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Report to Congressional Requesters

April 1993

# FDA PREMARKET APPROVAL

## Process of Approving Lodine as a Drug





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**United States**
**General Accounting Office**
**Washington, D.C. 20548**

**Human Resources Division**

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April 12, 1993

The Honorable William J. Hughes
Chairman, Subcommittee on Intellectual
Property and Judicial Administration
Committee on the Judiciary
House of Representatives

The Honorable Dennis DeConcini
Chairman, Subcommittee on Patents,
Copyrights, and Trademarks
Committee on the Judiciary
United States Senate

The Honorable Frank R. Lautenberg
United States Senate

Wyeth-Ayerst Laboratories, a division of American Home Products Corporation, is the beneficiary of a patent[1] for Lodine, a nonsteroidal, anti-inflammatory drug (NSAID). The patent for Lodine was granted in February 1978 and is scheduled to expire in February 1995. However, under provisions of the Drug Price Competition and Patent Term Restoration Act of 1984,[2] the patent expiration date was extended until February 1997.

Wyeth-Ayerst plans to seek passage of a private bill in the 103rd Congress that would provide for an extension of the Lodine patent term beyond 1997 because the company believes that the length of time needed to obtain FDA premarket approval was excessive. In this regard the company submitted a new drug application (NDA) to the Food and Drug Administration (FDA) in December 1982 for approval to sell Lodine, but FDA did not approve the application until January 1991. Wyeth-Ayerst contends that the 97-month period taken by FDA to grant approval deprived the company of a substantial period of effective patent protection.

To assist in congressional deliberations regarding the merits of extending the Lodine patent, your offices asked us to review the events surrounding the approval of Lodine and clarify the related circumstances. We did not

[1]Patent laws give inventors in the United States the right to exclude others from making, using, or selling their inventions for a period of 17 years. This right is granted in exchange for the public disclosure of their inventions.

[2]The patent term extension provisions of this act provide a means for restoring a limited portion of patent term where federal regulatory approval procedures, rather than the actions of the patentee, have reduced the exclusive marketing life of a new pharmaceutical, food, or color additive.

determine whether it would be appropriate to extend the patent term for Lodine.

We reviewed relevant documentation from both FDA and Wyeth-Ayerst files for December 1982 through January 1991 and interviewed agency and company officials. FDA and Wyeth-Ayerst officials did not always agree on the circumstances, and documentation of events was often contradictory or nonexistent.

Our work was performed from June through November 1992 in accordance with generally accepted government auditing standards. We discussed pertinent information contained in our report with FDA and Wyeth-Ayerst officials. In several cases, Wyeth-Ayerst officials disagreed with FDA's characterization of events. We note these differences in the relevant sections of the report. Officials from FDA's Center for Drug Evaluation and Research generally agreed with our characterization of events. However, in accordance with your request, we did not obtain written comments on a draft of this report.

## Background

FDA's Center for Drug Evaluation and Research reviews new drugs for which market approval is sought. Within the Center, the responsibility for approving NSAIDs rests with the Pilot Drug Evaluation Staff. When Wyeth-Ayerst submitted its Lodine NDA in 1982, the agency had already approved ten other NSAIDs, taking an average of 27 months to approve them.

The Pilot Drug Evaluation Staff assigns reviewers from various disciplines (such as medicine, pharmacology, and chemistry) to each NSAID application. These specialists evaluate a drug in terms of their own expertise. For example, pharmacologists evaluate test results on laboratory animals,[3] and medical reviewers evaluate clinical test results on humans.

FDA assigns review priority to NDAs based on the drug's chemical type and potential therapeutic benefit to the public. FDA assigned its lowest priority—a "C" ranking—to Lodine. This priority indicated the drug had essentially the same therapeutic importance and use as the other 10 NSAIDs already on the market. Other FDA priority review categories then in use

[3]Data about a drug's effects in animals help establish boundaries for safe use of the drug in human testing.

were: "A" drugs (expected important therapeutic gain) and "B" drugs (potentially modest therapeutic gain).

Wyeth-Ayerst alleges that its Lodine NDA was a victim of inordinate delays because (1) extraordinary circumstances required FDA to divert attention from reviewing the Lodine NDA and (2) FDA did not exercise due diligence in reviewing Lodine. Company officials argue that FDA concentrated on responding to congressional concern about other NSAIDs' safety and that this created a medical reviewer shortage. The company further alleged that FDA waited too long to assign medical reviewers and that the diversion of reviewers to other activities did not justify this delay.

