

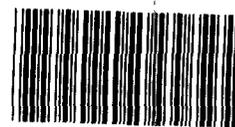


United States General Accounting Office  
Report to Congressional Requesters

April 1992

# FDA PREMARKET APPROVAL

## Process of Approving Olestra as a Food Additive



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**Human Resources Division**

B-247488

April 7, 1992

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

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

Since 1971, the Procter & Gamble Company (P&G) has been working to obtain premarket approval by the Food and Drug Administration (FDA) for Olestra—a noncaloric fat substitute with four U.S. patents<sup>1</sup> covering the substance. The initial patent expired in 1988, and the other three will expire in 1994. In 1991, bills<sup>2</sup> were introduced in the House and the Senate to extend the terms of Olestra's existing patents for 10 years, starting on the date of FDA approval.

P&G's belief that patent term extensions are justified rests largely on its claim that it developed a novel food additive for which FDA had no established regulatory approval path. P&G contends that approval was delayed because it had to help FDA pioneer a set of scientific and administrative procedures to review this substance.

To evaluate P&G's claim, hearings were held in August and October 1991 by, respectively, the Subcommittee on Patents, Copyrights, and Trademarks of the Senate Committee on the Judiciary and the Subcommittee on Intellectual Property and Judicial Administration of the House Committee on the Judiciary. During the hearings, another company alleged that P&G itself caused delays in approving Olestra. According to that company's testimony, P&G's own marketing decisions and its lack of diligence during the regulatory product approval process contributed significantly to the long period of time it is taking to obtain FDA's approval to market Olestra.

In an effort to weigh these accusations against P&G's claims supporting extension of Olestra's patent terms, you asked us to clarify the

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<sup>1</sup>A patent gives inventors exclusive right to make, use, or sell their inventions for 17 years.

<sup>2</sup>H.R. 2805 and S. 1506.

circumstances related to FDA's and P&G's actions during this 21-year period. To do so, we collected and analyzed pertinent documentation from both FDA's and P&G's files covering the period 1971 through March 1992 and interviewed their officials involved in the product approval and development process. Finally, on February 26, 1992, we met jointly with agency and company officials to clarify and better understand the circumstances surrounding P&G's efforts to obtain approval to market Olestra. Our results in this report are based primarily on documentation from, and interviews with, P&G and FDA. We did not determine whether it would be appropriate to extend the patent terms for Olestra.

We focused on three major factors that P&G believes justify an extension of its Olestra patent terms:

1. Lack of a clear regulatory approval path for Olestra within FDA,
2. Extensive amount of work between P&G and FDA before seeking FDA food additive review, and
3. The time needed to work with FDA officials to determine the sequence of the tests needed for Olestra approval and complete them.

Our work was performed from December 1991 through March 1992 in accordance with generally accepted government auditing standards. As requested by your offices, we did not obtain written comments on this report. However, we obtained the views of responsible agency and company officials during the course of our work and incorporated them where appropriate. Officials from P&G and from FDA's Center for Food Safety and Applied Nutrition (formerly the Bureau of Foods) and the Center for Drug Evaluation and Research generally agreed with our characterization of their respective positions.

## Principal Findings

Various factors have contributed to the extended period of time it is taking to obtain FDA approval of Olestra. Twenty-one years have elapsed since P&G obtained its first patent on the product. Although P&G viewed Olestra as a food additive, it was unusual in being also a "macroingredient," present in food in greater quantities than other additives.<sup>3</sup> Because FDA lacked a clear approval process for such substances in the 1970s and 1980s, P&G pursued approval for Olestra not only as a food additive but

<sup>3</sup>Food additives which could be present in amounts above 10 percent by weight in relation to the overall food product are called "macroingredients." Olestra is considered to be such a substance.

also as a drug. Between 1975 and 1985, P&G spent significant time and resources exploring the product's properties and its potential as a drug.

It was the decision to concentrate company resources on getting Olestra approved as a drug that a P&G competitor alleges cost the company valuable time. P&G officials deny this, stating that they pursued only one regulatory goal with FDA on Olestra: to follow the fastest possible route to approval, supported by appropriate safety data, of Olestra's use in foods. In response to our written questions, however, FDA stated that, had P&G focused on Olestra's use as a food additive in the early 1970s and pursued it vigorously, the company could have had a head start in resolving current safety questions.

In 1985, P&G learned that it might be able to make limited health claims about food products. Accordingly, in 1987 P&G submitted a food additive petition (FAP) for Olestra. The FAP raised issues with which FDA had little experience. Because Olestra was a unique substance, the agency's guidance was more tentative than usual. According to FDA, the knowledge gained from the Olestra review process could help the agency determine what testing is acceptable and help it establish an approval process for other macroingredients.

