United States General Accounting Office

GAO

Report to Congressional Requesters

August 2000

PRESCRIPTION DRUGS

Many Factors Affected FDA's Approval of Selected "Pipeline" Drugs

GAO/HEHS-00-140

Contents

Abbreviations

CAC	Carcinogenicity Assessment Committee
FDA	Food and Drug Administration
IND	investigational new drug
NDA	new drug application
NSAID	nonsteroidal anti-inflammatory drug
OTA	Office of Technology Assessment
PDUFA	Prescription Drug User Act of 1992

B-283293

August 10, 2000

Congressional Requesters

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Waxman-Hatch Act, sought to improve public health by encouraging the availability of more effective and affordable drugs while balancing the interests of generic and brand name pharmaceutical manufacturers.[1] The act provided the generic drug industry a simplified and faster review process for generic versions of brand drugs that are typically available to consumers at lower prices. The act also provided brand name drug companies an extension of the existing 17-year patent protection as an incentive to develop innovative new medications. For drugs that were not yet patented, or were patented but had not yet begun human clinical trials at the time of the law's enactment, the act provided up to a 5-year patent extension. However, the law limited the extension to 2 years if a patent for a drug had been issued and human clinical trials had begun at the time of the law's enactment. The 122 drugs that were limited to the 2-year extension are commonly referred to as "pipeline" drugs.

Recently, legislation (H.R. 1598 and S. 1172) was introduced to institute a process by which the manufacturers of pipeline drugs that took longer than 5 years to be approved and whose patents were still in effect could apply for a patent extension. Seven of the 122 pipeline drugs would be eligible for review under this proposal.[2] To assist the Congress as it considers this

[1]A brand name drug company manufactures drugs that are sold under a registered brand name either by its innovator (that is, the manufacturer that holds the patent on the drug) or by a company that has an exclusive license from the innovator to sell the drug. Generic drug companies sell equivalent versions of brand name drugs. A generic drug contains a biologically active drug identical to its brand name counterpart; however, the inactive ingredients and manufacturing process may differ. A generic drug, which cannot be marketed until the exclusive patent period for the brand name drug has expired, is normally sold under the drug's generic (that is, scientific) name.

[2]The seven drugs are Claritin (an antihistamine manufactured by the Schering-Plough Corporation), Relafen (a nonsteroidal anti-inflammatory drug used for relieving pain made by the SmithKline Beecham Corporation), Cardiogen-82 (a diagnostic imaging agent marketed by Bracco Diagnostics), Dermatop (a corticosteroid for skin conditions manufactured by Aventis Pharmaceuticals), Eulexin (a prostate cancer drug manufactured by the Schering-Plough Corporation), Nimotop (a calcium channel blocker made by the Bayer Corporation), and Penetrex (an antibiotic made by Aventis Pharmaceuticals).

proposal, you asked us to examine the Food and Drug Administration's (FDA) review and approval of the manufacturers' applications to market seven drugs that would be covered by the proposed legislation. Specifically, we examined (1) the review and approval times for the seven pipeline drugs in comparison with other drugs and the factors that contributed to the time FDA required to approve the three of the seven drugs for which the manufacturers agreed to supply us information and (2) whether the Congress based the 2-year patent extension granted to pipeline drugs on the assumption that FDA action on these drugs' applications would occur within the average length of time for FDA approval of new drug applications.

To examine these issues, we obtained information from FDA on drug approval times, reviewed drug files at FDA, and examined material provided by the drug companies that hold the patents for three of the seven pipeline drugs that would be covered by the proposal. Our examination of the factors that affected approval times for the four other drugs was limited because the manufacturers were either unable to supply or uninterested in supplying information we needed for our study.[3] We also reviewed the legislative history of the Drug Price Competition and Patent Term Restoration Act of 1984 and spoke with government and industry officials about the drug review process. (Detailed information about our methodology is in appendix I.) We conducted our work between October 1999 and June 2000 in accordance with generally accepted government auditing standards.

Results in Brief

The times taken to approve the seven pipeline drugs that would be eligible for review under the proposed legislation were significantly longer than the corresponding average approval times for pipeline drugs of the same chemical type and potential therapeutic benefit.[4] In all cases, the time from submission of applications to approval for the seven pipeline drugs ranged from 17 to 65 months longer than the average time for comparable pipeline

[3]The manufacturer of one drug could not provide us with information on its product while a second did not intend to request a patent extension. The two other companies said that the effort necessary to gather the data we needed would not be worthwhile.

[4]FDA classifies each product according to chemical type and therapeutic potential when it receives an application. In order to make our comparison groups as similar to the pipeline drugs as possible, we compare drugs only of the same chemical type and therapeutic potential. More information on these categorizations is in appendix I.

drugs. In general, the delays in FDA's approving the new drug applications for the three pipeline drugs on which our study focused were a result of concerns about the safety and efficacy of the drugs, as well as their chemical properties and manufacturing procedures. In addition, the applications for two of the drugs filed by the manufacturers lacked essential information. However, the specific concerns varied by drug. For Claritin, there was debate within FDA and with Schering-Plough on the significance of the animal carcinogenicity data for humans. FDA and Schering-Plough also disagreed on how the equivalence of two forms of the drug should be established. Regarding Relafen, FDA was concerned about adverse events associated with similar medications and believed there was a lack of information in the manufacturer's new drug application (NDA) on the chemical properties of the drug, including its composition and how it was manufactured. For Cardiogen-82, FDA found the NDA to be incomplete. The agency believed that the data that were initially submitted were insufficient to establish the efficacy of the drug and did not adequately describe the components of the drug and the manufacturing process.

The legislative history of the Waxman-Hatch Act does not explain the basis for the patent extension time periods and discusses the use of different extension periods only in general terms. The overall purpose of the patent extensions, according to the House Energy and Commerce committee report, was to create incentives for increased expenditures for research and development.[5] There is no explicit explanation, however, why a 2-year limit was chosen for pipeline drugs or why a 5-year limit was chosen for other drugs. A congressional staff member and pharmaceutical industry representative who were involved in the development of the act have written that the 2-year limit was originally suggested, in part, because it reflected the average NDA approval time.[6] However, we cannot substantiate that contention from the legislative history, and other possible explanations exist.

[5]H. Rep. No. 98-857, Part I, at 15, 40-41 (1984), reprinted in 1984 U.S.C.C.A.N. 2648, 2674. There was no conference report and no relevant Senate report language.

[6]A report issued by the Office of Technology Assessment (OTA) in 1981 stated that the average review time for NDAs "is frequently about 2 to 3 years." OTA, *Patent-Term Extension and the Pharmaceutical Industry* (Washington, D.C.: 1981), p. 66.

Background

In the development of a new drug, much happens before FDA becomes directly involved. Companies search for promising chemical entities, test them in their laboratories, and conduct animal studies using them, generally without FDA's direct involvement and often without FDA's knowledge. This is the "preclinical" stage of drug development. FDA must be directly involved before any testing on human subjects can begin in the United States. To get FDA's permission to begin clinical trials (studies in humans), a company must sponsor an investigational new drug (IND) application that summarizes the data that have been collected on the potential new drug and outlines the plans for the clinical trials. FDA does not approve INDs. Rather, an IND goes into effect and clinical trials can begin 30 days after FDA receives the IND, unless FDA objects to the clinical trials and places a clinical hold on it. Companies that develop innovator or brand-name drugs generally obtain a patent on the active ingredient used in the drug. They also obtain patents on the uses of drugs to treat certain diseases and conditions. Generally, patents are obtained before a company submits an IND to begin clinical trials.[7]

Before marketing a new prescription drug in the United States, the pharmaceutical company sponsoring the drug must obtain approval from FDA. To receive approval, the sponsor must demonstrate that the drug is both safe and effective for its intended use. It is the sponsor's responsibility to assemble all the evidence concerning the drug's safety and efficacy and supply it to FDA in an NDA. The NDA includes information on the drug's safety and efficacy, manufacturing procedures, and proposed labeling, which includes prescribed uses, warnings, and side effects. It is FDA's responsibility to conduct a comprehensive review of the NDA and to make decisions regarding approval of the new drug for marketing. Within FDA, the Center for Drug Evaluation and Research is responsible for reviewing new drugs. After an NDA is submitted, it is assigned to a specific review division in the center that has responsibility for the appropriate drug class. Within the division, reviewers from various disciplines such as medicine, chemistry, and pharmacology are assigned to the drug. These specialists evaluate the drug in terms of their own expertise. For example, pharmacologists evaluate test results on animals while medical reviewers

[7]When the Waxman-Hatch Act of 1984 was enacted, the term of a U.S. patent was 17 years, measured from the date of its grant (or issuance). As a result of the Uruguay Round of the General Agreement on Tariffs and Trade, the Uruguay Round Agreements Act was enacted in 1994, which lengthened the U.S. patent term to 20 years, measured from the date of the earliest application.

evaluate clinical test results in humans. The review process includes not only an ascertainment of the efficacy and safety of the drug but also an assessment of the quality of the methods, facilities, and controls used for manufacturing, processing, and packaging the drug.

At the beginning of the review process, a drug is assigned a review priority that is based on its potential therapeutic benefit to the public. This allows FDA to set priorities for reviews for different drugs, depending on their potential importance. As a result, NDAs for drugs receiving a high therapeutic ranking generally move more rapidly than others through the review process.

One factor that led to longer drug approval times in the 1980s and early 1990s was a lack of resources at FDA. To resolve this problem, the Congress enacted the Prescription Drug User Fee Act of 1992 (PDUFA), which authorizes FDA to charge drug manufacturers specified fees.[8] These fees were to be used to augment FDA resources devoted to reviewing NDAs in order "to significantly expedite the drug approval process." However, because the law was not passed until October 1992, the act had at most a minor effect on the majority of pipeline drugs.[9]

The Drug Price Competition and Patent Term Restoration Act of 1984 provided patented drug products with an extended term of protection to compensate for delays occurring as a result of regulatory review. At the same time, the process for approving and marketing generic drugs was made easier and quicker. The legislation granted patent extensions of up to 5 years for nonpipeline drugs and up to 2 years for pipeline drugs. The total of a drug's remaining patent life after FDA approval and any patent extension could not exceed 14 years.

[8]FDA was permitted to assess three types of fees on drug companies: (1) a one-time fee for the submission of a human drug application, (2) an annual fee for each prescription drug product being marketed, and (3) an annual fee for each establishment manufacturing prescription drugs.

[9]For more information on the act, see *FDA User Fees: Current Measures Not Sufficient for Evaluating Effect on Public Health* (GAO/PEMD-94-26, July 22,1994).

Lengthy Review Times Were Caused by a Number of Factors

The seven pipeline drugs covered by the proposed legislation had longer approval times than comparable products.[10] The long approval times of the three pipeline drugs we examined in detail generally resulted from concerns about the safety and efficacy of the products as well as their chemical properties and manufacturing procedures. However, the specific reasons for their longer approval times varied considerably for Claritin, Relafen, and Cardiogen-82.

The Approval Times for the Seven Pipeline Drugs Exceeded the Times for Other Drugs

The approval times for the seven pipeline drugs covered by the proposed legislation were longer than those for comparable drugs. The approval time for each of the seven drugs ranged from 17 to 65 months longer than the average approval time for all pipeline drugs of the same chemical type and therapeutic potential. The fastest of the seven drugs to be approved, Cardiogen-82, had a longer approval time than about 85 percent of comparable pipeline drugs. We also found that the seven drugs had longer approval times than all but four comparable drugs approved between 1983 and 1985, around the time Waxman-Hatch was passed. Finally, we compared the approval times for the seven pipeline drugs with the approval times for comparable drugs in the same therapeutic class (for example, nonsteroidal anti-inflammatory drugs). Because of the small number of drugs in five of the classes, we were able to compare approval times in only two classes. The average approval times for Relafen and Cardiogen-82 were longer than those for similar products. More information on approval time comparisons is given in appendix II.

Several Factors Delayed FDA's Approval of Claritin

The Claritin NDA was submitted on October 31, 1986, and approved on April 12, 1993, a total approval time of 77.4 months. This was almost 3 years longer than the average 42.5 months for similarly classified pipeline drugs—new molecular entities that offered little or no therapeutic gain compared with existing therapies.

