FDA Could Make Abbott Pull Synthroid, Popular Thyroid Drug, From the Market

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WASHINGTON -- The Food and Drug Administration has told the makers of Synthroid, one of the nation's most frequently prescribed drugs, that the medicine has a "history of problems" and cannot be recognized as "safe and effective."

The agency's statements raise the possibility that the 40-year-old drug, which has never been officially approved for use by the FDA, will be subject to regulatory action that could, in the extreme, include removal from the market -- a process that could begin as early as August.

Four years ago, the FDA said that makers of thyroid drugs like Synthroid, known generically as levothyroxine sodium, needed to get FDA approval for the drugs to continue marketing them. Abbott Laboratories, which acquired Synthroid's maker earlier this year, has said it will submit an application to the FDA detailing the drug's safety and efficacy and that it is confident the drug will be allowed to stay on the market. The company said this week that its reading of FDA notices indicated that it had to submit its application to the agency by Aug. 14.

But a spokeswoman for the FDA said the regulatory notices the agency has published on Synthroid and its competitors "don't include a provision" related to simply submitting an application by Aug. 14. The agency has not decided what it would do if the Aug. 14 deadline came and went before the drug received approval. But it would not rule out asking for the drug's removal and noted that there are two other approved drugs in Synthroid's class that could fill any void left by Synthroid.

Jane Axelrad, an FDA official, did note that "even if we were to decide it is appropriate to remove Synthroid from the market, it would take time for the patients to go to their doctors" and get prescriptions for new medications. "You can't just snap your fingers and take all Synthroid from the market on Aug. 15th."

The regulatory skirmishes between the FDA and Synthroid's maker date back a decade, when the drug was in different corporate hands. It is taken by patients who have hypothyroidism or other disorders of the thyroid, and such thyroid replacement therapy usually continues throughout the patient's lifetime. Synthroid had sales of $541.3 million in 2000 and, ranked by number of prescriptions written, was the third most frequently prescribed drug in the country, according to data compiled by IMS Health.
Synthroid went on the market more than four decades ago and never received formal approval from the FDA. Such approval was required, the FDA's spokeswoman said, but neither the agency nor the drug's current owner knows why it was never received. In the mid-1990s, the FDA began compiling data on adverse events associated with the use of Synthroid as well as with the use of its competitors. In 1997, it noted that "almost every manufacturer" of such drugs had reported recalls because of potency problems.

When such potency problems occur, the finely calibrated drug regimens that patients with thyroid problems need are likely to go astray, meaning their thyroids will function at less than the desired levels or go into overdrive -- problems the FDA found in its review.

"You have people going from hypothyroidism to hyperthyroidism every time they refill their prescriptions," said Mary Shomon of Kensington, Md., a patients activist and author of a book on thyroid problems, who added that she receives hundreds of e-mails a week from patients experiencing problems with their drugs. Patients "can swing from feeling like they are having a heart attack to feeling lethargic and experiencing weight gain," she said.

Further, she said, people who get a bad batch of the drug may not ever know it, because their symptoms aren't properly diagnosed. "In many cases, a doctor might say your last test results were normal, so it's not your thyroid," said Ms. Shomon, who has been an outspoken critic of some of the practices of Synthroid's owners. 'He might say, 'Get some more sleep' or 'Don't eat so much.'"

In 1997, the FDA notified makers of levothyroxine sodium that it was going to regulate the drug and that makers would have to submit so-called "new drug applications" establishing their drugs' safety and efficacy. In April 2000, the FDA extended the deadline for such approval to Aug. 14, 2001. The FDA noted that companies "may continue to market their products until Aug. 14" and that makers who marketed their drugs "without an approved application after that date would be subject to regulatory action."

Two other drugs -- Levoxyl from King Pharmaceuticals Inc. and Unithroid from Watson Pharmaceuticals Inc. and Jerome Stevens Pharmaceuticals Inc. -- have applied for and received approval from the FDA. "We understood that we had to have an approval by Aug. 14, 2001, and we still understand that to be the case," said James Green, a spokesman for King. "Of course, we are approved now. We take comfort in that."

Mr. Green said that it took about 10 months for the FDA to approve King's application, and that the company is now "preparing for the possibility" that it will have to fill a void in the market in August. Mr. Green estimates that Synthroid holds 60% of the U.S. market for levothyroxine sodium, while King's Levoxyl has 25%.

Instead of submitting its own application, Synthroid's maker at the time -- Knoll Pharmaceuticals -- submitted a "citizen's petition" requesting that the FDA determine that Synthroid is "generally recognized as safe and effective" and not subject to regulation as a new drug, FDA records show. In late April, however, the FDA replied to the petition, noting that the drug's composition has been changed repeatedly and that the drug "has a long history of manufacturing problems," including recalls and plant inspection violations from the early 1990s through 1998.

The reply also said that a history of potency failures "indicates that Synthroid has not been reliably potent and stable" and that the evidence "suggests that Synthroid has stability, potency and consistency problems." It concluded that when "patients receive tablets that are filled with a product of unpredictable potency, therapy with levothyroxine sodium is neither safe nor effective. ... If Synthroid continues to be marketed without an approved application, patients may be subject to future changes that could affect" the product without notice or prior FDA approval.

The letter has made the rounds of patients groups. This week, a consumer activist group called the Gray Panthers wrote Abbott asking why preparing an application for the FDA has taken four years. A member of
Congress, Republican Rep. Ken Calvert of California, has also expressed interest in the issue, querying one of Synthroid's competitors about whether it could fill the gap were Synthroid to be forced off the market. That company, Watson, replied that it was confident it could meet the demand and that plans are in place to scale up production.

An Abbott spokeswoman said that during the two most recent inspections of its Synthroid plant, the FDA found no violations in its manufacturing processes, and that the product has a four-decade track record with millions of patients using it. The company also said it will submit its application to the FDA "shortly."

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