ONE HUNDRED EIGHTH CONGRESS

Congress of the United States

House of Representatives

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June 24, 2003

The Honorable Tommy G. Thompson
Secretary of Health and Human Services
Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Mr. Secretary:

On May 30, you replied to my inquiry about prescription drugs on the market that never have been approved by the Food and Drug Administration (FDA). I am writing today with followup questions.

First, I would like to clarify two portions of my initial request to which your letter was not responsive. In my March 25 letter, I requested a list of all drugs that are presently on the market that have not been approved. Your letter stated that FDA "does not publish a list." I am assuming that despite the fact that this list is not published, FDA is in fact aware of all the drugs that are on the market that are not approved. The alternative — that drugs are marketed without agency approval and without agency knowledge — would point to a glaring gap in the drug regulatory framework. I am thus requesting that you send me a complete list of these drugs.

Similarly, I requested a list of all drugs that were marketed without FDA approval that have subsequently received approval in recent years, as well as a list of all drugs that were marketed without FDA approval that have subsequently been taken off the market in recent years. Your letter provided several examples, but failed to provide a comprehensive list. I am thus once again requesting that you provide this information.

Second, in view of the enforcement policy expressed in your letter, I would like to draw your attention to a specific unapproved drug that should be considered a high priority for agency action: Microencapsulated pancreatic enzymes, a specific class of widely used drugs for cystic fibrosis.

In your letter, you wrote that "[b]ecause of a need to prioritize its activities, FDA has not reviewed the regulatory status of many of these products." You also stated that unless "FDA has specific information that questions the safety or effectiveness of a particular product, enforcement action is generally deferred."

Microencapsulated pancreatic enzymes fall into the category of drugs that have never been approved by FDA. Because many of the 30,000 adults and children with cystic fibrosis in this country[1] suffer from a lack of pancreatic enzymes that digest fats and proteins, supplementation with microencapsulated pancreatic enzymes is essential for their nutrition and growth. However, the efficacy and safety of the supplemental enzymes are dependent on the amount of enzyme that reaches the small intestine. When this delicate balance is thrown off, several problems can occur.

If too much active enzyme reaches the small intestine, as may be the case for high-strength pancreatic enzyme products, patients may develop colonic strictures that can result in severe intestinal obstruction requiring surgery.[2] Conversely, some products may have insufficient enzyme or the capsules of some products may dissolve in the acidic environment of the stomach, which causes the enzyme to degrade before it reaches its target area.[3] If an insufficient amount of pancreatic enzyme reaches the small intestine, the patient may suffer from fat and protein malabsorption, both of which can lead to malnutrition and increased susceptibility to lung infections and lead to premature death.[4] Malabsorption from insufficient enzyme supplementation can even lead to intestinal obstruction in cystic fibrosis patients.

Clearly, pancreatic enzyme products need careful oversight. However, because these products were first marketed before the passage of the 1938 Federal Food, Drug, and Cosmetic Act, they are subjected to little regulation. As a result, an alarming number of patients became ill in the early 1990s after taking unapproved products.[5] In response to these problems, the FDA announced a rule under which all over-the-counter enzyme products would have to be approved by the agency for safety and effectiveness.[6] This rule, while well intentioned, led manufacturers to market the products as unapproved prescription drugs.

In 1995, FDA indicated its intent that "pancreatic insufficiency drug products marketed by prescription also have an approved [New Drug Application]" and stated that "the agency will

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[1] *What is CF?* Cystic Fibrosis Foundation (online at http://www.cff.org)

[2] Rosalind Smyth et al., *Fibrosing Colonopathy in Cystic fibrosis: Results of a Case-Control Study*, Lancet, 1247–1251 (Nov. 11, 1995).

[3] Leslie Hendeles, Pharm.D. et al., *Treatment Failure after Substitution of Generic Pancrelipase Capsules,* Journal of the American Medical Association, 2459–2461 (May 9, 1990).

[4] *Pancreatic Enzymes: Unapproved, Causing Problems*, Pharmacy Today (Mar. 2001)

[5] *Id.*

[6] 60 Federal Register 20162-20165.

address this subject further in a future issue of the Federal Register."[7] However, eight years later, the FDA has yet to take action. Consequently, pancreatic enzyme products are still unapproved, and adverse events still occur. Dr. Preston W. Campbell, medical director of the National Cystic Fibrosis Foundation, receives approximately one adverse event report a month related to pancreatic enzymes. The most recent report was received by Dr. Campbell on May 30, 2003.[8]

By requiring a New Drug Application for these products, FDA could approve those products that deliver the right dose of medication consistently to the small intestine of cystic fibrosis patients and reject those that fail to do so. FDA could also set appropriate dosage and warnings for the products. I urge you to instruct FDA to take these steps as soon as possible.

I request a reply to this letter by July 8, 2003.

Sincerely,

Henry A. Waxman
Ranking Minority Member

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[7] *Id.*

[8] E-mail Correspondence from Preston Campbell, Medical Director of the National Cystic Fibrosis Foundation to minority staff, Government Reform Committee (June 19, 2003).