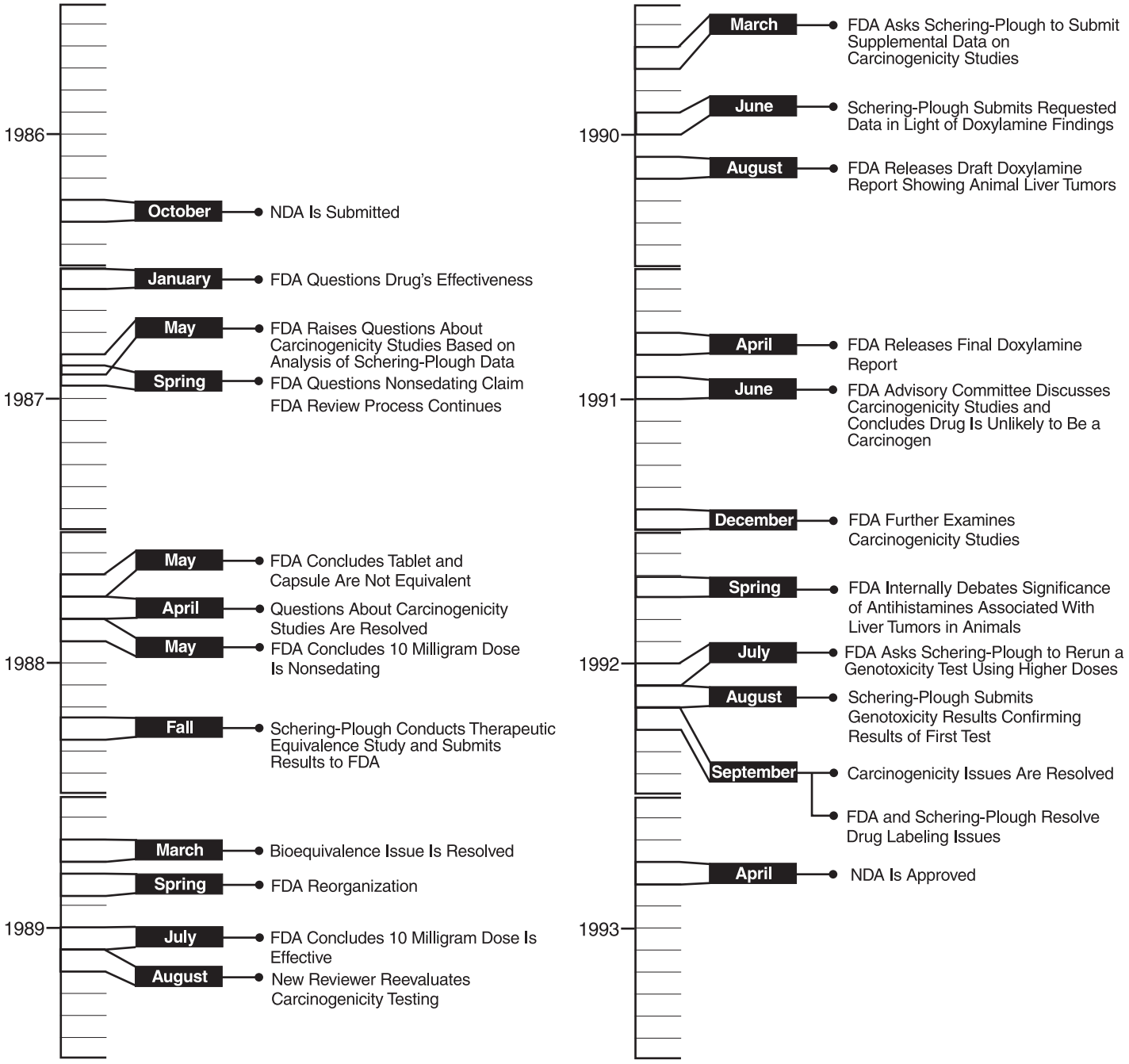
[10]In this report, "comparable" refers to drugs that FDA classified as being of the same chemical type and therapeutic potential. See appendix I for a discussion of the categorizations.

Two principal concerns about Claritin contributed to the delay. First, FDA and Schering-Plough disagreed about whether the safety of Claritin had been adequately demonstrated.[11] Specifically, they held different views on how the results of animal carcinogenicity tests should be interpreted.[12] Second, FDA and Schering-Plough disagreed on whether or not the tablet form of the drug that the company wanted to market had been shown to be equivalent to the capsule form that had been tested. In addition to these issues, FDA raised questions about whether or not Claritin induced drowsiness and its effectiveness. Figure 1 is a timeline showing the major events in the approval of Claritin. See appendix III for more information on the Claritin approval process.

[11]The name of the company when the NDA was submitted was Schering Corporation. The name was later changed to Schering-Plough Corporation.

[12]Carcinogenicity refers to the ability of a chemical or other substance to produce cancer.

Figure 1: Timeline of Events Affecting Claritin's Approval, 1986–93



Carcinogenicity Studies

The major issue that delayed the approval of Claritin was the potential significance of animal carcinogenicity data for humans. The studies Schering-Plough submitted in the Claritin NDA showed evidence of increased tumors in male mice and male and female rats. After receiving and analyzing additional data from Schering-Plough, the FDA reviewers concluded that these findings should not delay approval of the drug. Thus, in April 1988, about 18 months after the NDA was filed, the carcinogenicity questions appeared to have been resolved. However, in spring 1989, following an FDA reorganization, the Claritin NDA was transferred to a new division and new reviewers were assigned. While we have no evidence that the reorganization affected the approval of Claritin, Schering-Plough contends that the reorganization resulted in inefficiencies and delay when new reviewers re-reviewed data that had been accepted by the first reviewers.

FDA's new concerns regarding the animal carcinogenicity data from the Claritin studies may have been affected by the findings of unpublished animal tumor studies on another company's antihistamine, doxylamine. Schering-Plough officials believe that FDA officials were influenced by these studies that indicated that doxylamine was associated with liver tumors in rats and mice. Schering-Plough contends that this may have heightened FDA's concerns about the significance of animal tumor findings in other antihistamines. Schering-Plough acknowledges that the tumor issues FDA raised in 1989 regarding Claritin dealt with the same type of data discussed in the doxylamine study. Moreover, FDA records indicate that much of FDA's review from 1989 to 1992 was conducted in the context of the doxylamine findings and what these indicated about the safety of other antihistamines.

When the carcinogenicity study issue was reopened in 1989, there was considerable discussion between FDA and Schering-Plough on the proper interpretation of the animal findings. In 1991, an FDA advisory committee concluded that Claritin was unlikely to be carcinogenic. Despite this conclusion, some FDA officials were still concerned about the significance of the animal carcinogenicity data. Eventually, this issue was resolved in the summer of 1992 when FDA requested and Schering-Plough agreed to redo a previously submitted test at a higher dose. The results of this test were negative.

Schering-Plough officials believe that FDA's reevaluation of the carcinogenicity issue was unnecessarily prolonged. They note that the labeling requirements for carcinogenicity in 1993 were very similar to those

that FDA recommended and Schering-Plough agreed to in 1989. However, FDA officials told us that simply because the results of FDA's reexamination did not ultimately produce any changes in the label does not mean that the inquiry was inappropriate. The information resulting from the inquiry in this case could have contributed to FDA's conclusion that the original labeling requirements were appropriate.

FDA's resolution of the carcinogenicity issue was made more difficult by the large amount of controversy in the field of toxicology regarding animal carcinogenicity studies. Expert opinion was divided on the relevance of particular tests and how other tests should be conducted and analyzed. Thus, when FDA was attempting to reach a decision on the approval of Claritin, there was no consensus in the scientific community about how best to develop and evaluate animal carcinogenicity data.

Bioequivalence

The carcinogenicity issue might not have resurfaced if the approval of Claritin had not been delayed by concerns about the bioequivalence of the capsule used in the clinical trials and the tablet form of the drug that the company planned to market. Schering-Plough contends that FDA's concerns were unfounded. After FDA biopharmaceutics experts reviewed the 13 studies Schering-Plough submitted to establish the bioequivalence of the tablet and capsule, they concluded that the data did not support that they were equivalent. This issue arose because of disagreement between FDA and Schering-Plough about how to demonstrate bioequivalence. Once ingested, Claritin is rapidly converted to a primary metabolite that is largely responsible for the drug's effectiveness.[13] Consequently, Schering-Plough believed that the bioequivalence of the parent drug should be ignored and only the metabolite should be studied for bioequivalence. FDA disagreed, noting that the drug is not completely metabolized and that the bioequivalency for both the parent and metabolite needed to be established. Schering-Plough and FDA agreed that the bioequivalence of the metabolite had been shown. Schering-Plough acknowledged that it could not show the bioequivalence of the parent compound with its studies, and the company decided to conduct a study in which the tablet, capsule, and a placebo were compared in approximately 450 patients. The study was conducted in fall 1988 and submitted to FDA in November 1988. After reviewing these data, FDA concluded that the equivalence of the

[13]A metabolite is any substance produced or used during metabolism (digestion). In drug use, a metabolite usually refers to the end product (what remains after metabolism).

tablet and capsule had been established. Thus, approximately 2-1/2 years after the NDA was submitted, the bioequivalency issue was resolved.

Sedation and Effectiveness

Concurrent with the bioequivalence issue, FDA also raised questions about the claim that Claritin was nonsedating and about the drug's effectiveness. FDA reviewers saw indications in the NDA that drowsiness was among the most frequent adverse reactions from Claritin. They eventually concluded that the 10 milligram dose Schering-Plough intended to market was no more sedating than a placebo but that the 40 milligram dose was more sedating. Soon after receiving the NDA, FDA reviewers raised a number of issues with Schering-Plough about the design and results of the studies submitted in the NDA, including indications that the 10 milligram doses were not very effective while the 40 milligram doses were effective. After further analysis of the data, FDA concluded that the 10 milligram dose was effective. The resolution of these issues meant that if other concerns were addressed, the 10 milligram dose of Claritin could be marketed and labeled as nonsedating.

Safety and Manufacturing Concerns Delayed the Approval of Relafen

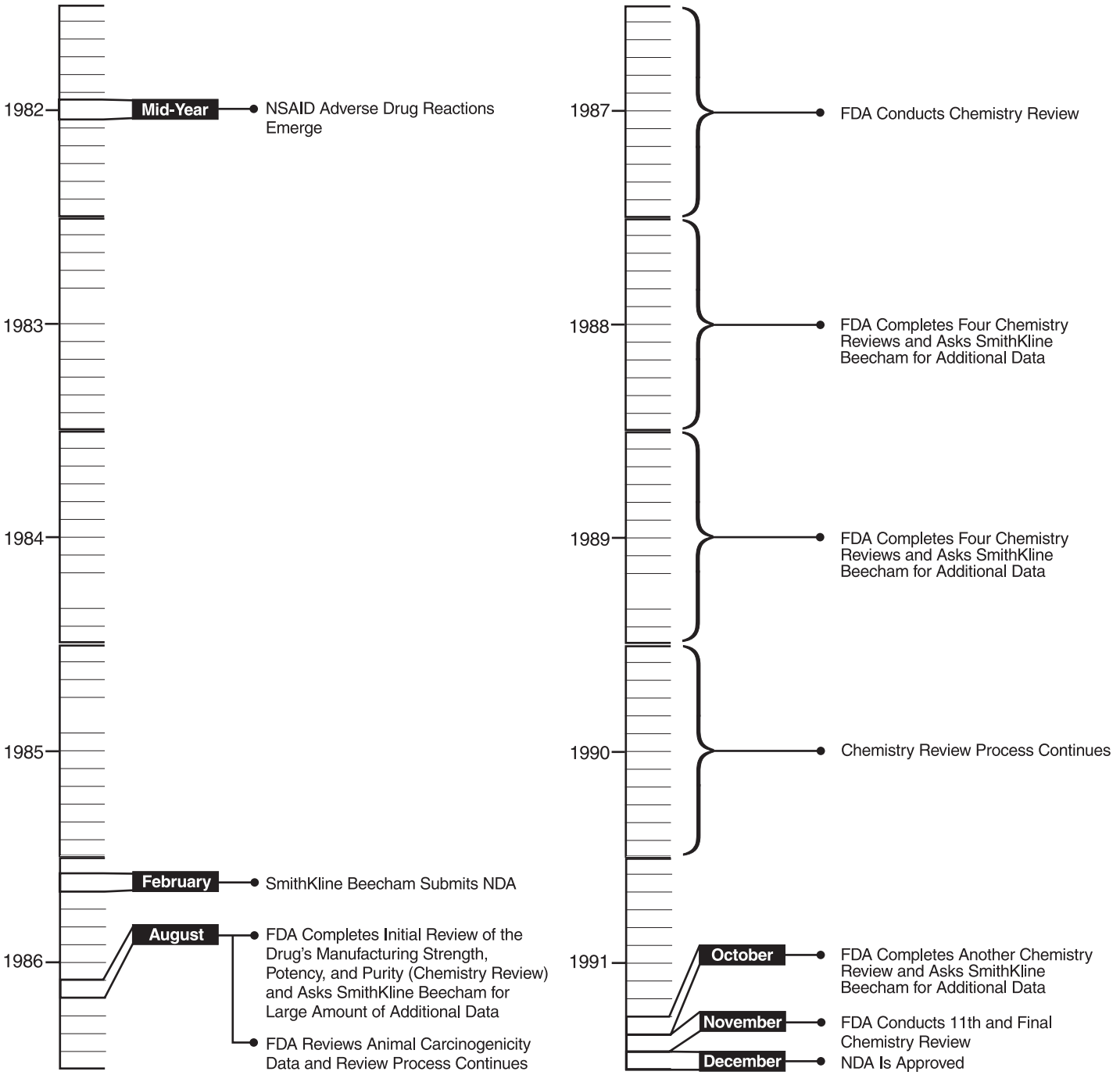
The total approval time for Relafen was 70.5 months, from February 6, 1986, to December 24, 1991. This was more than a year longer than the 57.6 month average for other drugs in the same therapeutic class (nonsteroidal anti-inflammatory drugs, or NSAIDs) that were approved between 1975 and 1993 and that FDA classified as new molecular entities that offered little or no therapeutic gain. The approval time for Relafen was greater than about 67 percent of NSAIDs.

