



Center for Drug Evaluation and Research
U.S. Food and Drug Administration
U.S. Department of Health and Human Services

REGULATORY SCIENCE IN ACTION

ENHANCING DRUG SAFETY & MANUFACTURING QUALITY AT FDA WITH RESEARCH

Scientific knowledge steers the drug approval decision-making process of the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA). Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products. Knowledge gained from CDER science and research increases the certainty and consistency of regulatory decisions, and contributes to the development of regulatory guidance documents and best practice standards for pharmaceutical companies.

Many of the Center’s research activities are driven by a wide range of questions about drug safety and manufacturing quality that arise during our review of data gathered both before and after a drug is marketed. The Center uses many different technologies and scientific approaches to assess the risk of medications. Research projects range from investigating the specific underlying causes of adverse drug effects to developing new methods that identify safety issues.

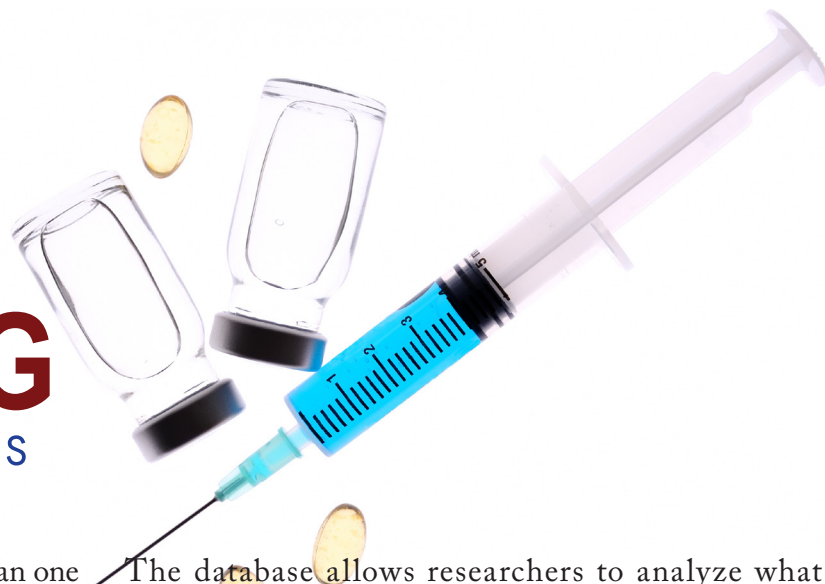
Many of CDER’s research projects involve extensive collaborations with other government agencies, universities, hospitals, and pharmaceutical companies. The following pages present several key examples of how CDER scientists are expanding the field of regulatory science by researching a wide variety of critical areas that impact drug safety and manufacturing quality.

“What will really improve drug safety is for us to improve the science of safety, and we are working on that. We are working on better ways to detect safety signals, and we’re working on the mechanistic side to figure out what causes drug safety problems and how they could be prevented.”

Dr. Janet Woodcock
Director of the Center for Drug Evaluation and Research
from an interview with Life Science Leader¹

Read more about the Center for Drug Evaluation and Research at:
<http://www.fda.gov/Drugs/default.htm>

¹<http://lifescienceleader.com/component/k2/item/3827-janet-woodcock---cder-safety-and-the-cutting-edge>



PREDICTING

DRUG-DRUG INTERACTIONS

A significant number of consumers take more than one drug at the same time, which may cause unanticipated adverse effects or worsen known side effects. In a study of older adults, nearly 1 in 25 individuals were potentially at risk for a major drug-drug interaction.² FDA researchers are working to understand why these drug-drug interactions occur so that they can provide the best guidance to health care professionals and patients on how to avoid or reduce harmful effects when multiple drugs are taken together.

A particular type of drug-drug interaction that is being found in increasing frequency involves transporter proteins in the body’s cells. These transporter proteins, or transporters, are located at the cell surface and can affect how drugs move into and out of cells and tissues. When multiple drugs are taken together, transporters may change how the body absorbs, distributes, and excretes each individual drug.

FDA researchers, working with the University of California, San Francisco, created a public database containing molecular and cellular laboratory data, and clinical data on 31 of the most relevant transporters. These data were collected from hundreds of sources, including in-depth investigations led by FDA researchers.

The database allows researchers to analyze what already is known about the impact of transporters on an affected drug’s distribution in the body. This information can then be used to better predict which drugs may lead to adverse effects when taken in combination with other drugs or dietary supplements. If these predictions are confirmed after further testing, instructions on how to avoid adverse drug-drug interactions can then be included in the drug labels.