Also a source of delay was the broad range of Olestra's intended uses, as cited in P&G's 1987 petition, which required the company to respond to reviewers' questions about all intended uses. P&G's strategy until 1990, when it did narrow down its FAP, was to introduce Olestra in a wide variety of products. However, the petition created major challenges for FDA reviewers because P&G's test results and other data applied to various formulations and potentially broad uses of Olestra, such as shortenings, salad oils, cooking oils, and snacks (potato chips, corn chips, and the like).

Another lengthy process concerned developing testing protocols and conducting tests for Olestra. P&G first needed to develop, in collaboration with FDA, innovative approaches for testing macroingredients. FDA stated that it preferred tests to be sequential rather than concurrent because some were done simply to design more conclusive studies.

P&G believes that only completion of a study of Olestra's effects on pigs stands between Olestra and FDA approval. Although P&G expresses concern about the need to conduct the pig study, FDA insists it is necessary.

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## Background

P&G developed Olestra as a nonabsorbent lipid<sup>4</sup> food additive that is chemically different from ordinary fat substances because its molecules are too big to be broken down by the body's digestive juices. Consequently, it passes through the digestive system without being measurably absorbed.

Olestra also differs from other food additives in that it is a "macroingredient." Typically, a food additive is used in amounts below 1 percent by weight in relation to the overall food product. However, Olestra may be present in some foods in amounts well above 10 percent. Existing FDA safety tests involve feeding animals large amounts—100 times the expected level of human consumption. In the case of Olestra, however, testing techniques cannot be used with the estimated consumption volume required to test safety.

Different units of FDA regulate foods and drugs—including food additives and new drugs. The Center for Food Safety and Applied Nutrition regulates food additives, while the Center for Drug Evaluation and Research approves new drugs. A food additive manufacturer must show that an additive is safe; a drug sponsor, that a drug is both safe and effective. The two centers operate independently but cooperatively and, for companies pursuing both approval paths, can work with the company concurrently.<sup>5</sup>

The formal approval process for food additives is initiated by the manufacturer filing a food additive petition. Similarly, the formal process for drug approval is initiated by the sponsor filing a new drug application (NDA).<sup>6</sup> A food additive petition or NDA can be filed at any time the petitioner believes it has the data necessary to satisfy FDA reviewers. It is common for a manufacturer to interact informally with FDA about the contents of anticipated submissions before filing a formal food additive petition or drug application.

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<sup>4</sup>A broad classification of fatty acids and triglycerides that have fatty properties, but do not dissolve in water.

<sup>5</sup>In practice, most sponsors primarily focus on approval of a substance through either the drug or food path—depending on the intended use of the product and claims it will make on the label.

<sup>6</sup>An NDA is an application requesting FDA approval to market a new drug for human use. It contains data from human clinical studies needed for FDA review from specific technical viewpoints such as chemistry, medical, and pharmacology.

## Clarification of Circumstances Surrounding Olestra

P&G officials first met with FDA's Bureau of Foods in May 1971 to discuss Olestra. The same year, P&G obtained its first patent on the product. In the 21 years between then and March 1992, important actions relating to Olestra have been taken, as table 1 highlights, and views on these actions have differed widely. A discussion of the chronology of Olestra follows.

**Table 1: Highlights of Olestra Approval Process Chronology (1971-92)**

Date	Action
May 1971	First meeting held between P&G and FDA
April 1973	Human studies initiated by P&G
November 1975	Investigational New Drug application filed with FDA by P&G
May 1982	First rat study discussed by P&G and FDA
October 1984	FDA liberalizes its policy on companies making health claims on food additives
April 1987	Food Additive Petition filed with FDA by P&G
August 1988	Investigational New Drug application inactivated by P&G
October 1989	Second rat study required by FDA
July 1990	P&G narrowed Food Additive Petition to savory snacks
March 1992	P&G conducting pig study required by FDA

### May 1971-November 1975

When P&G officials met with FDA's Bureau of Foods in 1971 concerning Olestra, they shared with the agency the company's discovery and its plans to perform controlled human feeding studies. P&G hoped the studies would culminate in FDA approving Olestra as a food additive. In 1973, P&G initiated human and animal studies to learn more about the biological and safety effects of this substance.

### November 1975-April 1987

After concluding some of its human studies in June 1975, P&G's results demonstrated that the primary noticeable biological change attributable to Olestra was a reduction in serum cholesterol. In its meetings with FDA, P&G discussed its intention to conduct more research to substantiate Olestra's cholesterol-reducing effects. FDA advised P&G that if it planned to make lower cholesterol health claims, Olestra would be regulated as a drug. P&G filed an investigational new drug (IND)<sup>7</sup> application in November 1975, and documents maintained by FDA covering the next 10 years refer to the company's tests for safety and efficacy. Company officials explained that P&G filed an IND and primarily focused on the drug approval path because it believed this was the most expedient regulatory path for FDA approval.

<sup>7</sup>An IND application gives FDA a vehicle for controlling drug manufacturers' human clinical testing of a new molecular entity prior to approval and marketing.