Questions regarding Relafen's safety and its manufacturing process were the principal factors that delayed its approval. In the early 1980s, several NSAIDs were associated with severe adverse reactions, including fatal and nearly fatal events. These adverse reactions received a significant amount of media coverage and congressional hearings were held. While these events did not involve Relafen and occurred before the Relafen NDA was filed, SmithKline Beecham officials suggested that adverse reactions in these other NSAIDs were unfairly associated with Relafen and slowed its approval.[14] FDA officials acknowledged that they became more cautious in their review of new NSAIDs following the disclosure of the adverse events. However, FDA officials told us that missing and incomplete information in

[14]The Relafen NDA was originally submitted by the Beecham Group. In 1989, the company merged with SmithKline Beckman to form SmithKline Beecham.

the Relafen application slowed the approval process. Although FDA then allowed incomplete applications to be filed (before PDUFA was enacted in 1992), agency officials said that the Relafen NDA was of especially poor quality. FDA repeatedly requested additional information from SmithKline Beecham about several issues regarding Relafen's manufacturing process. For example, FDA requested information about the quality of the substances used in the drug. The company did not always address these concerns in a timely and complete manner. Because the additional submissions did not always adequately address the issues FDA raised, SmithKline Beecham had to submit more data on a number of occasions before a resolution was reached. These issues persisted over a fairly long time and, according to FDA documents, delayed the approval of the application. However, SmithKline Beecham officials suggested that the review of these issues was an ongoing process that did not delay the review of the drug. They stated that FDA did not communicate with company officials during the first 3 to 4 years of the Relafen review about clinical issues. While there was no documentation of such reviews being done during this period in the FDA files, we cannot conclude with certainty that these reviews did not occur because the information may have been missing. (Figure 2 shows the major events in the review of Relafen.)

Figure 2: Timeline of Events Affecting Relafen's Approval, 1982–91



According to SmithKline Beecham officials, FDA policy delayed the review of the efficacy and safety of Relafen. Company officials told us that they received unofficial oral comments from an FDA division director that the agency was reviewing only one NSAID at a time after the Relafen application was submitted. However, FDA officials we spoke with were unaware of such a policy for NSAIDs. We located only a summary document prepared after the NDA was approved that described the efficacy of the drug and did not find documents in FDA's Relafen files that indicated when the agency's safety and efficacy review began. We did find a pharmacology review conducted within 6 months of the NDA submission date that addressed carcinogenicity data in animals, but the document did not indicate whether or not a medical officer had been assigned. See appendix III for a complete discussion of Relafen's approval.

Efficacy and Manufacturing Issues Delayed the Approval of Cardiogen-82

The NDA for Cardiogen-82, a radioactive diagnostic agent, was submitted to FDA on December 28, 1984, and approved on December 29, 1989.[15] The average total approval time for new molecular entities that offered little or no therapeutic gain in this therapeutic class (radioactive diagnostic aids) approved between 1975 and 1993 was 49.3 months, 11 months shorter than the review time for Cardiogen-82. Approximately 60 percent of drugs in this therapeutic class were approved faster than Cardiogen-82.

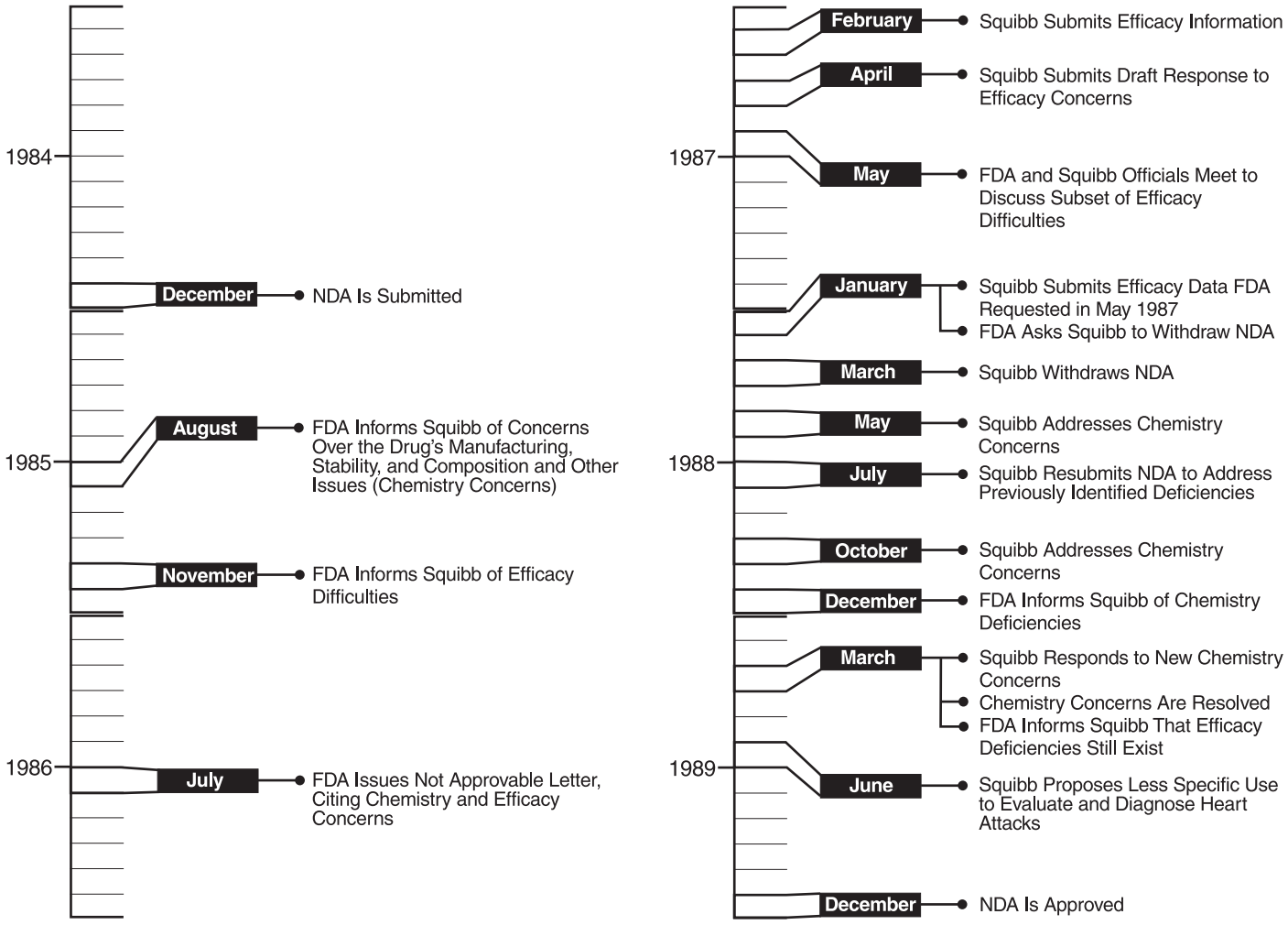
FDA questioned information in the chemistry and manufacturing section of the Cardiogen-82 NDA and the section assessing the efficacy of the drug. These concerns resulted in FDA's sending a "not approvable" letter to the manufacturer in July 1986 stating that the drug could not be approved without additional information being submitted. The manufacturer submitted information to address some of the issues raised by FDA. However, in January 1988, FDA asked the company to withdraw the NDA from consideration until it was ready to complete the application. The company withdrew the NDA from consideration for approval in March 1988 and then resubmitted it in July 1988 with new information. Thus, while the drug took 60 months to be approved from its original submission, FDA spent 24 months (from July 1986 to July 1988) waiting for the company to submit a complete response to issues raised in the not approvable letter. Similar calculations for other radioactive diagnostics that were new molecular entities that offered little or no therapeutic gain indicate that this

[15]Cardiogen-82 is a radioactive dye that is injected into a patient's bloodstream to distinguish normal from abnormal middle muscular layers of the heart wall.

adjusted average review time was 35.5 months, approximately the same as for Cardiogen-82.[16] Approximately 50 percent of these drugs were reviewed faster than Cardiogen-82. (See figure 3 for a timeline of the Cardiogen-82 approval.) More detail on the approval of Cardiogen-82 is given in appendix V.

[16]This alternative measure of approval time is calculated by FDA and does not include the time it takes a manufacturer to resubmit an NDA after a not approvable letter is issued, the length of time a drug is withdrawn by the manufacturer from consideration for approval, and the time it takes a manufacturer to resubmit an application when FDA "refuses to file" the NDA as well as the time from FDA's receipt of the application to the refusal to file action. FDA can refuse to file an application if it finds that the NDA is not sufficiently complete to permit a substantive review.

Figure 3: Timeline of Events Affecting Cardiogen-82's Approval, 1984–89



FDA found that the NDA did not contain a full statement of the components and quantitative composition of the drug and lacked adequate information on the methods used in the synthesis, extraction, isolation, and purification of the drug product. Although FDA had informed Squibb of these problems in August 1985, the company had not addressed them when the not

approvable letter was issued in July 1986.[17] New chemistry data were submitted in response to the not approvable letter in May 1988 and more information was submitted in October of that year. However, FDA found that there were still deficiencies in the NDA regarding the composition and manufacturing of the drug. These were sent to the company in December 1988 and resolved in March 1989.

In the not approvable letter, FDA cited several concerns about the adequacy of the testing that was done to show the efficacy of Cardiogen-82 in humans. For example, the studies that were submitted to support efficacy and safety used a specific method for injecting Cardiogen-82 into the body. However, different methods were described in the proposed package insert for the drug, and these methods had not been tested in the clinical trials. FDA believed that an additional study was needed to show that the patient would receive the prescribed dose using these other methods. Also, the design and analysis of the studies were problematic as FDA was concerned that there were inadequate numbers of patients and no justification was given for excluding some of them from the analyses. Finally, FDA noted that the results of the studies varied according to what device was used to judge the effectiveness of Cardiogen-82. Different devices gave different indications of how well the drug worked.

After receiving the not approvable letter in July 1986, Squibb made several submissions to address the issues FDA raised and met with agency officials in May 1987 to specifically discuss several of them. However, FDA found these responses to be incomplete and informed Squibb in March 1989 that some of the clinical data would need to be reanalyzed.