“The database has served as a valuable resource for the FDA and is helping to guide clinical studies and our recommendations.”

Shiew Mei Huang
Acting Director,
CDER’s Office of Clinical Pharmacology

This database has served as a valuable resource for the development of the FDA draft guidance for industry.³ This publication is helping to guide pharmaceutical companies in their design of clinical studies on drug transporter interactions and the absorption, distribution, metabolism, and excretion properties of drugs.

To see the database, please visit the website:

<http://bts.ucsf.edu/fdatransportal>

To read about the Office of Clinical Pharmacology, please visit the website:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm106189.htm>

For additional information related to drug interactions, please visit the website:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>

²JAMA, December 24/31, 2008—Vol 300, No. 24

³www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

PREDICTING

ADVERSE DRUG EFFECTS ON THE HEART

Cardiac safety concerns are a leading reason why pharmaceutical companies withdraw drug applications prior to approval and why approved drugs are removed from the market. For example, the FDA removed the antihistamines Seldane (terfenadine) and Hismanal (astemizole) and the heartburn medicine Propulsid (cisapride) from the U.S. market because some healthy patients experienced a life-threatening cardiac arrhythmia, or abnormal heart beat, while taking these medications.

"We hope to identify patterns that will help us predict which patients are at an increased risk for cardiovascular side effects. This knowledge can guide the development of safer treatments."

Dr. Norman Stockbridge
CDER's Office of Drug Evaluation I
Division of Cardiovascular and Renal drugs

One method the FDA uses to identify cardiac side effects is to look for abnormalities in electrocardiograms (ECGs) from patients exposed to a new drug during clinical trials. For example, a measurement of cardiac function called the QT interval is calculated from ECGs, and a QT interval longer than normal may indicate that the drug causes a potentially fatal cardiac arrhythmia. However, it is not always easy to establish what is normal or abnormal since ECGs may have variable quality and all require analysis by an expert

cardiologist. In addition, very small increases in the QT interval appear to carry risk, so studies that assess cardiac drug effects require collection of many thousands of ECGs.

To look beyond individual ECG readings within studies, FDA scientists, in collaboration with ECG manufacturers and pharmaceutical companies, developed a standard for the collection of digital ECGs.⁴ The data standard enabled creation of a database, named the ECG Warehouse, that now contains more than 6 million digital ECGs, all with individual, expert-determined QT intervals. This warehouse serves the immediate purpose of allowing staff to determine the quality of the data used to assess which drugs prolong the QT interval.

Computer programs also have been developed to help analyze the vast amounts of data and to automate the determination of the QT interval to reduce the time and cost incurred with expert evaluation. In addition to facilitating the review of new drug applications, the ECG Warehouse provides a unique resource with which to address a variety of research questions. For example, research shows that women naturally have longer QT intervals than men without any drug exposure and also are at a higher risk of arrhythmias.⁵ Researchers at FDA, sometimes working with academic collaborators, are examining the ECG Warehouse to see if patient factors, such as gender, may be linked to drug-induced arrhythmias.

Read about CDER's Office of Drug Evaluation I, Division of Cardiovascular and Renal drugs at:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm290673.htm>

⁴<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf>

⁵J Electrocardiol 2007 Jul; 40(3): 228-34

SCREENING

OF IMPORTS TO DETECT HARMFUL PRODUCTS

Dietary supplements, drug ingredients, and drug products from other countries may enter the United States at different places, such as border crossings, mail facilities, and import centers. The vast majority of FDA-regulated imports pose no concern, however, the number of imports is increasing and the number of imports that FDA wishes to examine based on risk also continues to increase. Until recently, only a limited number of products could be examined since all samples had to be sent to FDA district laboratories for time-consuming analyses.

Now, FDA is looking into the potential to use advanced portable technologies to rapidly screen a larger number of drug and dietary supplement products in the field, while only sending suspected tainted samples to the district laboratory for further investigation. These technologies must be reliable, able to withstand constant relocation, and accurate under field conditions. Technologies such as Raman and Near Infra-Red Spectroscopy, and Ion Mobility and X-Ray Fluorescence Spectrometry have been adapted for handheld use and similar technologies are being used to screen for explosives at airports.

FDA scientists have launched various experiments to test the ability of these technologies to be adapted for screening imports in the field. Instruments are being used to test for the presence of diethylene glycol, a very toxic chemical which has been found in foreign markets to be substituted for ingredients commonly used in U.S. drug products.



