LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

FEBRUARY 2016

KEY FINDINGS

FDA publishes guidance on human factors review for devices, combination products

The FDA published two draft guidance documents and one final guidance document to address the incorporation of human factors studies in the development of medical products and combination products. The guidance documents add to two existing documents on human factors: one on human device factors in medical device design and one on safety considerations to minimize medication errors.

The first draft guidance, called List of Highest Priority Devices for Human Factors Review, addresses what devices require human factors data to be included in premarket submissions. The medical devices the FDA says require human factors data are those that it believes have the potential to cause serious harm if used improperly, such as anesthesia machines, duodenoscopes, automated external defibrillators, infusion pumps, robotic surgery devices and ventilators, among others. Premarket submissions for devices listed in the draft guidance should include a human factors test report and data, or a detailed rationale for not including such information.

The second draft guidance document addresses the incorporation of human factors studies in the development of combination products, which include any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device and a biological product. The draft guidance, called Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, provides recommendations on what human factors information should be included in investigational or marketing applications for combination products, and outlines the different types of human factors studies and how they may add to safety and efficacy evaluations. The FDA provides illustrations of how human factors assessments can be used in different types of combination products and in different clinical settings.

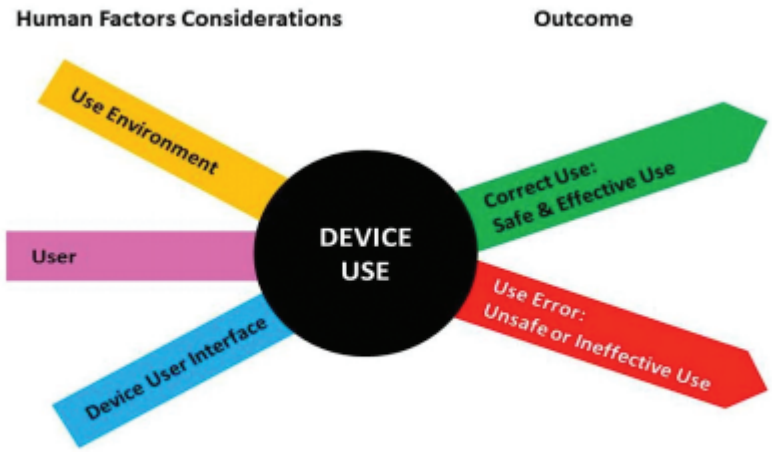


Figure 1. Interactions among HFE/UE considerations result in either safe and effective use or unsafe or ineffective use.

Source: Applying Human Factors and Usability Engineering to Medical Devices – FDA

The third guidance published, a final guidance called Applying Human Factors and Usability Engineering to Medical Devices, addresses implementation of human factors and usability design in medical device development. It seeks to ensure device user interfaces are designed to eliminate or reduce, to the greatest extent possible, use errors that may cause harm. It encourages medical device makers to incorporate human factors or usability engineering processes in the development process, particularly for the user interface, and calls on device makers to provide a report charting what human factors or usability engineering processes have been followed, as well as any initial assessments and human factors validation testing, results and findings. The new guidance supersedes guidance issued in 2000 on incorporating human factors engineering into medical device risk management, and it incorporates feedback suggested to make it more readable and understandable. The guidance explains the three major components of the device-user system in which human factors and usability engineering should be considered – device users, device use environments and device user interfaces.

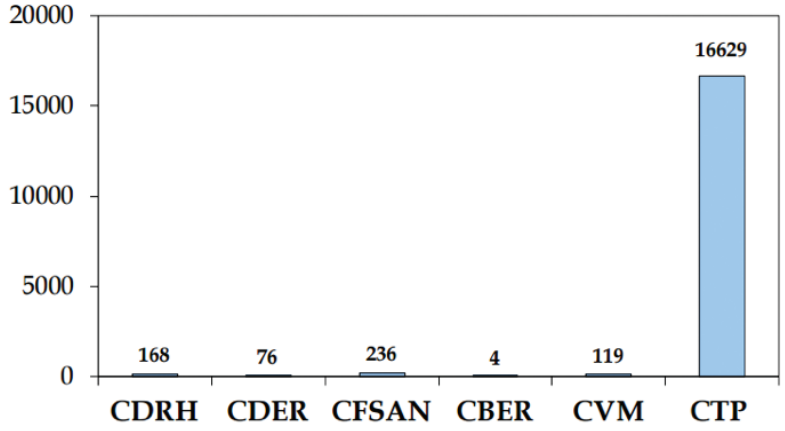
FDA enforcement statistics for FY 2015 point to more enforcement by CDRH than by CDER

The FDA's annual enforcement statistics show an overall spike in warning letters, but only a small proportion of these letters were issued by the Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research (CDER). The statistics also point to a decline in seizures, a bump in injunctions and an uptick in recalls, particularly by CDRH.