FDA's concerns with data showing the efficacy of the drug continued in the summer of 1989. Squibb officials then suggested approving the drug on the basis of its general usefulness in evaluating heart attacks rather than the purpose described in the NDA, assessing the specific location of heart problems. While FDA did not believe it was ideal to approve the drug for the alternative use, it noted that as long as the drug is of some value it could be approved. It was agreed that Cardiogen-82 was useful in evaluating and

[17]The Cardiogen-82 NDA was filed by Squibb Diagnostics, the manufacturer of the drug. Bracco Diagnostics Inc. purchased the NDA from Squibb in July 1994 and now markets the drug. However, since Squibb was solely involved in the NDA review process, we refer to Squibb in our discussion of Cardiogen-82's approval.

diagnosing heart attacks, and in December 1989, Cardiogen-82 was approved for this purpose.

Bracco officials have suggested two reasons to help explain the lengthy approval time for Cardiogen-82. First, the FDA officials doing the chemistry and medical reviews changed during the approval process. While this could lengthen the approval time as new reviewers evaluated the data, we were unable to determine how much, if at all, it did so. Second, Bracco has stated that a 5-year FDA approval time was not unusual for medical imaging products that were being reviewed around the time Cardiogen-82 was evaluated and that the dialogue between the company and FDA was typical of that for NDAs. We found that 40 percent of comparable radioactive diagnostics were approved more slowly than Cardiogen-82 in the years we examined (1975–93). Also, an FDA official told us that there was a backlog of NDAs in FDA's Division of Medical Imaging and Surgical-Dental Drug Products in the late 1980s and early 1990s.

The Legislative History Does Not Indicate a Basis for a 2-Year Patent Extension Limit

The legislative history of the Drug Price Competition and Patent Term Restoration Act of 1984 explains only in general terms why an extension was authorized for pipeline drugs and does not explain why it was limited to 2 years. Testimonial evidence, outside the legislative history, from the counsel to the Pharmaceutical Manufacturers Association (now the Pharmaceutical Research and Manufacturers of America) when the Waxman-Hatch Act was being considered as well as the Counsel to the House Energy and Commerce Committee's Subcommittee on Health and the Environment suggests that the 2-year extension may have been based on an assumption that drugs in the FDA pipeline would likely be approved within 2 years of their NDA's filing. However, there is no explicit recognition in the history that the Congress adopted the provision for this reason.

Before Waxman-Hatch was enacted, the Congress had debated the need for a patent term extension law for a number of years. Two issues that were debated concerned the limit of the extension period and whether or not drugs that were already patented should be eligible for an extension. One proposal would have authorized an extension equal to the regulatory review period with a limit of 7 years and would have applied to drugs regardless of when they were patented. Another proposal would have allowed the same extension period but would have limited the extension to drugs patented after a law was enacted. The provision that was ultimately enacted established two limits: a 2-year limit for drugs that had already

been patented and were undergoing clinical trials (pipeline drugs) and a 5-year limit for drugs patented after enactment or patented before if they were not yet undergoing clinical trials.[18]

The legislative history of the Waxman-Hatch Act offers no explanation for why the Congress set the patent extension for pipeline drugs to 2 years rather than some other period. The only relevant committee report, by the House Energy and Commerce Committee, states generally that the overall purpose of providing additional patent protection was "to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket government approval." The report adds that different maximum periods of extension were established "to provide greater incentive for future innovations." [19] There is no specific explanation for why a 2-year limit was chosen for pipeline drugs and why a 5-year limit was chosen for other drugs.[20] If the 2-year period was originally suggested by one or more of the parties involved in the negotiations because it reflected the average NDA approval time, as some now maintain, the legislative history does not indicate that the Congress adopted it for that reason.[21] The 2-year extension could also have been the result of a compromise between some seeking extensions for all products and others opposed to any extensions. Moreover, the courts warn that when attempting to determine the purpose of a law, one must use information that is not part of the history generated by the Congress during

[18]The Counsel for the Generic Pharmaceutical Industry Association has described the evolution of the bill as "a unique legislative process which, in reality, was a congressionally supervised negotiation between the generic and brand-name pharmaceutical industries in which the parties were compelled to reach a compromise by the legislature." See Alfred B. Engelberg, "Special Patent Provisions for Pharmaceuticals: Have They Outlived Their Usefulness?" *Journal of Law and Technology*, Vol. 39 (1999), p. 389.

[19]H. Rep. No. 98-857, Part I, at 15, 40-41 (1984), reprinted in 1984 U.S.C.C.A.N. 2648, 2674.

[20]References throughout the legislative history justify patent extensions on the basis that they will motivate future innovation generally but do not explain the distinction between the 2-year period for pipeline drugs and the 5-year period for other products. See, for example, S. Rep. No. 97-138, pp. 6-7: "[The bill] will provide added cash flow to finance the costly future research efforts. Moreover, it will increase the expected returns from new drug innovations, thereby providing both the incentive and economic capability to conduct expensive long-term research and development."

[21]An FDA report issued in 1985 stated that the average approval time for all new molecular entities in 1984 was about 3¼ years. If the average time needed by an applicant to respond to an FDA action is subtracted from this length, the average approval time is approximately 2¼ years. HHS, *New Drug Evaluation: Statistical Report* (Washington, D.C.: 1985), p. 53.

consideration of the bill with great caution, if at all.[22] This is in part because, as here, it is not possible to establish that the information was known to the legislators considering and voting on the bill.

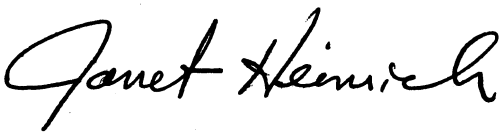
Agency and Drug Manufacturers' Comments

We provided a complete draft of this report to the Commissioner of FDA and relevant parts of the draft to the companies whose drugs we reviewed in depth. The companies were given only the parts of the draft that dealt specifically with their drug or that cut across all the pipeline drugs. The companies were not given the sections of the report that dealt specifically with other manufacturers' drugs. FDA responded that the report accurately reflects the facts of the cases and is fairly presented. The agency also provided technical comments that we incorporated as appropriate. The manufacturers generally found our characterization of the major issues in the review processes of the drugs to be accurate. However, there was some concern that certain issues were not explained completely enough. We revised sections of the report to include more detail where appropriate. Other comments led us to make clarifications to the text. Schering-Plough officials were concerned that our discussion of the delay in Claritin's approval caused by FDA's investigation of the potential carcinogenicity of the drug might lead readers to believe that there were lingering concerns about the drug's safety. The company wanted to emphasize that FDA determined the drug to be safe and effective and that there are no remaining carcinogenicity concerns.

We are sending copies of this report to the Honorable Donna E. Shalala, Secretary of Health of Human Services, and the Honorable Jane E. Henney, Commissioner of FDA. We are also sending copies to appropriate congressional committees and others who are interested.

[22] *Cavallo v. Utica-Watertown Health Insurance Company*, 3 F. Supp. 2d 223, 230 (D.N.Y. 1998). See *HHS v. Finkelstein*, 496 U.S. 617, 631, 632 (Justice Scalia, concurring in part, stated that "arguments based on subsequent legislative history … should not be taken seriously, not even in a footnote").

If you or your staff have any questions, please contact me at (202) 512-7114 or John Hansen, Assistant Director, at (202) 512-7105. Robert M. Copeland, Julian Klazkin, and Lawrence S. Solomon were the major contributors to this report.



Janet Heinrich
Associate Director, Health Financing
and Public Health Issues

List of Requesters

The Honorable Orrin G. Hatch
Chairman
The Honorable Patrick Leahy
Ranking Minority Member
Committee on the Judiciary
United States Senate

The Honorable Richard J. Durbin
The Honorable Paul Wellstone
United States Senate

The Honorable Sherrod Brown
The Honorable John Conyers, Jr.
The Honorable John D. Dingell
The Honorable Bart Gordon
The Honorable Jim McDermott
The Honorable Robert Menendez
The Honorable Ed Pastor
The Honorable Steven R. Rothman
The Honorable Pete Stark
The Honorable Ellen O. Tauscher
The Honorable Henry A. Waxman
House of Representatives

Scope and Methodology

We assessed the factors that affected the approval times for three pipeline drugs that were in regulatory review for more than 5 years. We studied in detail the approval of only three of the seven drugs covered by the proposed legislation because the manufacturers of the four other drugs were unable either to provide us with review information or chose not to have their drugs included in our study. The three drugs we studied are Claritin (an antihistamine manufactured by the Schering-Plough Corporation), Relafen (a nonsteroidal anti-inflammatory drug used for relieving pain and made by the SmithKline Beecham Corporation), and Cardiogen-82 (a diagnostic imaging agent marketed by Bracco Diagnostics Inc). The four other drugs covered under the legislation are Dermatop (a corticosteroid for skin conditions that is manufactured by Aventis Pharmaceuticals), Eulexin (a prostate cancer drug manufactured by the Schering-Plough Corporation), Nimotop (a calcium channel blocker made by the Bayer Corporation), and Penetrex (an antibiotic made by Aventis Pharmaceuticals).

We determined the factors that affected the amount of time the Food and Drug Administration (FDA) took to approve Claritin, Relafen, and Cardiogen-82 by reviewing relevant FDA division files. These files provide a comprehensive account of FDA's actions and company responses. For additional information, we met with FDA officials who were involved in the approval of these drugs and reviewed other files when necessary. In addition, to the extent available, we obtained similar information from the manufacturers of each of the three drugs. We also spoke with company officials to obtain their positions.

We calculated the approval times of the seven pipeline drugs covered by the proposed legislation. This time began when the sponsor submitted the new drug application (NDA) to FDA in order to market the drug and ended when FDA approved the application. We put these times into context by comparing them with approval times for drugs of the same chemical type

and therapeutic potential.[1] Our analyses were limited to drugs approved between January 1, 1975, and April 12, 1993. We began our analyses with 1975 because FDA began to classify drugs by therapeutic potential in that year. We ended our analysis with drugs approved on April 12, 1993, because that was the date Claritin was approved. In addition, the Prescription Drug User Fee Act was enacted in 1992 in order to augment FDA's resources devoted to reviewing NDAs. Because this was so soon after the enactment of the Prescription Drug User Fee Act of 1992 (PDUFA), it is unlikely that the law had more than a minimal effect on the approval times for these drugs. We included all drugs approved until April 12, 1993, in order to make

[1]In order to make our comparison groups as similar as possible to the pipeline drugs, we used FDA's categorizations of drugs by chemical type and therapeutic potential to classify all the drugs. We then compared only similarly classified products. FDA assigns each drug to a chemical type category when it receives an application. FDA uses seven categories for chemical type; however, the seven pipeline drugs fall into only two of the categories. Six of the drugs are classified as a type 1 or "new molecular entity." These are drugs that are not marketed in the United States by any drug manufacturer. The seventh drug (Dermatop) is classified as type 2, a "new ester, salt, or other noncovalent derivative." For a type 2 drug, the active component of the drug is marketed in the United States, but this particular salt, ester, or derivative is not.

Similarly, FDA classifies each drug by its therapeutic potential when it receives an NDA. The NDAs in this study were all submitted before 1992. At that time, therapeutic potential was primarily classified according to three types:

"Type A, important therapeutic gain: the drug may provide effective therapy or diagnosis, by virtue of greatly increased effectiveness or safety, for a disease not adequately treated or diagnosed by any marketed drug. Or the drug may provide improved treatment of a disease through improved effectiveness or safety, including decreased abuse potential.

"Type B, modest therapeutic gain: the drug has a modest, but real, potential advantage over other available marketed drugs. Examples include greater patient convenience, elimination of an annoying but not dangerous adverse reaction, potential for large cost reduction, less frequent dosage schedule, or useful in a specific subpopulation of those with disease (for example, those allergic to other available drugs).

"Type C, little or no therapeutic gain: the drug essentially duplicates in medical importance and therapeutic usage one or more already marketed drugs, offering little or no therapeutic gain over existing therapies."

In 1992, FDA began to classify NDAs as eligible for priority (P) or standard (S) review. Most NDAs that formerly would have been classified type A or B are now classified P, and those that were formerly classified type C are now classified S.