In January 1991, FDA concluded that Lodine was effective for treatment of analgesia and osteoarthritis and granted Wyeth-Ayerst approval to market Lodine for those conditions. Although the company has not received approval to claim that Lodine is safe and effective for rheumatoid arthritis, research is continuing, and the company plans to submit an indication for rheumatoid arthritis when this research effort is completed.

## Results in Brief

In 1982, FDA was faced with the unusual situation of having to resolve problems that were occurring because patients were having adverse reactions with several approved NSAIDs. Because of these public health concerns FDA began to review new NSAID applications, including the Lodine NDA, more closely to assure that any newly approved NSAID would not cause similar conditions. As a result, FDA's average time for reviewing NSAID applications doubled after 1982. In addition, FDA assigned a lower priority of review to Lodine compared with other NSAIDs that had higher therapeutical values.

Wyeth-Ayerst claims that FDA was responsible for unwarranted delays—adverse drug reactions, lack of medical review, and the Canadian carcinogenicity concern—that occurred between 1982 and 1986. The company also claims that FDA began to devote more attention to the application beginning in December 1986.

FDA disagrees with Wyeth-Ayerst's belief that FDA did not exercise due diligence in reviewing the Lodine NDA and took too long in assigning medical reviewers. FDA officials' position is that the Lodine application was very difficult to review because the submissions were voluminous and the clinical tests had many flaws. In addition, a concern raised by the Canadian government that Lodine was potentially carcinogenic in animals

caused the agency to delay assigning medical reviewers. FDA claims that if a potential exists that an NDA may be terminated, it will not assign a medical reviewer because of resource demands.

## Principal Findings

The following sections discuss the major events that transpired from when the Lodine NDA was filed in December 1982 until it was approved in January 1991.

The major events were (1) the average processing time for NSAIDs increased, (2) the data supporting the Lodine NDA was difficult to review, and (3) the Canadian government raised a safety carcinogenicity issue concerning Lodine.

### NSAID Review Time Increased

Wyeth-Ayerst believes that FDA diverted its attention to unexpected events that increased FDA's review time for the Lodine NDA. Wyeth-Ayerst's request for a 70-month patent term extension was based on the 97 months that FDA took to approve Lodine less the 27-month average review time. The company expected FDA to take 27 months to approve the Lodine NDA because this was FDA's average time for approving all new NSAID applications before December 1982.

However, in 1982, when Wyeth-Ayerst submitted the original Lodine application, events were occurring that doubled this average. Furthermore, Lodine had a low review priority within FDA because comparable drugs were already on the market, and NSAIDs with the lowest review priority, such as Lodine, generally move slower through the FDA review process. Whereas the average approval time for all NSAIDs jumped from 27 to 53 months, the average approval time for "C" NSAIDs like Lodine jumped from 31 to 73 months.[4] The Lodine NDA took 24 months longer than the 73-month average because of other mitigating circumstances described later in this report.

From mid-1982 through mid-1987, FDA faced an unusual set of events. Reports of fatal, near-fatal, and other adverse reactions to four approved NSAIDs alarmed the public, the Congress, and FDA. Manufacturers removed or halted sales on the four NSAIDs, and the Congress held several hearings about reported side effects. During this time, FDA received criticism of its

[4]For the period 1974 to 1982, the 27-month average included 10 NSAIDs—6 priority "C" NSAIDs averaged 31 months; and 4 priority "B" NSAIDs averaged 21 months. For the period 1984 to 1991, the 53-month average included 12 NSAIDs—7 priority "C" NSAIDs averaged 73 months; 4 priority "B" NSAIDs averaged 25 months; and one priority "A" drug was 28 months.

NSAID approval process. In December 1982, just after this crisis began, Wyeth-Ayerst submitted the Lodine NDA.

The problems with the NSAIDs did not cause FDA to shift staff from the Lodine review. Instead, its officials said that reviewers began looking closer at new NSAID applications to assure the new drugs were not causing similar adverse reactions. This made reviews of these drugs more time-consuming.

In addition, during the time Lodine was in the FDA approval pipeline, the agency was also reviewing (1) higher priority NSAIDs, (2) other "C" priority NSAIDs received before the Lodine NDA, and (3) paper NDAs.[5] FDA officials stated that management decided to give a high priority to paper NDAs to make new generic drugs available to the public as soon as possible.