The results from the portable instruments are being verified by retesting samples with traditional laboratory analyses. In ongoing pilot programs, five portable ion mobility devices used for identifying dietary supplements containing undeclared drug ingredients have successfully been deployed across the United States.

The FDA is determining the best way to expand these efforts to establish more effective ways of protecting consumers from dangerous imported products.

Read about the FDA's Office of Regulatory Affairs:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/default.htm>

Read about CDER's Office of Pharmaceutical Science:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088761.htm>

Read about CDER's Office of Compliance:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm081992.htm>

ENSURING

HIGH-QUALITY DRUG MANUFACTURING

FDA is encouraging pharmaceutical companies to shift to a proactive approach that emphasizes controlling the quality of drugs during the manufacturing process. This can prevent problems that could lead to recalls of drug batches or even contribute to severe drug shortages.

Certain drugs, such as injectable and ophthalmic products, must be kept sterile during manufacturing, so processes and controls must be established to prevent contamination. For example, FDA researchers are examining if failures of sterilizing filters can explain recent product sterility failures and how filtration processes can be designed to mitigate such risks. The results of these studies will form the basis for FDA recommendations on filters to help maintain drug product sterility during manufacturing.



A very precise manufacturing “recipe” is established to get a consistent drug product. For example, a certain amount of ingredient must be added at the right time and/or temperature during the process. However, not all steps in the manufacturing process are equally critical to the quality of the final drug product. Therefore, it is important to most tightly control those ingredients and steps that have the greatest effect on drug behavior in the body.

FDA scientists are conducting research to assist pharmaceutical companies in identifying these critical aspects of recipes prior to setting up the manufacturing process and evaluating how best to monitor and control these aspects once manufacture has begun. For example, they are examining the effects of manufacturing processes such as fluid-bed granulation on the uniformity of drug tablet production, and of cell culture methods on the consistency of biotechnology products.

“We are working to make sure patients get the right quantity of drug, free from contaminants.”

Dr. Helen Winkle
Director,
CDER’s Office of Pharmaceutical Sciences

This is one of the many examples of how FDA’s research helps pharmaceutical manufacturers create safer and more effective drug products.

Read about CDER’s Office of Pharmaceutical Science:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088761.htm>

INVESTIGATING

THE RISKS OF ANESTHETICS & SEDATIVES IN CHILDREN

More than one million infants and young children receive anesthesia and sedatives every year during much-needed surgical procedures. However, some recent studies in juvenile animals have raised concerns over potential negative effects of anesthetic exposure on the developing brain and the central nervous system. Certain anesthetics and sedatives in these studies were found to affect learning and memory.⁶

The academic anesthesia community and the FDA realized that more data were needed to determine whether similar effects might occur in pediatric patients. Since this was a significant undertaking, a public-private partnership called SmartTots was initiated by the FDA in collaboration with the International Anesthesia Research Society. Members of the partnership include professional anesthesiology societies, academic research institutions, patient advocacy groups, pharmaceutical companies, and other government and nonprofit organizations.

Clinical, animal, and population-based studies have been initiated to determine if there are problems seen with particular doses, lengths of anesthetic exposure, or the number of times children are exposed to certain anesthetics. The FDA wants to know if there are specific ages when children are most vulnerable to anesthetic and sedative effects, and if any effects are long-lasting or temporary. If effects do occur, the agency intends to determine how they can be prevented or reduced.

“The overarching objective of this initiative is to address major gaps in scientific information concerning the safe use of anesthetics and sedatives in children and ultimately to ensure that these drugs are safe and effective for children undergoing surgical procedures.”

Dr. Bob Rappaport
CDER’s Office of Drug Evaluation II
Division of Anesthesia, Analgesia,
and Addiction Products



For more information please visit the websites:

<http://www.smarttots.org/>

http://www.fda.gov/Drugs/ResourcesForYou/ucm245926.htm?utm_source=fdaSearch&utm_medium=website&utm_term=woodcock%20research&utm_content=48

⁶<http://www.smarttots.org/keyResearchPoints.html>



KNOWLEDGE GAINED FROM CDER SCIENCE AND RESEARCH INCREASES THE CERTAINTY AND CONSISTENCY OF REGULATORY DECISIONS, AND CONTRIBUTES TO THE DEVELOPMENT OF REGULATORY GUIDANCE DOCUMENTS AND BEST PRACTICE STANDARDS FOR PHARMACEUTICAL COMPANIES.