The chemical type and therapeutic potential codes can be combined. For instance, a 1A drug is a new molecular entity that offers an important therapeutic gain. We compare only similarly classified drugs. For example, if a pipeline drug was classified 1C (new molecular entity with little or no therapeutic gain) we compared it only to other 1C products.

the comparisons as similar as possible. The few pipeline drugs that were approved after April 12, 1993, and any other potential comparison drugs approved after this date are not included in our analyses. We calculated approval times for three comparison groups. First, we calculated the approval times for 110 pipeline drugs.[2] Second, we determined the approval times for drugs that were approved in 1983, 1984, and 1985. These include 1984, the year Waxman-Hatch was enacted, and the years preceding and following. These were included to provide an estimate of expected drug approval times when the legislation was being considered. Finally, we determined the average approval times for drugs in the same therapeutic class as the seven pipeline drugs.

To determine the approval times for the seven pipeline drugs and the comparison groups, we reviewed published FDA reports that summarize drug approval information, including approval times. We also obtained additional information from the agency, such as whether FDA had issued a not approvable letter informing the company of the deficiencies in the application. We then calculated average approval times and various measures of the spread of the data.

To understand why the Congress limited the patent extension for pipeline drugs to 2 years, we developed a detailed legislative history of the Waxman-Hatch Act that we based on hearings, committee reports, and floor debate. We also obtained related information from the drug manufacturers.

[2]There were a total of 122 pipeline drugs. Twelve of them were biologics or were approved after April 12, 1993, and therefore did not meet our criteria for inclusion.

Approval Time Comparisons

Each of the seven pipeline drugs covered by the proposed legislation required more than 5 years to be approved. In order to provide the context for the length of these approval periods, in this appendix we compare the approval times for these seven drugs with three groups: (1) all comparable pipeline drugs, (2) other drugs that were approved near the time Waxman-Hatch was enacted, and (3) other drugs in the same therapeutic classes.

Comparison With Other Pipeline Drugs

One of the criteria for a pipeline drug's eligibility for a patent extension under the proposed legislation is that the approval time must have been at least 5 years. This review time is defined as the total period between submission of the NDA and its final approval. As table 1 shows, the seven pipeline drugs required longer approval times than did the average pipeline drug. The approval time for each of the seven drugs ranged from 17 to 65 months longer than the average approval time for all pipeline drugs of the same chemical type and therapeutic potential. We determined that the percentile rankings for the seven drugs range from the 85th percentile for Cardiogen-82 to the 100th for Dermatop, Eulexin, and Nimotop.[1]

Table 1: Pipeline Drug Approval Times in Months

Drug	Chemical type and therapeutic potential	Number of pipeline drugs of this type and potential	Approval time	Average approval time for pipeline drugs of this type and potential[a]	Approval time percentile for this drug
Cardiogen-82	1C	67	60.1	42.5	85th
Claritin	1C	67	77.4	42.5	92nd
Dermatop	2C	4	68.4	35.3	100th
Eulexin	1B	29	100.0	35.5	100th
Nimotop	1A	10	75.4	29.9	100th
Penetrex	1C	67	62.3	42.5	86th
Relafen	1C	67	70.5	42.5	88th

Note: The average review time for all 122 pipeline drugs, including biologics and those approved after Claritin, was 38.6 months.

[a]The range of total approval times was 9.5 to 75.5 for 1A drugs, 13.0 to 100.0 for 1B drugs, 15.0 to 122.5 for 1C drugs, and 17.8 to 68.4 for 2C drugs.

[1]A percentile divides a set of values into parts. For instance, the 85th percentile indicates that about 85 percent of the pipeline drugs had shorter approval times and 15 percent had longer approval times than the comparison drug.

Comparison With Drugs Approved Near the Time Waxman-Hatch Was Enacted

Only four drugs approved between 1983 and 1985 had longer approval times than at least one of the seven pipeline drugs.[2] As shown in table 2, the average approval time decreases as FDA's assessment of a drug's therapeutic potential increases. The only 1A medication (a new molecular entity with the highest therapeutic potential) among the seven pipeline drugs is Nimotop. Its approval time (75.4 months) was three times greater than the average total approval time (25.2 months) for 1A drugs in 1983-85. Moreover, its approval time was longer than for any 1A drug during that period.[3] The only 1B pipeline drug (a new molecular entity with moderate potential) covered under the proposed legislation is Eulexin. Similarly, its approval time (100 months) was greater than the longest 1B approval time between 1983 and 1985.[4] The four 1C pipeline drugs (new molecular entities with little or no therapeutic gain over existing therapies) all exceeded the average approval time (40.3 months) for 1C drugs in 1983 to 1985. However, none of the four exceeded the longest approval time during that period for similarly classified products. The 68.4 month approval time for Dermatop, the one 2C drug (a new ester, salt, or other noncovalent derivative that offers little or no therapeutic gain over existing therapies) covered under the proposed legislation, was longer than for any other 2C drug approved between 1981 and 1986.

[2]The four drugs were Glucotrol (104.2 months), Merital (72.1 months), Micronase (131.3 months), and Nenphroflow (69.3 months).

[3]There were major disagreements between FDA and the sponsor about the adequacy of the data in the Nimotop NDA. The sponsor withdrew the application twice for a total of 15.7 months. This accounts for part of but not all the lengthy review process.

[4]Eulexin was never approved to be used alone, as was sought in the NDA. In September 1987 (7 years after the NDA was originally filed), the manufacturer of the drug submitted new data to support the use of the drug as part of a combination product. If only the approval time for Eulexin as part of combination product is considered, the approval time (16.0 months) is well within the range of total approval times between 1983 and 1985 for 1B drugs.

Table 2: Average Total Approval Time for Drugs Approved 1983-85 in Months

Drug classification	Number of drugs approved	Total approval time for specific pipeline drugs in this classification	Average total approval times for this classification	Range of total approval times for this classification
1A	9	Nimotop: 75.4	25.2	6.1 to 39.8
1B	24	Eulexin: 100.0	27.5	10.6 to 58.7
1C	33	Cardiogen-82: 60.1 Claritin: 77.4 Penetrex: 62.3 Relafen: 70.5	40.3	15.0 to 131.3
2C (drugs approved 1981-86)[a]	7	Dermatop: 68.4	30.8	17.8 to 50.4

[a]Only two 2C drugs were approved in 1983-85. In order to have enough drugs to allow us to calculate meaningful statistics for this classification, we used drugs that were approved in 1981-86.

Comparison With Drugs in the Same Therapeutic Class

We also compared the approval times for the seven pipeline drugs with the approval times for drugs in the same therapeutic class that were classified as the same chemical type and therapeutic potential. Because of the small numbers of drugs in five of the classes, we were able to compare approval times in only two classes. This analysis shows similar results to our previous analyses. The approval times for Relafen (a nonsteroidal anti-inflammatory drug) and Cardiogen-82 (a radioactive diagnostic agent) are longer than average approval times for similar products.[5] More information on these comparisons is given in appendixes IV and V.

[5]While we compared Cardiogen-82 with other radioactive diagnostic agents, the claim made for it in the NDA was unique.

Approval Process for Claritin

Schering-Plough Corporation holds a patent for Claritin, a nonsedating antihistamine used to prevent or relieve symptoms of hay fever and other allergies. Claritin is the top-selling antihistamine in the United States, with $1.5 billion in 1999 sales. The patent for Claritin was filed on June 18, 1980, and issued on August 4, 1981. It is scheduled to expire on June 19, 2002.

When the Claritin NDA was submitted to FDA in 1986, there was one nonsedating antihistamine on the market (Seldane) and another (Hismanal) had been submitted for approval. (Hismanal was approved on December 29, 1988.) On the basis of Claritin's potential therapeutic benefit to the public, FDA assigned Claritin its lowest review priority—a C ranking. This means that FDA determined that there was little or no therapeutic gain from the drug compared with already marketed drugs.

Schering-Plough contends that the lengthy review period (77.4 months) FDA took to grant marketing approval for Claritin deprived the company of a large period of patent protection. Schering-Plough contends that the lengthy review process resulted from (1) FDA's re-reviewing data from the animal carcinogenicity studies, (2) FDA's not accepting reasonable data showing the bioequivalence of the capsule and tablet formulations, (3) an insufficient number of reviewers at FDA to evaluate NDAs during this period, and (4) a reorganization at FDA that resulted in the Claritin NDA being transferred to a new division.[1]

The Approval Time for Claritin Was Longer Than Average

Schering-Plough submitted a new drug application to FDA on October 31, 1986, for approval to sell Claritin. The NDA was approved on April 12, 1993, the approval process taking a total of 77.4 months. This was about 3 years longer than the 42.5-month average approval time for 1C pipeline drugs. The approval time for about 92 percent of these drugs was shorter than for Claritin. In addition, the approval time was longer than that for all but 3 of the 33 1C drugs approved between 1983 and 1985.

Because only three nonsedating antihistamines (and only one other 1C antihistamine) were approved between January 1, 1975, and April 12, 1993, we did not calculate average approval times for this therapeutic class. However, Claritin had the longest approval time of all these drugs. The

[1]Bioequivalence refers to whether drugs in different forms (in this case, tablets and capsules) are absorbed into the human body in equivalent ways.

other 1C nonsedating antihistamine (Hismanal) was approved in 46.1 months.

The Approval Process Was Complex

Schering-Plough submitted 37 major amendments to the Claritin NDA during the 77 months it was being considered by FDA. A major amendment involves a relatively large amount of new data (for example, a reanalysis of a completed study or results of an additional study) being submitted to the agency. FDA decides whether an amendment is classified as major or minor. The amendment may be submitted either at the sponsor's own initiative or in response to an issue raised by FDA. For Claritin, 30 of the amendments were responses to FDA concerns. In an earlier report, we found that 97 percent of approved NDAs submitted from 1987 to 1992 had 10 or fewer major amendments.[2] While the number of amendments may indicate problems with the NDA, FDA told us that it is not necessarily the case. In our analysis of the Claritin NDA, we found that there were substantial differences in the nature of the major amendments and the amount of data submitted. Eighteen of the amendments dealt with establishing the equivalence of the capsule and tablet forms of the drug or the animal carcinogenicity studies and the remaining 19 covered a number of topics including required safety updates, reports of studies completed after the NDA was submitted, and foreign labeling. In addition, despite the large number of major amendments, FDA neither refused to file the application nor issued a not approvable letter, and the company never withdrew the drug from consideration.[3]

There were indications from FDA during the approval process that progress was being made. For instance, before an October 22-23, 1987, meeting of the Pulmonary-Allergy Drugs Advisory Committee to discuss the efficacy and sedative effects of the drug, an FDA official told a Schering-Plough representative not to be concerned because the drug had already been shown to be equivalent to Seldane (which had already been approved). Also, before the Advisory Committee meeting, FDA officials

[2] *FDA Drug Approval: Review Time Has Decreased in Recent Years* (GAO/PEMD-94-26,Oct. 20, 1995).

[3] Once an NDA is received, FDA has 60 days to determine whether it will be officially filed. FDA can refuse to file an application if it finds that the NDA is not sufficiently complete to permit a substantive review. After reviewing the NDA, the agency can issue a not approvable letter if it determines that NDA "does not provide the substantial evidence of safety and effectiveness required."

told the company that they had not encountered any actual review problems. The Advisory Committee recommended approval of the drug at that meeting. In a March 13, 1989, letter to FDA, Schering-Plough wrote that its understanding (based on a conversation with the Acting Division Director) was that only a minor safety concern was holding up approval of the drug. The company complained that this could easily be addressed in the label. On March 23, 1989, the Acting Division Director at FDA responded that it was attempting to make its part of the review process final.

However, during this period FDA also gave indications to Schering-Plough that it was having difficulty with the NDA. For instance, on June 13, 1988, Schering-Plough called FDA to ask if FDA was ready to discuss labeling for the drug. The FDA official responded that it usually has serious labeling discussions only when the agency believes it is nearing an approvable letter and that this was not yet the case with Claritin. On January 13, 1989, Schering-Plough called FDA to schedule a meeting with the agency in order to precipitate approval of the drug. It was told that the meeting should not even be considered until completion of the medical, biopharmaceutical, and biometrics reviews.

Despite these problems, the NDA appeared to be nearing approval in 1989. The stated purposes of a meeting of FDA officials on February 28, 1989, were to discuss particular issues raised in the biopharmaceutical review and to "tie up loose ends" in it and the medical review before an anticipated approval. In June 1989, FDA cancelled a meeting with Schering-Plough because FDA officials believed that an "approvable" letter would soon be issued.[4] On July 21, 1989, an Acting Division Director held a meeting with other FDA officials to discuss approvability and labeling with the intention of moving toward a final action. In his September 11, 1989, review of the NDA, the Acting Division Director wrote that the efficacy and safety of the drug had been shown and the bioequivalence issues had been settled. He noted that both the medical officer and group leader recommended approval. The Acting Director concluded that, with recommended label changes, the NDA was approvable.