## Application Difficult to Review

Wyeth-Ayerst believed that FDA was not diligent enough when reviewing the Lodine application and waited too long to assign a medical reviewer. However, according to FDA officials, this was a very difficult application to review. Officials maintain that the Lodine submissions were piecemeal, voluminous, disorganized, and the clinical tests had flaws.

### Piecemeal Submissions

Wyeth-Ayerst submitted the Lodine NDA in a piecemeal fashion, and did not submit enough data to prove efficacy until September 1989, or nearly 7 years after the original Lodine submission, FDA officials argue. The company's intent was to obtain approval for Lodine to be sold to treat both arthritis and analgesia. However, the company only requested approval for analgesia in the original NDA because, according to FDA, the company's clinical data supporting Lodine's use for arthritis was not ready.

FDA officials said that the original NDA lacked sufficient safety data even for analgesia approval. In an October 1983 amendment to the Lodine NDA, the company provided additional safety data for analgesia and added rheumatoid arthritis and osteoarthritis to the NDA. However, it was not until after the company provided two studies in a September 1989 submission that FDA deemed the NDA approvable for osteoarthritis. Lodine has not been approved for rheumatoid arthritis.

Wyeth-Ayerst submitted voluminous amendments to the original application between 1983 and 1989. Of the more than 2,100 volumes

[5]Paper NDAs are generally supported by published research rather than original studies conducted by the sponsor. Paper NDAs are submitted when seeking approval for new generic drugs.

submitted by the company, over 1,400 were part of amendments to the original application. (For a list of major submissions and volumes, see app. II.) FDA officials said that an NSAID application has no average size, but the Lodine NDA was much larger than most reviewed. According to Wyeth-Ayerst officials, the reason for the voluminous NDA was that testing of Lodine continued while FDA was reviewing the NDA. As a result, the company was reporting updated data throughout the long review period.

FDA officials also contended that poor organization of the amendments added to the difficulty. An FDA official said that the piecemeal and poorly organized submissions caused reviewers to constantly backtrack to answer questions arising from the more recent submissions. FDA officials asserted that (1) the main points were not clear, (2) the company modified previously reviewed interpretations, and (3) data were not appropriately linked together. Wyeth-Ayerst officials, on the other hand, believed that the Lodine application was not piecemeal or incomplete but instead, subject to ongoing clinical trials. Because the Lodine NDA was pending for so long, additional information from these trials had to be added to the record. The company maintains that these additional submissions provided FDA with updated clinical results, rather than supplementing the original application.[6]

## Adequacy of Clinical Studies

Weaknesses in the clinical data submitted by the company also delayed approval of Lodine because FDA officials believed the clinical tests had used dosages that were too low to prove safety and efficacy. Wyeth-Ayerst officials told us that FDA did not inform the company of the minimum acceptable dosage until January 1989 and that the company responded by compiling and submitting necessary data within 9 months.

Wyeth-Ayerst officials said that if FDA had performed an adequate medical review sooner and informed the company of the dosage level it required, the company would have submitted this data much earlier. FDA's Chief Medical Reviewer said that he had been aware of the weaknesses in the clinical tests that supported the NDA submissions between 1982 and 1984, and orally communicated his concern to the company. He did not document the contacts. Wyeth-Ayerst officials denied receiving feedback regarding clinical deficiencies.

According to FDA officials, another problem was the design of Wyeth-Ayerst's clinical trials. For example, agency officials said that

[6]In January 1988, in an attempt to help FDA complete its review, Wyeth-Ayerst resubmitted the NDA in computer form. Although the electronic version initially had errors, FDA and Wyeth-Ayerst officials said that it ultimately expedited the review.

patients in a study were asked questions that were not specific enough to address a physical condition, and this resulted in a misleading high number of possible drug reactions that were not relevant to Lodine. In fact, in some cases, groups that were receiving placebos (inert or nondrug substances) experienced more adverse affects than patients receiving Lodine.

Sometime between 1989 and 1991, the FDA staff director developed a special mathematical procedure that would identify those patients that were having adverse affects from Lodine with the patients whose adverse affects were not related to the drug. Developing the mathematical procedure took about 6 months.

Wyeth-Ayerst officials agreed that problems did exist with the clinical trial methodology and that FDA did considerable work to obtain interpretable results. However, Wyeth-Ayerst believes that these problems occurred after 1986—a time period that the company believed that FDA was diligently reviewing the Lodine NDA. Further, company officials argued that clinical trial designs always contain some flaws.