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By the early 1980s, research data showed that Olestra was not reducing the serum cholesterol levels of clinical trial participants by at least 15 percent. Thus, it did not meet FDA's minimum requirement for approval as a drug and P&G would be unable to market it as an over-the-counter drug. But company officials believed they would be able to make limited health claims because FDA had allowed Kellogg's All-Bran cereal to make cancer prevention claims in 1984. In a 1985 meeting with P&G, FDA officials had explained that the agency had liberalized its attitude towards companies making health claims about food products. In light of this meeting, P&G switched its focus to the food approval path and filed a FAP in April 1987.

P&G contends that it always pursued the quickest way to obtain premarket approval for Olestra. The company put more resources into drug approval, officials explained, because this path already had testing protocols that P&G could follow to prove that Olestra was safe.

A competitor argued that P&G took a risk in developing and planning for Olestra to be marketed as an over-the-counter drug. P&G's plans for this fell through, the competitor alleges, when hopes for significant cholesterol-reduction properties were not borne out in the clinical trials. In P&G's view, it was consistently diligent in working to obtain premarket approval but until April 1987 lacked sufficient data to support a food additive petition.

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#### April 1987-July 1990

When P&G submitted its FAP in 1987, FDA's Center for Food Safety and Applied Nutrition began to critically study and respond to it. Before FDA can approve a food additive, it must estimate the amount of the substance that will likely be ingested by the "heavy eater" so as to ensure the food additive's safety at that level of consumption.

FDA's documentation shows that P&G's 1987 FAP contained a broad scope of uses for Olestra, which FDA believed would make the company's job of proving safety time consuming and demanding. The 1987 FAP was quite broad even though FDA officials had suggested as early as 1971 that the company should identify a specific use for Olestra to eliminate the number of questions FDA would have on each use. P&G officials believe that their 1987 FAP adequately addressed all safety issues and claimed that narrowing down Olestra's use was unnecessary in the 1970s. They added that in 1986, FDA agreed on Olestra's potential exposure—only to reverse itself later.

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Not until the 1987 FAP was filed did staff from FDA's Center for Food Safety and Applied Nutrition review the Olestra petition comprehensively and in detail, they say. FDA cannot formally respond to a food additive manufacturer until a food petition is submitted. At that time, reviewers began review and evaluation of the large amounts of data contained in the petition. Much of the data P&G submitted pertained to earlier compositions of Olestra, which differed from that covered by the petition, reviewers found. After sorting through and reviewing the data, FDA concluded in 1989 that additional safety and nutritional tests were necessary.

P&G argues that FDA reversed itself in 1989 by requiring the company to perform a second nutritional test on another rodent species. P&G officials claim that in 1982, FDA Bureau of Food reviewers indicated that no follow-up to a 1982 rodent study was needed due to the reviewers' understanding that Olestra is not absorbed or metabolized in the body. Disagreeing, FDA reviewers state that the final decision on the need for a second rodent study could be determined only through a formal review of the test data submitted as part of the FAP in 1987. FDA reviewers told P&G in 1989 that, because of Olestra's potential for substantial human exposure and the existing absorption and toxicity data, they were now convinced of the need for a second rodent study.

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## July 1990-March 1992

In July 1990, P&G responded to FDA's request to narrow down its intended use of Olestra. The company submitted a revised FAP identifying Olestra's use as a fat substitute in savory snacks, such as potato chips. According to FDA officials, the narrowing down substantially helped P&G by eliminating many of the reviewers' safety questions on a variety of possible uses. P&G officials insist that their 1987 FAP adequately supported Olestra's potentially broad uses.

Given FDA's estimate of consumption, data from the petition showed that Olestra could have an adverse nutritional effect (severe vitamin depletion) and that safety was not yet assured. Therefore, FDA concluded, large animal testing—in the form of a pig study—was needed. As of March 1992, the company was conducting a pig study to measure the effects of Olestra on the level of fat-soluble vitamins in pigs. The results of this pig study are pivotal in obtaining FDA approval of Olestra as a food additive.

P&G officials believe that the pig study is costly, creates delays, and is unnecessary to prove Olestra's nutritional and safety effects. The company believes that its human clinical studies in the early 1980s already measured

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vitamin depletion levels in the blood. P&G consultants believe this measurement to be more accurate than that generated from a study of the vitamin effects of Olestra in pigs' livers, as FDA required. FDA insists that this study is essential to proving Olestra's safety in the quantity that might be ingested by the heavy eater.

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Unless you publicly announce its contents earlier, we plan no further distribution of this report until 10 days after its issue date. At that time, copies will be sent to appropriate congressional committees and subcommittees, the Secretary of Health and Human Services, the Commissioner of Food and Drugs, and other interested parties. It also will be made available to others on request.

This report was prepared under the direction of Mark V. Nadel, Associate Director for National and Public Health Issues, who may be reached on (202) 512-7119 if you or your staff have any questions. Other major contributors are listed in appendix I.

*for Edward A. Bensmore*

Lawrence H. Thompson  
Assistant Comptroller General



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