[4]FDA can issue an approvable letter when it has determined that the NDA has provided substantial evidence of the safety and effectiveness of the drug but "additional information must be submitted or a specific condition must be agreed to by the applicant" before the NDA can be approved.

Concerns About the Results of Animal Carcinogenicity Studies Delayed the Drug's Approval

The principal issue that delayed Claritin's approval was concern at FDA about the potential significance of animal carcinogenicity studies. This concern was raised early in the review process but appeared to have been settled about 1-1/2 years after the NDA was submitted. The issue resurfaced about a year later. While it is unclear exactly why this occurred, one factor might have been the finding that another antihistamine was associated with liver tumors in rats and mice. This was the primary issue that FDA dealt with from 1989 until the drug was approved in 1993.

A number of tests are used to assess the carcinogenicity of a drug, including ones with animals. Throughout this report, we refer to carcinogenicity studies that have been conducted with animals. Substances that cause or promote tumors in laboratory animals are not necessarily carcinogenic in humans. Because of this uncertainty, a range of other studies and information is used to assess the risk of tumors in humans, and an assessment is made by examining the bulk of the evidence.

The Carcinogenicity Studies Concern Appeared to Be Settled but Then Resurfaced

FDA found indications of carcinogenicity in the studies Schering-Plough submitted. In May 1987, the reviewing pharmacologist found some evidence of carcinogenicity in mice and rats. On several occasions after this, initially on August 17, 1987, FDA requested that Schering-Plough retabulate existing data. After this additional information was reviewed, a statistical review dated April 14, 1988, found some evidence that Claritin led to increased liver adenomas and benign tumors in male mice when administered at high doses but concluded that there was no increase in carcinomas.[5] Following this assessment, the reviewing pharmacologist concluded in an April 26, 1988, memorandum that the drug was approvable from a toxicology perspective if there was disclosure in the product labeling of the findings from the rat and mouse carcinogenicity studies. However, in August 1989, a new reviewing pharmacologist noted that additional data were needed to properly evaluate the rat studies.

Schering-Plough contends that a spring 1989 FDA reorganization was a major factor in delaying the Claritin approval process. When this reorganization occurred, the Claritin NDA was transferred from the Division of Surgical-Dental Drug Products to the Division of Oncology and

[5]An adenoma is a noncancerous tumor or growth arising in the lining or inner surface of an organ; a carcinoma is a cancerous tumor.

Pulmonary Drug Products. While the medical officer remained the same, new reviewers (including a new primary pharmacologist) were assigned to examine other aspects of the NDA. Schering-Plough believes that the new reviewers needed additional time to familiarize themselves with the data. In so doing, issues were raised that appeared to have been settled about 16 months earlier.

Schering-Plough speculates that FDA officials may have been influenced by then unpublished findings of a study by FDA's National Center for Toxicological Research on doxylamine, another antihistamine. The results indicated that doxylamine was associated with liver tumors in rats and mice. This could have heightened FDA's concerns about the significance of the animal tumor findings in other antihistamines for humans, since toxic issues are sometimes common across entire drug classes.[6] Schering-Plough notes that the concerns FDA raised in 1989 related to findings of liver toxicity in the long-term rat and mouse carcinogenicity studies, the same type of data discussed in the doxylamine study.

We found evidence of the importance of the doxylamine study in the FDA files on Claritin, although none of the evidence addresses whether this caused the carcinogenicity studies issue to be reevaluated. It is unclear when the results of the doxylamine study became known within FDA, although we do know that the draft report was released in August 1990. However, the importance of the study in the review of Claritin is clear. In April 1991, FDA decided not to schedule a meeting with Schering-Plough until the company had a chance to review the published doxylamine report. Also, a meeting of the Pulmonary and Allergy Drug Product Advisory Committee was held on June 13-14, 1991, in which the toxicology of antihistamines was discussed with regard to the doxylamine data. Finally, the division director noted in his final safety and efficacy summary October 19, 1992, that since his last review on September 11, 1989, there had been a reconsideration of the carcinogenicity study results as similar findings had been reported for other antihistamines.

[6]Safety concerns in medications in a therapeutic class can lead to FDA's investigating these concerns more carefully in other drugs in that class. See, for example, *FDA Premarket Approval: Process of Approving Ansaid as a Drug* (GAO/HRD-92-85, Apr. 17, 1992).

FDA Questioned the Adequacy of the Carcinogenicity Testing

After the carcinogenicity study issue resurfaced, FDA became concerned that the carcinogenicity testing for Claritin was inadequate. At a November 16, 1989, meeting with Schering-Plough, FDA officials informed the company that they were concerned about the effects of Claritin on the animal liver, including tumor formation. On January 19, 1990, at the request of the Division of Oncology and Pulmonary Drug Products, the Carcinogenicity Assessment Committee (CAC) reviewed the Claritin carcinogenicity studies.[7] The committee concluded that the studies showed a possible increase in mouse and rat liver tumors but noted that it found the data difficult to evaluate fully because of the way the tests were conducted and analyzed. It recommended that, at a minimum, a complete rereading of all the mouse and rat liver slides be conducted. CAC also suggested that a repeat of the mouse carcinogenicity study might be necessary if the approximate maximum tolerated dose was not used.[8] The committee was also concerned about the interpretation of the mouse lymphoma assay and believed that if the data were important, the study might need to be repeated. In March 1990, FDA requested carcinogenicity data from the rat and mouse studies to address the issues CAC raised. Schering-Plough submitted the information on June 19, 1990. FDA's review of these data concluded that the maximum tolerated dose had not been used in the mouse toxicity study. The rereading of the slides essentially confirmed the original findings. It showed increased liver adenomas and carcinomas in male mice. The rat studies were found to be equivocal.

CAC met again on November 2, 1990, but reached no firm conclusions on the significance of the animal liver tumor findings in the carcinogenicity studies of Claritin. The committee was satisfied with the rereading of the mouse and rat slides, and it was agreed that the reanalysis of the results did not significantly alter the outcome of either study. However, although it was agreed that the maximum tolerated dose was not used in the mouse study, opinion was divided on the need to repeat it. The committee did agree that the maximum tolerated dose had been used in the rat study.

[7]CAC is made up of FDA staff members from several reviewing divisions and outside consultants.

[8]The maximum tolerated dose is the highest dose that causes no more than a 10 percent weight decrement, compared with the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animals' natural life span.

Much of the discussion regarding the significance of the carcinogenicity studies concerned the location and type of the animal tumors. There was a significant increase in liver adenomas in male mice. There was much debate in the CAC about the importance of such an increase at a site where there is a high spontaneous rate of such tumors. It was agreed that an increase in adenomas at such a site is not as serious as an equivalent increase at a site with a low spontaneous incidence rate. There was also disagreement about whether adenomas progress to carcinomas.

On June 13-14, 1991, the Pulmonary-Allergy Drugs Advisory Committee (which had recommended approval of the drug in October 1987) met to discuss the toxicology data in light of the doxylamine findings. Schering-Plough officials presented data from the Claritin rat and mouse studies, concluding that the drug presented no cancer risk to humans. An FDA official described the abnormalities that were found and expressed concerns about the dosing levels used in the mouse study. The committee voted five to one that Claritin was unlikely to be a human carcinogen, although it unanimously agreed that the data were not sufficient to support a conclusion regarding the drug's human carcinogenic potential. On September 9, 1991, the reviewing FDA pharmacologist wrote in his review that the NDA was approvable from the standpoint of pharmacology and toxicology.

Other FDA officials remained concerned about the implications of the carcinogenicity study results of Claritin because of several findings. These included, first, the mouse carcinogenicity study being done at a fourth to a third of the maximum tolerated dose, doses that FDA was concerned might be too low to fully evaluate the carcinogenic potential of the drug. Second, there were three marginal findings of tumors in rats. Third, the mouse lymphoma assay was positive in the absence of metabolic activity. Fourth, there were positive findings of increased tumors in the mouse study. Finally, although there was no clear increase in carcinomas in mice, FDA did not find their absence reassuring because the tests were not done at the maximum tolerated dose.

Some officials within FDA remained concerned about the maximum tolerated dose not being used in the mouse studies. These officials believed that because this dose had not been used, the findings in these studies were suspect. However, Schering-Plough argued that the doses used in the study were satisfactory. The company had told the Pulmonary-Allergy Drugs Advisory Committee that for the long-term mouse carcinogenicity study it used doses of up to 200 times the clinically effective dose, corresponding to

blood levels of Claritin 4 times the level that would occur in humans and blood levels of the metabolite 18 times the human level.

One component of FDA's concern about the results of the carcinogenicity studies of Claritin resulted from a genotoxicity test known as the mouse lymphoma assay.[9] Schering-Plough contended that the positive finding in this assay in the absence of metabolic activity was in fact a false positive and should be disregarded because of negative results in all other genotoxicity screens. Furthermore, it believed that this assay might give an inappropriately high incidence of false positive results and be highly influenced by toxicity considerations. Some FDA officials did not believe the findings should be dismissed. One FDA official noted that each genotoxicity test asks a different question. Consequently, a different genotoxicity that is negative cannot negate a positive finding in the mouse lymphoma assay.

FDA raised another genotoxicity issue in May 1992. FDA determined that the Ames/Salmonella test (another screen for genotoxicity) that Schering-Plough submitted in the original NDA was invalid because the doses that had been used were too low. FDA believed that the repetition of the Ames test with higher concentrations could lead to a final conclusion on Claritin's mutagenic activity. One reviewer noted that because of weak tumor-causing responses in the animal tests, Claritin's potential for genotoxic activity needed to be investigated fully before considering approval. Schering-Plough believed that the original dosing was appropriate and stated in a letter to FDA the rationale for the doses used in the Ames test. However, FDA disagreed and on July 20, 1992, asked Schering-Plough to conduct a second Ames test using higher doses of the drug, and the company agreed to do so. The results were submitted in August and the company reported that the results were negative. In September, FDA informed Schering-Plough that the second Ames test was satisfactory and that FDA wanted to move along with an approvable action after receipt and approval of a new safety update. FDA and Schering-Plough then worked on an appropriate label, and the drug was approved in April 1993.

Schering-Plough contends that FDA's reevaluation of the carcinogenicity study data resulted in the company's losing about 4 years of effective patent protection. The company notes that the labeling requirements for the

[9]Genotoxicity refers to the adverse health effect a chemical has on genes and chromosomes. Genotoxicity tests are used to identify carcinogens.

animal tumor issue that was adopted in 1993 were very similar to those FDA proposed and Schering-Plough agreed to in 1988. However, FDA officials told us that the fact that the results of FDA's investigation did not lead to significant label changes does not necessarily mean that the inquiry was inappropriate. FDA officials were uncertain that Claritin met the safety requirements for its being approved and, consequently, investigated the drug until they were convinced that the carcinogenicity data concerns should not cause the drug to be kept off the market. The information resulting from the inquiry could have contributed to FDA's believing that the original labeling requirements were appropriate. When FDA approved the drug, it was implicitly acknowledging that the carcinogenicity issue had been satisfactorily addressed.

FDA Needed to Develop a Policy but Expert Opinion Was Divided

The Claritin NDA appears to have been caught in an internal policy debate at FDA regarding the marketing status of antihistamines with low-grade positive carcinogenicity findings and whether these drugs were approvable. The decision was made more difficult by the large amount of controversy in the field of toxicology about animal carcinogenicity studies. Opinion was divided regarding the relevance of animal carcinogenicity studies for humans, including the high level of sensitivity of these studies, the need to use the maximum tolerated dose in animal cancer studies, the interpretation of marginal findings in animal studies, the importance of any findings that might be based on physiologic mechanisms (which may or may not be species-specific), and the relevance for humans of findings in animal livers.[10] Thus, FDA was in a position in which it needed to develop a policy but could not look to the scientific community for consensus.