In addition, an anonymous letter was received by FDA in 1986, alleging that Wyeth-Ayerst was manipulating its Lodine clinical trial results. This undermined FDA's confidence in the data's credibility and caused FDA reviewers to take additional time to look at the data more carefully. FDA inspectors could not prove the allegation, but concluded that the company's internal controls over the trial results were not adequate to assure that the data could not be manipulated. According to FDA officials, the company acknowledged this weakness and established a system for better control over the trial data.

## Canadian Government Concern

Independent of the FDA review, the Canadian government was reviewing an application to market Lodine in Canada. During its review, Canada raised a carcinogenicity safety issue in May 1984 to FDA concerning Lodine. However, Wyeth-Ayerst contends that FDA took too long to resolve the carcinogenicity safety issue. Because of its limited staffing resources, FDA wanted to resolve this issue before assigning a medical reviewer to the Lodine application.

In February 1983, Wyeth-Ayerst filed an application with the Canadian government to market Lodine in that country. About 6 months before submitting the January 1985 updated safety and clinical trial data to FDA,

the company notified FDA that the Health Protection Branch (HPB)—the Canadian equivalent to the FDA—was concerned that Lodine might be potentially carcinogenic in animals. Although FDA officials believed that the evidence did not link Lodine to cancer, they felt they needed to assess Canada's analysis to assure that the drug was safe for humans.

About January 1986, HPB informed FDA that it was satisfied that Lodine was not a carcinogen. However, one Canadian pharmacology reviewer disagreed with the official HPB position and, in February 1986, sent his analysis to FDA. Two FDA pharmacologists separately reviewed the Canadian's analysis in March and July 1986, respectively, and concluded that cancer was not a concern.

Wyeth-Ayerst believes that FDA was not justified in taking more than a year after being notified of Canada's concern to resolve the carcinogenicity issue. They argue that FDA had the same data as HPB and should have completed its analysis and drawn a conclusion without waiting for HPB's results. However, according to FDA officials, different reviewers looking at the same data often get different results. FDA officials said that it was essential to review the Canadian reviewer's analysis to assure themselves that they were looking at the same data and evaluate why the Canadian reviewer's results differed from their own.

## Medical Reviewer

The medical reviewer, who evaluated the December 1982 and October 1983 submissions, left the agency in November 1985. Between Wyeth-Ayerst's January 1985 update and June 1986, FDA did not assign another medical reviewer to Lodine. According to FDA officials, they waited until June 1986 because they wanted to resolve the carcinogenicity issue raised by the Canadian government. Agency officials said that if this animal safety concern had proven valid, Wyeth-Ayerst might have stopped developing Lodine. However, Wyeth-Ayerst officials argued that Lodine's development was never doubtful, and the Canadian issue did not justify FDA's delay in assigning another medical reviewer.

A newly assigned medical reviewer did not begin working on Lodine until about December 1986 because he was completing work on another drug. According to FDA officials, when the medical reviewer started, he initially examined all of the previously reviewed submissions and read the comments made by the previous reviewer. Wyeth-Ayerst officials stated that the new medical reviewer did not actually start reviewing the January 1985 submission until about 1988. The company further contends that it should not be penalized for the time spent by the new reviewer

before 1988 to familiarize himself with prior submissions. We found, however, that whenever a company submits a major update, FDA reviewers go back to the prior submissions. This is to assure themselves that data necessary to perform the review are present and consistent among all of the submissions.

Unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days after its issue date. At that time, copies of this report will be sent to appropriate congressional committees and subcommittees, the Secretary of Health and Human Services, the Commissioner of Food and Drugs, and other interested parties. It also will be made available to others on request.

I may be reached at (202) 512-7118 if you or your staff have any questions. Other major contributors are listed in appendix III.

