the labeling restrictions and indications for use.

Subsequently, thirteen cases of blood dyscrasia associated with the use of dypyrone were reported to FDA during the period from 1966 through 1975. Then of the thirteen cases were identified as agranulocytosis and four of the cases resulted in death.

In view of the toxicity of dipyrone, substantiated by the above, and the present availability of effective orally administered alternative drug products (e.g., aspirin and acetaminophen) and nonpharmacologic methods of antipyrietc therapy, the Director of the Bureau of Drugs published a Notice of Opportunity for Hearing in the Federal Register of September 3, 1976 (41 FR 37386) proposing the withdrawal of all NDA's (17) currently held for

dipyrone by nine different manufacturers. Subsequently, in the Federal Register of June 17, 1977 (42 FR 30893) a final order was published to withdraw all NDA's for human drugs containing dipyrone in that the drug had not been shown to be safe for use upon the basis of which the appiications were approved. In addition, all drug products that were identical, related, or similar to one of the drug products previously holding an approved NDA were subject to the notice.

The effective date of the announcement was June 27, 1977, and shipments thereafter in interstate commerce of the drugs listed in that notice, or of any identical, related, or similar product, not the subject of an approved NDA, was unlawful based on Section 505.

Part 201.311 of the CFR will be deleted as a result of withdrawal of the approvals for these NDA's. Attached are copies of the letter issued to firms in your District, and an information copy of the form letter to those Districts with no applicable firms. The Division of Drug Labeling Compliance will monitor the firms' replies, furnish the District with copies of such replies, and issue assignments where indicated. Although this is not a DESI drug, the same procedures for follow-up will be utilized.

Please submit labeling and FD-3033's for any additional drug products for human

use containing dipyrone or aminopyrine so that we may institute follow-up where indicated.

Albert Lavender, Chief
Prescription Drug Compliance Branch

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

November 4, 1977

REGULATORY LETTER

CERTIFIED

File No.: 77-HFD-313-
PRODUCT:

Gentlemen:

This letter is in reference to the drug product listed above which you market containing aminopyrine or dipyrone.

Title 21 of the Code of Federal Regulations Part 3.44, recodified as 21 CFR 201.311, copy enclosed, declared all drug preparations for human use containing aminopyrine or dipyrone to be new drugs and subject to the requirements of Section 505 of the Federal Food, Drug, and Cosmetic Act. New evidence of clinical experience, not contained in New Drug Applications filed pursuant to Section 505, or not available until such applications were approved, evaluated together with the evidence available when the applications were approved, showed that such drugs are not shown to be safe for use under the conditions of use on the basis of which the applications were approved as set forth in that regulation.

The Food and Drug Administration published in the Federal Register of September 3, 1976 (41 FR 37386) a Notice of Opportunity for Hearing proposing to withdraw approval of the New Drug Applications for drug products for human use that contained dipyrone, a sodium sulfonate derivation of aminopyrine. The action was takn on the basis of new reports of agranulocytosis, sometimes fatal, associated with the use of dipyrone and because of the present availability of effective alternative drug products and effective non-pharmacologic therapy that thave less potential for risk.

The Notice stated that the failure of the manufacturer or distributor of any identical, related, or similar drug product to submit objections and a request for hearing would result in the withdrawal of approval of the New Drug Applications and in regulatory action against all such products. The Food and Drug Administration received no objections or requests for hearing from you pursuant to that Notice with respect to the drug product listed above. Subsequently, on June 17, 1977, a notice was published in the (42 FD 30893), withdrawing approval of the New Drug Applications of all dipyrone and aminopyrine containing products. Copies of both these Federal Register notices are enclosed.

It is the opinion of the Food and Drug Administration that your drug product listed above is identical, related, or similar to the drugs for which the New Drug Applications have been withdrawn pursuant to the Federal Register notice of June 17, 1977. Accordingly, continued marketing of the above named drug product without an approved New Drug Application constitutes a violation of Section 505 of the Federal Food, Drug,and Cosmetic Act, 21 U.S.C. 355. It is our position that such drugs have not been shown to be safe for use upon the basis of which the applications were approved, and pursuant to the authority set forth in Section 505(e), the above notices were published.

We request that you reply within ten (10) days after receipt of this letter, stating the action you will take to discontinue the marketing of your product listed above, and any identical or similar products containing aminopyrine or dipyrone which you may market. If any significant stocks of the drug remain in trade channels at this time, we will require that they be recalled down to the retail level. If such corrective action is not promptly undertaken, the Food

and Drug Administration is prepared to initiate legal action to enforce the law. The Federal Food, Drug, and Cosmetic Act provides for seizure of illegal products, injunction against the manufacturer or distributor of such products, and criminal prosecution of individuals and companies who manufacture or distribute illegal products (21 U.S.C. 332 and 334).

We request that your reply include (1) an estimate of the size and frequency of shipments within the past 12 months; (2) an estimate of the amount of the drug listed above that is in inventory under your control and that which remains in channels of distribution outside your control; (3) in the event that you have already discontinued marketing this drug product, the date of discontinuance; and (4) your intentions with respect to the disposition of your inventory and the withdrawal of outstanding stocks from trade channels.

Your reply should be directed to Michael A. Chappel, Project Officer, Prescription Drug Compliance Branch (HFD-313), Divsion of Drug Labeling Compliance, Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland, 20857.

Sincerely yours,

T.E. Byers
Associate Director for Compliance
Bureau of Drugs

Enclosures:
FR 9/3/76
FR 6/17/77
21 CFR 201.311