FDA and Schering-Plough Disagreed on How to Demonstrate Bioequivalence

Schering-Plough believes that FDA's concerns about the bioequivalence of the capsule and tablet forms of Claritin were unfounded and resulted in unnecessary delay in the drug's approval. The clinical trials of Claritin tested a capsule rather than the tablet Schering-Plough planned to market. Although this is not uncommon, the NDA sponsor needs to show that the two dosage forms of the drug are equivalent in order to obtain FDA's approval.

[10]Sensitivity refers to an organism's being highly responsive or susceptible. In this case, animals were viewed as being highly likely to develop tumors.

Before the NDA was filed, Schering-Plough informed FDA that it planned to seek approval to market the tablet form of the drug instead of the capsule that had been used in the clinical trials. FDA had no objections to Schering-Plough's pursuing this strategy. However, after FDA biopharmaceutic experts reviewed the 13 studies Schering-Plough submitted to establish the bioequivalence of the tablet and capsule, they concluded that the data did not support such a finding. In reviews dated May 25, 1988, and August 22, 1988, the FDA official reviewing these data wrote that the application was unacceptable.

This issue arose because of disagreement between FDA and Schering-Plough on what needed to be done to demonstrate bioequivalence. Claritin is rapidly converted to a primary metabolite.[11] Consequently, Schering-Plough believed that the bioequivalence of the parent drug should be ignored and only the metabolite should be studied for bioequivalence. FDA disagreed, noting that the drug is not completely metabolized and that the bioequivalency for both the parent and metabolite needed to be established. The difficulty was establishing bioequivalence for the parent compound because Schering-Plough and FDA agreed that the bioequivalence of the metabolite had been shown.

Given this disagreement, the company decided to conduct a therapeutic equivalence study in which the tablet, the capsule, and a placebo were compared in approximately 450 patients. The study was conducted in the fall of 1988 and the results were submitted to FDA on November 23, 1988. FDA pharmacologists concluded in January 1989 that while bioequivalence had not been shown with traditional methods, the point would be moot if the therapeutic equivalence study was acceptable. Consensus was reached at FDA in March 1989 that the results of the therapeutic equivalence study adequately demonstrated equivalent efficacy. Thus, approximately 2-1/2 years after the NDA was submitted, the bioequivalency issue was resolved. This position was confirmed by the responsible Acting Division Director at FDA, who concluded in his September 11, 1989, review that the 450-person clinical study established the equivalence of the tablet and capsule.

[11]A metabolite is any substance produced or used during metabolism (digestion). In drug use, a metabolite usually refers to the end-product (what remains after metabolism).

Other Issues That Arose During the Approval of Claritin

While not as significant as carcinogenicity and bioequivalence, several other issues may have affected the approval of Claritin. FDA had some concerns about the data that were submitted to support the claim that Claritin was nonsedating, and there were also questions about the effectiveness of the 10 milligram dose of the drug. In addition, there is evidence to suggest that the 1989 reorganization resulted in Claritin's receiving a lower review priority in the new division than it would have had in the original division. Conversely, it appears that the approval of Claritin may have been given a higher priority at FDA when concerns about the toxicity of already marketed antihistamines arose.

FDA Questioned Whether Claritin Was Nonsedating

Schering-Plough claimed that Claritin was a nonsedating antihistamine, something that would distinguish it from all but one antihistamine on the market when the NDA was filed. Soon after receiving the NDA, FDA reviewers began to examine whether the drug had sedative effects. They identified a number of issues regarding the availability and quality of the data on sedation as well as indications that the drug might be sedating. For instance, in an October 1987 review, an FDA official concluded that no definitive conclusions on sedation resulting from the 10 milligram dose could be drawn because of the flawed nature of the studies.

In spring and summer 1987, FDA reviewers raised concerns that the studies submitted in the NDA did not show nonsedation. They found indications that drowsiness was among the most common adverse reactions and was somewhat dose-related—that is, the tendency to induce sedation increased with larger doses. In November 1987, the FDA medical officer concluded that sedation would have to be included in the label as an adverse reaction. As FDA continued to assess this issue in 1988, it concluded that the 10 milligram dose was no more sedating than a placebo. However, it also found that the 40 milligram dose was more sedating.[12] In a letter to Schering-Plough on May 16, 1988, the Acting Director of the Division of Surgical-Dental Products informed the company of these conclusions.

[12]Schering-Plough had plans to market only the 10 milligram dose. Because of this, Schering-Plough officials questioned the appropriateness of FDA's presenting data on the 40 milligram dose to an advisory committee. FDA responded that it was primarily for completeness and that the difference in efficacy and sedation between the two doses was a basic part of the evaluation.

FDA Questioned Claritin's Effectiveness

While FDA was assessing the bioequivalence and sedation issues, it was also examining the efficacy of Claritin. Soon after the NDA was filed, FDA reviewers began to examine the efficacy of the 10 milligram dose. In a January 9, 1987, telephone conversation, the FDA medical officer told a Schering-Plough official that it appeared that the 10 milligram dose was not very effective but that the 40 milligram dose was effective. An FDA statistical review completed in July 1987 raised a number of issues about the design and results of the studies, including indications that the drug was not effective. The reviewer concluded that the studies failed to provide substantial evidence that the drug was effective. FDA sent these concerns to the company on August 6, 1987, and the company responded by letter later that month. At its October 22-23, 1987, meeting, the Pulmonary-Allergy Drug Advisory Committee concluded that the minimum clinically effective dose was 10 milligrams. As the review process continued in 1988 and 1989, the FDA medical officer expressed his concern that 10 milligrams was not the optimal dose. However, by July 1989, a consensus had developed at FDA that 10 milligrams was effective.

Schering-Plough's Response

Schering-Plough believes that the issues of nonsedation and effectiveness did not at all delay FDA's approval of the Claritin NDA. We thought that it was important to note that there were issues in addition to carcinogenicity and bioequivalence about which FDA had concerns. FDA's analysis of these issues took up resources which, if used differently, could have decreased the approval time. In addition, these concerns continued to be discussed within FDA at least until 1988 for nonsedation and 1989 for effectiveness. Consequently, an early resolution of the bioequivalence issue would not necessarily have resulted in an earlier approval.

The FDA Reorganization May Have Decreased the Review Priority of Claritin

Schering-Plough contends that the spring 1989 FDA reorganization resulted in Claritin's receiving a lower review priority in the new reviewing division than it would have had in the previous division. The evidence for this position is mixed. The therapeutic potential classification of C for Claritin stayed the same after it was transferred. However, the new division approved more higher-priority A and B drugs than the old division, thus

relatively de-emphasizing the C drugs. Therefore, relative to the other drugs in the two divisions, Claritin's priority decreased.[13]

Approval May Have Been Aided by Toxicity Concerns in Other Antihistamines

The approval of Claritin may have been aided by unexpected adverse events being associated with other nonsedating antihistamines. In FDA's deliberations on the carcinogenicity studies of Claritin, it was noted that marketed antihistamines did not produce the same animal tumor findings as demonstrated in the Claritin studies. Consequently, because of these safety concerns, FDA believed that the approval of Claritin might be inappropriate since it offered limited or no benefit over the other drugs. This view began to change in the early 1990s, when both Seldane and Hismanal, the only nonsedating antihistamines on the market, were linked to cardiac events. As this developed, FDA officials started to believe that it would be beneficial to have Claritin for sale. The practical effect of this development was to increase the therapeutic potential of Claritin, because it now appeared to offer some benefit beyond previously approved drugs. The Division Director wrote in his October 19, 1992, final safety and efficacy summary that because Claritin at clinically useful doses is no more sedating than placebo, a slight uncertainty regarding the mechanism by which Claritin promotes animal tumors is acceptable, given the cardiotoxicity associated with Seldane and Hismanal.

[13]Because the numbers of reviewers in the two divisions were comparable, differences cannot be explained by staffing levels. However, because we have no information on drugs that were not approved, we cannot ascertain the workload for each division.

Approval Process for Relafen

SmithKline Beecham Corporation holds the patent for Relafen, a nonsteroidal anti-inflammatory drug (NSAID) that is used to relieve symptoms of osteoarthritis and rheumatoid arthritis. Relafen had U.S. sales of $405 million in 1999, making it the largest selling prescription NSAID in the country. The patent for Relafen was issued on December 13, 1983, and is scheduled to expire on December 13, 2002. The company filed a new drug application with FDA on February 6, 1986, for approval to sell Relafen. On the basis of Relafen's therapeutic potential, FDA assigned Relafen its lowest review priority, a C ranking. This means that FDA determined that the medication would provide little or no therapeutic gain compared with an already marketed drug. The NDA was approved on December 24, 1991. SmithKline Beecham contends that the 71 month review period taken by FDA to grant approval caused it to lose valuable patent life from the marketing of the drug.

During the early 1980s, before the approval of Relafen, some NSAIDs already on the market were associated with fatal and other serious adverse reactions.[1] SmithKline Beecham contends that these problems, in effect, slowed down the review time of Relafen because FDA officials were concerned that other drugs in the NSAID class might have similar problems. In addition, SmithKline Beecham claims that there were prolonged periods when FDA did not provide feedback regarding the agency's assessment of the safety and efficacy of the drug. Instead, the company believes that FDA focused the majority of its resources on reviewing the chemistry and bioequivalence data rather than on the clinical information. Furthermore, SmithKline Beecham stated that only one NDA was being reviewed at a time within the NSAID class. As a result, the company claims that Relafen was placed in a queue and not reviewed in a timely manner. It also argues that the lack of resources at FDA contributed to delaying Relafen's approval.

Approval Time for Relafen

The approval time for Relafen was 70.5 months. This exceeded the average approval time of 57.6 months for the 13 category 1C NSAIDs approved during 1975 to 1993 (with a range of 20.3 to 122.5 months). As a result, the approval time for Relafen was greater than about 67 percent of the NSAIDs. The approval time for Relafen exceeded the longest approval time of all 1C

[1]Oraflex was voluntarily withdrawn from the market by the manufacturer on August 5, 1982, while Zomax was withdrawn in March 1983. Feldene is still available, although it was relabeled in 1983.

drugs approved between 1983 and 1985, around the time the Waxman-Hatch Act was passed.

However, the picture for Relafen changes if the drugs are divided into those approved before and after 1984. In the early 1980s, several NSAIDs already on the market were found to be associated with adverse reactions. Consequently, FDA became cautious about approving new drugs in this class. The average approval time for NSAIDs approved before 1984 was 30.8 months, with a low of 20.3 months and a high of 48.2. The average time for drugs approved between 1984 and 1992 was 80.7 months, with a range of 45.9 to 122.5.[2] Relafen, which was approved in 1991 and had an approval time of 70.5 months, is actually below the average for 1C NSAIDs approved after the safety concerns were raised. Approximately half of these drugs had shorter approval times than Relafen and half took longer to be approved.

Missing and Incomplete Information in the Relafen NDA

NDAs are complex documents that require a significant amount of information from drug manufacturers. NDAs that are fairly complete can lessen the time FDA requires for review. The FDA officials we spoke with told us that the Relafen NDA had a significant amount of incomplete and missing information.[3] For example, the company was attempting to get a specific type of liquid dose approved but did not supply complete information that could validate the contents of this liquid. As a result of the incomplete application, SmithKline Beecham had to submit several amendments to the application and respond to FDA questions. According to FDA officials, the submission and review of these amendments and requests for additional information increased the review time of the NDA, although the extent of this increase cannot be specifically quantified.

[2]These times reflect that there were no 1C NSAID approvals from April 1982 until December 1985.

[3]When the Relafen NDA was submitted, FDA allowed incomplete applications to be submitted. However, FDA officials indicated that the Relafen NDA had more missing and incomplete information than was usually found in other NDAs. With the passage of the Prescription Drug User Fee Act of 1992, incomplete applications are no longer permitted.

FDA Efficacy and Safety Review of Relafen

FDA files contain little evidence of communication between the company and FDA about drug efficacy during the approval process. SmithKline Beecham suggested that FDA delayed the review of efficacy of the drug. According to company officials, FDA did not communicate with SmithKline Beecham about the drug's clinical review for the first 3 to 4 years following the submission of the NDA. While there was no documentation of such reviews being done during this period in the FDA files, we cannot conclude with certainty that these reviews did not occur because the information may have been missing.

