



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

FEB 22 2011

The Honorable John F. Kerry
United States Senate
Washington, D.C. 20510-2102

Dear Senator Kerry:

Thank you for your letter of October 5, 2010, cosigned by Senator Scott P. Brown, on behalf of families who have suffered as a result of the use of diethylstilbestrol (DES).

The adverse effects on pregnant women and their children caused by the use of DES are a tragedy. According to the Centers for Disease Control and Prevention, research has now concluded that women prescribed DES while pregnant had a 30 percent higher risk of developing breast cancer than unexposed women and women in the general population. Research has also confirmed that female children born to women exposed to DES while pregnant are at an increased risk for a rare type of vaginal and cervical cancer; reproductive tract structural differences; pregnancy complications and infertility. In addition, research has found an increased risk for non-cancerous epididymal cysts, which are growths on the testicles, among males exposed to DES prior to birth.

DES was the first synthetic estrogen and was approved by the Food and Drug Administration (FDA or the Agency) in 1941 for the treatment of gonorrheal vaginitis, atrophic vaginitis, menopausal symptoms, and postpartum lactation suppression. A few years later, FDA approved DES for the prevention of miscarriages, using an increasing dosing regimen. In April 1971, the *New England Journal of Medicine* published a report showing a link between DES and a rare vaginal cancer in the female offspring of patients who used the product during pregnancy. FDA issued a Drug Bulletin in November 1971, advising physicians to stop prescribing DES to pregnant women because of that cancer link. In 1975, FDA withdrew from the market DES products containing 25 mg or more, and required that the labels of 5 mg tablets contain the warning: "This drug product should not be used as a postcoital contraceptive." In 1978, FDA removed the approval of the postpartum lactation suppression indication, and by the 1990's the only approved indications for DES were treatment for advanced prostate cancer and advanced breast cancer in post-menopausal women. Eventually the uses of DES dwindled to a few veterinary uses, so in 1997, the last U.S. manufacturer stopped making and marketing the drug. In 1998, FDA listed DES on a *Federal Register* notice of drugs that had been withdrawn or removed from the market for reasons of safety or effectiveness.

FDA is charged by Congress with the responsibility of ensuring that drugs on the U.S. market are both safe and effective. Unfortunately, all drug products pose risks as well as benefits, and, even today, all the risks of a drug may not be known at the time of

approval. Before approving a drug, FDA considers the known risks associated with the drug along with the potential benefits the drug will provide. Decisions about regulatory action in response to evidence of a drug safety risk are complex, taking into account many factors. Often, as more becomes known about the potential risks or benefits of a drug, its FDA-approved labeling will be revised so that it better reflects risks in the post-market setting.

Though the safety of drugs and other products regulated by FDA has always been, and continues to be, a key focus of Agency programs, fortunately, today, FDA has many more tools for identifying, monitoring, and mitigating drug risks than it did 70 years ago when DES was approved, including the MedWatch program and new authorities provided by the Food and Drug Administration Amendments Act of 2007 (FDAAA). The MedWatch program, established by FDA in 1993, encourages voluntary reports from consumers and health professionals. Reports submitted to MedWatch are added to existing data in our Adverse Event Reporting System (AERS) database and reviewed by FDA's post-marketing safety staff. The collected reports are monitored and observed for emerging patterns. One or two well-documented case reports may provide an early signal of unexpected safety issues and lead to additional evaluation. We carefully evaluate and analyze all reports that are available to us and make recommendations for possible actions, if the science-based risk evaluation warrants the actions.

Because no amount of premarket study can provide the full information about what the benefits and risks of a new drug will be when it is used by the general population, FDAAA provided important new authorities to enhance our ability to monitor approved drugs after they are marketed and to take definitive action when needed. These authorities include the ability to require drug sponsors to conduct post-marketing studies and clinical trials, make certain safety-related labeling changes, and develop and put into place risk evaluation and mitigation strategies (REMS)—all with the goal of better identifying and managing the risks of drugs on the U.S. market.

FDAAA also required us to develop methods to obtain access to disparate data sources and to establish a post-market risk identification and analysis system to link and analyze health care data from multiple sources. In May 2008, FDA launched the Sentinel Initiative with the ultimate goal of creating and implementing the Sentinel System—a long term national, integrated, electronic system for monitoring the safety of FDA-approved drugs and other medical products. The Sentinel System will enable FDA to actively gather information about the post-market safety and performance of its regulated products—a significant step forward from our current, primarily passive safety surveillance systems. The law set a goal of access to data from 25 million patients by July 2010 and 100 million patients by July 2012. With the assistance of a wide array of collaborating institutions throughout the United States, FDA met the July 2010 goal for access to patients' electronic health care data and is already working toward the patient data access goal of 100 million patients by 2012.

We hope that our newer tools for identifying, monitoring and mitigating, drug risks will prevent other tragedies like those brought about by the widespread use of DES. We are

committed to providing the public with timely and accurate drug safety information, and we recognize the critical responsibility that FDA has to protect the safety of the public's health.

Thank you again for contacting us concerning this matter. Please let us know if you have any further questions. The same letter has been sent to Senator Brown.

Sincerely,


for Jeanne Ireland
Assistant Commissioner
for Legislation