Leslie G. Aronovitz
Associate Director, Health
Financing Issues

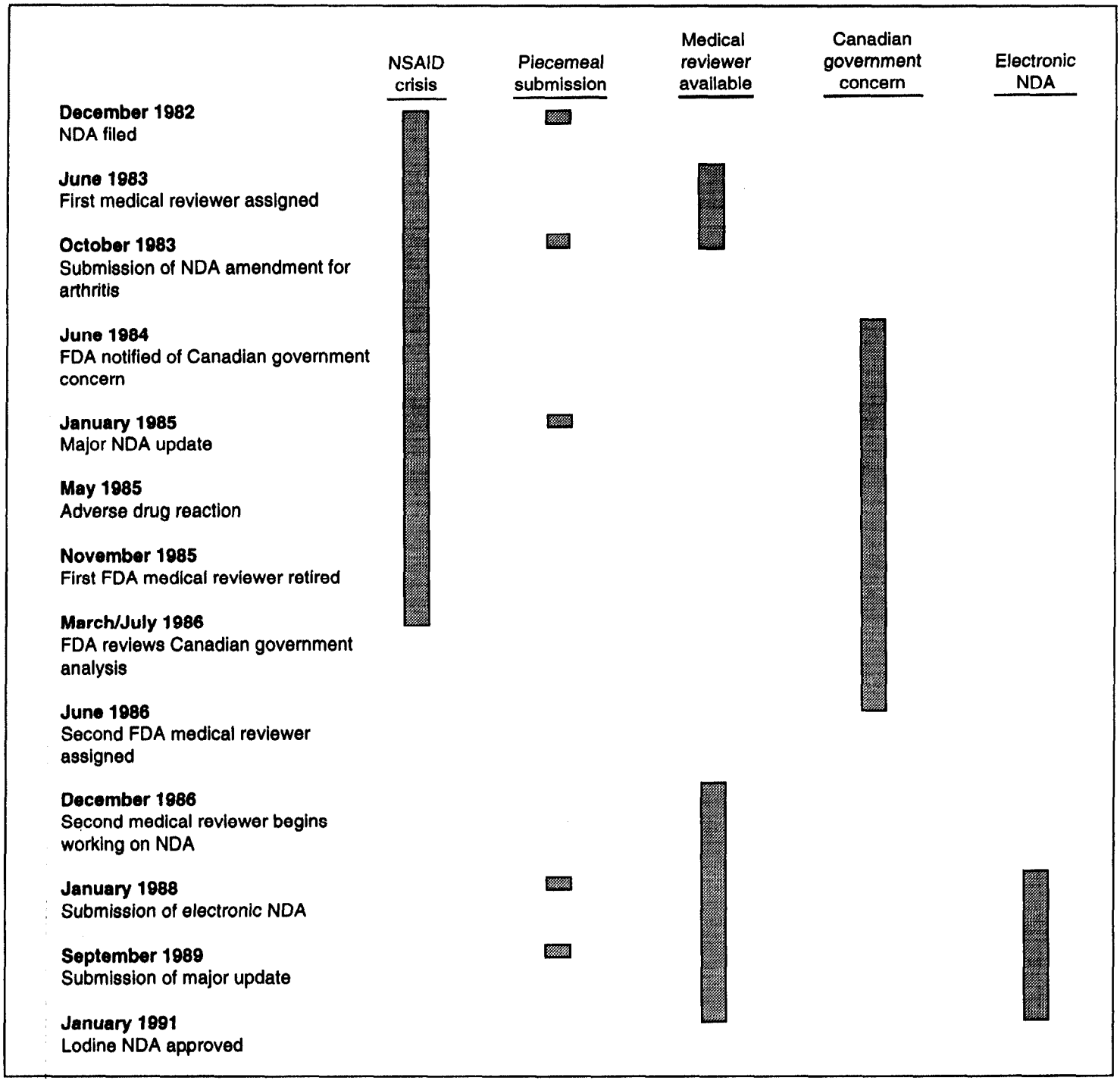
# Contents



**Abbreviations**

| | |
|---|---|
| ADR | adverse drug reaction |
| FDA | Food and Drug Administration |
| GAO | General Accounting Office |
| HPB | Health Protection Branch |
| NDA | new drug application |
| NSAID | nonsteroidal, anti-inflammatory drug |

# Timeline of Events Affecting Lodine Approval (1982-91)



# Wyeth-Ayerst's Major Submissions

| Date | Phase of process | Number of volumes |
|---|---|---|
| 12/82 | Initial NDA—Analgesia | 702 |
| 10/83 | Amendment—Osteoarthritis and Rheumatoid Arthritis | 235 |
| 1/85 | Update—safety and clinical trials | 194 |
| 5/85 | Adverse drug reactions (ADRs) | 280 |
| 9/89 | Update—safety and clinical trials | 718 |
| **Total** | | **2,129** |

Note: Although the table shows the major submissions, not all submitted volumes are listed.

# Major Contributors to This Report

| | |
|---|---|
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