We located a comprehensive summary of the safety and efficacy of Relafen that was developed after the final approval of the NDA, but it did not chronicle the clinical review throughout the approval process. We did identify a pharmacology review that was conducted about 6 months after the NDA was submitted that dealt with animal tumors, but the review did not indicate whether or not a medical officer had been assigned.

Serious Adverse Reactions Among Other NSAIDS

In many cases, adverse drug reactions are common within a drug class. As a result, all NSAIDs could potentially share common adverse reactions. In 1982, more than 9 years before FDA approved Relafen, three of the NSAIDs on the market (Feldene, Oraflex, and Zomax) had reports of fatal and nearly fatal reactions. Oraflex and Zomax were subsequently removed from the market, while Feldene was relabeled in 1983 and remains on the market. Another NSAID (Suprol) was taken off the market in 1987 because of adverse effects on the kidneys. SmithKline Beecham claims that the close attention given to the adverse events of these other drugs caused FDA to be overly cautious in its review of Relafen. Between 1982 and 1987, the Congress held several hearings about the adverse reactions of NSAIDs.[4] During these hearings, the FDA approval process was criticized. It was noted that the manufacturers had not reported a large number of adverse reactions to FDA. Because of the serious concerns over public health, FDA began to review new NSAID applications in a more detailed manner to help ensure that NSAIDs under review would not cause similar problems if they were approved. However, according to SmithKline Beecham officials, the resulting attention given to the problems of the other NSAIDs was unfairly

[4] *FDA Premarket Approval: Process of Approving Ansaid as a Drug* (GAO/HRD-92-85, Apr. 7, 1992) and *FDA Premarket Approval: Process of Approving Lodine as a Drug* (GAO/HRD-93-81, Apr. 13, 1993).

cast upon Relafen. The manufacturer of one of these other drugs stated that the adverse drug reactions associated with NSAIDs on the market at that time were not unknown before concern was raised in the Congress and were not beyond what might be expected. However, these concerns led FDA to examine the safety of new NSAIDs in more detail. As a result, there were no 1C NSAID drug approvals from April 1982 until December 1985.

Further, according to SmithKline Beecham officials, the Division Director commented that a moratorium was placed on approvals because it was his opinion that enough NSAIDs were already on the market.[5] SmithKline Beecham officials contend that only one NDA was then being reviewed at a time, further slowing the approval of Relafen. However, FDA officials told us that they did not recall such a policy.

Chemistry Issues Delayed Approval

According to FDA's files, several issues regarding the chemistry of Relafen surfaced during the NDA approval process. For example, FDA officials requested that SmithKline Beecham provide more complete information about the purity and stability of the drug and various specifications used in the manufacturing process to ensure the drug's quality. Predominately, FDA officials requested chemistry information from the company that was missing or incomplete in the original NDA. FDA officials told us that these chemistry concerns were "technical."[6] These concerns were a result of 11 separate chemistry reviews FDA conducted between February 1986 and November 1991. SmithKline did not address many of the chemistry concerns identified in the early FDA reviews to FDA's satisfaction until the latter part of the approval process. In some cases, FDA files show that agency staff had to repeatedly ask the company to address certain issues and that chemistry concerns persisted for more than 5 years. Although we were unable to find documentation of the final resolution of these chemistry concerns, we did locate information about an amendment submitted on November 14, 1991, that contained responses regarding the chemistry concerns. Given that the drug was approved within 6 weeks of this date, we assume that FDA was satisfied with the company's responses.

[5]FDA questions whether such a moratorium was placed on NSAID approvals.

[6]FDA uses technical comments to ask a drug manufacturer to clarify or provide more information about a specific issue.

Approval Process for Cardiogen-82

Cardiogen-82 is a radioactive diagnostic agent that is administered by intravenous injection. It is used in adults with suspected heart attacks to distinguish normal from abnormal middle muscular layers of the heart wall. The patent for Cardiogen-82 was filed on November 21, 1980, and issued on August 23, 1983. It is scheduled to expire on August 23, 2002.

FDA received the NDA from Squibb Diagnostics, the manufacturer of the drug, on December 28, 1984.[1] When the NDA was submitted, a number of radioactive diagnostic products were already on the market. On the basis of its assessment of the therapeutic potential of the drug, FDA assigned Cardiogen-82 its lowest review priority, a C ranking.[2] This means that FDA believed that the medication would provide little or no gain compared with an already marketed drug. The NDA was approved on December 29, 1989, 60 months after it was submitted. The average approval time during 1975 to 1993 for 1C drugs in this therapeutic class (radioactive diagnostic aids) was 49.3 months, with a low of 19.9 months and a high of 83.5. About 60 percent of drugs in this class were approved faster than Cardiogen-82.

FDA had concerns with the chemistry and manufacturing section of the NDA and the section assessing the efficacy of the drug. These concerns resulted in FDA's sending a not approvable letter to Squibb on July 3, 1986, stating that the drug could not be approved without additional information from the company. On February 26, 1987, Squibb submitted clinical information to FDA and requested a meeting to discuss a subset of the clinical issues raised by FDA in the not approvable letter. The meeting was held on May 5, 1987. On January 5, 1988, Squibb submitted information requested by FDA at the May 5 meeting. FDA wrote to Squibb on January 27, 1988, 19 months after the not approvable letter was issued, asking the company to voluntarily withdraw the application until all requested information was provided. FDA noted that Squibb had not yet provided a complete response to the deficiencies discussed in the not approvable letter. The manufacturer withdrew the application on March 3, 1988, and then resubmitted it with additional information on July 11, 1988. Thus, while the drug took 60 months to be approved from its original submission, in effect, FDA waited 24 months from July 1986 to July 1988 for Squibb to submit a complete response to the not approvable letter. FDA tracks the

[1]The drug is manufactured by Bristol Myers Squibb Company and marketed by Bracco Diagnostics Inc., which purchased the drug from Squibb in July 1994.

[2]A C ranking was given, even though the claim being made for Cardiogen-82 was unique.

time it takes companies to resubmit an application following a not approvable letter or withdrawal of the drug. The agency subtracts this time from the total approval time for a drug. The agency refers to this as "FDA approval time."[3] The FDA approval time for Cardiogen-82 was 35.5 months. The average FDA approval time for other 1C radioactive diagnostics was also 35.5 months (with a range of 18.6 to 56 months). Approximately 50 percent of 1C radioactive diagnostics were approved faster than Cardiogen-82 when FDA approval time is considered.

Bracco officials contend that one reason for the lengthy review process was the change in FDA reviewers during the approval process. We found that the individuals doing the chemistry and medical reviews did change. However, while this could lengthen the review process, we were unable to determine whether this had any effect on the approval period.

Bracco officials have also noted that a 5-year FDA approval time was not unusual for medical imaging products that were being reviewed around the time Cardiogen-82 was evaluated. Also, they believe that the dialogue between the manufacturer and FDA was typical of that for NDAs. We found that 40 percent of comparable radioactive diagnostics were approved more slowly than Cardiogen-82 in the years we examined (1975-93). Also, an FDA official told us that there was a backlog of NDAs in FDA's Division of Medical Imaging and Surgical-Dental Drug Products in the late 1980s and early 1990s.

FDA Found the NDA Difficult to Evaluate

Overall, FDA reviewers found the NDA to be confusing, incomplete, poorly organized, and filled with unexplained discrepancies. They noted that the case reports for individuals in the studies gave a different impression than what was presented in the summaries and tables. Also, FDA found that it was unable to determine how many patients were enrolled in the studies or how many studies were conducted. FDA officials also noted that some reports that the manufacturer had submitted to FDA were not referred to in

[3]In addition to the time associated with a not approvable letter and a drug's withdrawal, FDA approval time does not include the time involved when the agency "refuses to file" an application. FDA can refuse to file an application if it determines that the information contained in the NDA is not sufficient to permit a substantive review. FDA approval time excludes the time from FDA's initial receipt of an NDA to the refusal to file action and the time from refusal to file to resubmission.

the NDA. Moreover, an FDA official concluded that none of the studies were designed to examine the use of the drug as discussed in the NDA.

Deficiencies in the Chemistry Section of the NDA

The chemistry review of the Cardiogen-82 NDA began within 2 months of the application's being filed, and the deficiencies found in the chemistry review were conveyed by letter to the manufacturer on August 15, 1985. In the initial FDA chemistry review, the reviewer noted that FDA had found a number of deficiencies before the NDA was submitted and the manufacturer had been informed of these concerns at that time.[4] The reviewer also found a number of problems with the NDA, and the manufacturer was informed of these concerns in the August 1985 letter. Among these difficulties were (1) the lack of a full statement of the components and quantitative composition of the drug product; (2) inadequate manufacturing information, including information on the methods used in the synthesis, extraction, isolation, and purification of the drug product; (3) failure to include adequate laboratory test procedures to ensure that the finished drug product conforms to appropriate standards of strength, quality, and purity; (4) reservations about the adequacy of the stability tests for the drug; and (5) shortcomings in the proposed label for the drug. On July 3, 1986, FDA sent Squibb a not approvable letter citing the same chemistry problems that had been sent to the manufacturer nearly 11 months earlier.

Squibb submitted a chemistry amendment on May 4, 1988, in response to the issues FDA raised in the not approvable letter. An additional chemistry amendment was submitted on October 3, 1988. However, after reviewing the submissions, FDA found that a number of deficiencies remained. These were sent to the company on December 15, 1988. Squibb discussed them with FDA on February 24, 1989, and responded to them on March 3, 1989. A chemistry review completed on March 10, 1989, concluded that there were no remaining chemistry questions.

[4]On September 9, 1982, FDA had sent the manufacturer a chemistry deficiencies letter. According to FDA, these deficiencies were still present when the NDA was submitted on December 24, 1984, and they persisted for some time.

FDA Identified Problems in Data Supporting the Efficacy of the Drug in the Not Approvable Letter

FDA also cited clinical deficiencies in the July 3, 1986, not approvable letter. For example, the studies that were submitted to support the efficacy and safety of the drug used a different method for injecting Cardiogen-82 into the body than were identified in the proposed package insert included in the NDA. FDA believed that additional studies were needed to show the proper use of these other methods. Also, FDA found problems with the design of the submitted studies. Agency officials were concerned that there were too few patients on which to base approval. In addition, the results of the clinical trials varied according to what device was used to judge how well the drug worked. Different devices gave different indications of the effectiveness of the drug. FDA had previously informed Squibb about many of these problems in a November 12, 1985, meeting.

Approximately a month after the not approvable letter was issued, the company informed FDA that it intended to file an amendment addressing FDA's concerns. Squibb submitted clinical information to FDA in February 1987 and, at FDA's request and in preparation for a meeting, submitted a draft response to the efficacy concerns in April 1987. Agency and Squibb officials met on May 5, 1987, to discuss several of the clinical issues raised in the not approvable letter. The information requested by FDA was submitted to the agency on January 5, 1988.

However, FDA still had concerns about the data that were used to support the efficacy claims for Cardiogen-82. FDA reviewers found that they could not determine how many patients had been studied. Also, FDA was concerned that some patients were excluded from analyses without appropriate justification. In addition, FDA found that the tabulated data often seemed to give a picture of the effectiveness of the drug different from that of the raw data.

In a March 29, 1989, letter, FDA informed Squibb that there were still a number of problems with the NDA and that it would be necessary to reanalyze and reorganize the clinical data. FDA and Squibb officials met on April 3 and 13, 1989, to discuss the issues raised in the letter. At the April 13 meeting, Squibb noted that it no longer had the data and was unsure whether they could be retrieved from the investigators because the studies had been completed a number of years earlier. FDA told Squibb that it should attempt to retrieve all the data. On June 9, 1989, Squibb informed FDA that it had found all the original patient scans but that analysis would be difficult because of necessary computer conversions.

In June 1989, Squibb officials suggested approving the drug for a narrower indication than was described in the NDA, with the promise that it would analyze the data on the original claim within 6 months.[5] While FDA did not believe it was ideal to approve the drug for the alternative claim, the drug could be approved as long as it was of some value. It was agreed at FDA that Cardiogen-82 was useful in the evaluation and diagnosis of heart attacks, and in December 1989 Cardiogen-82 was approved for this purpose.

[5]The use sought in the Cardiogen-82 NDA was for assessing the specific location of heart problems. The new claim was for the drug to be used to distinguish normal from abnormal middle muscular layers of the heart wall in patients with suspected heart attacks.

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