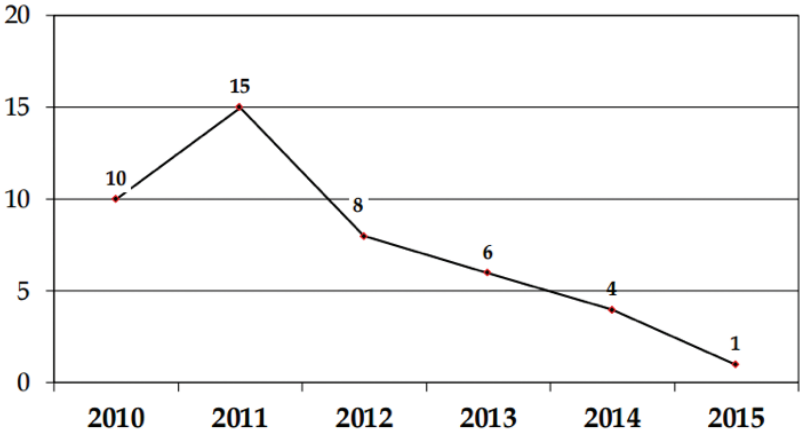
In fiscal year 2015, the FDA issued more than 17,000 warning letters, seized one drug product, served 21 injunctions, recalled more than 9,000 products and delivered 14 drug debarments. The agency's annual enforcement statistics point to both lulls and rises in the regulatory body's enforcement activity.

A marked 17,232 warning letters were sent in 2015, notably higher than the 8,690 issued in 2014 and significantly higher than the mere 673 issued in 2010. However, these were issued primarily by the Center for Tobacco Products, which accounted for 16,629. The Center for Food Safety and Applied Nutrition (CFSAN) issued the second highest number of letters (236); followed by the CDRH, with 168; the Center for Veterinary Medicine (CVM), with 119; and CDER, with 76.

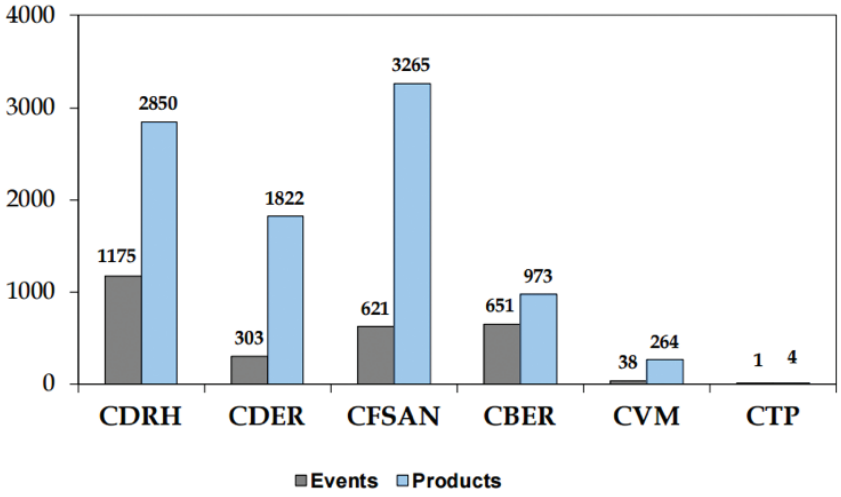
Warning Letters by FDA Center
Fiscal Year 2015



FDA Seizures
Fiscal Years 2010 – 2015



Recalls By FDA Center - All Classes
Fiscal Year 2015



Source: FDA Enforcement Statistics Summary Fiscal Year 2015 – FDA

The figures point to an ongoing decline in FDA seizures, from 15 in 2011 to just one in 2015. The CDER was the only division to seize a product during the year. Injunctions, on the other hand, climbed from 10 in 2014 to 21 in 2015 — the highest number in recent years (2010: 17; 2011: 16; 2012: 17; 2013: 19). Of these, CDRH was responsible for four, and CDER was responsible for three. The CFSAN issued the most injunctions, 12, while the remaining two were issued by the CVM.

CDRH led the pack for recalls, with a total of 1,175 recall events affecting 2,850 products. Most of these recalls were class II (1,068), while class III recalls accounted for a small portion (69). CDER accounted for 303 recall events affecting 1,822 products, while CFSAN saw 621 recall events affecting 3,265 products, and the Center for Biologics Evaluation and Research (CBER) saw 651 recalls affecting 973 products. Recalls by the CVM and CTP were not as frequent and affected far fewer products.

FDA publishes updated guidance on selective safety data collection for late-stage premarket, postapproval clinical studies

The FDA revised and finalized guidance published in 2012 to help clarify safety data requirements during late-stage trials. The guidance is designed to help drugmakers strike a balance between collecting data that isn't pertinent and collecting sufficient data to characterize a drug's safety profile.

The FDA altered and finalized guidance initially published in 2012 on safety data requirements for late-stage premarket and postapproval clinical trials. The guidance, called Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations, discusses when selective safety data collection should be considered.

In modifying the original guidance, the FDA took into consideration public comments requesting more detail and examples. The authority says it modified the document to provide further clarification on the specific types of safety data and circumstances that may be appropriate for selective collection, as well as to offer more information on safety data reporting issues. The FDA suggests sponsors discuss their plans for selective safety data with FDA review divisions at appropriate times, such as end-of-phase II meetings. The agency notes that the guidance is not meant to affect reporting of postmarketing adverse events pertinent to an approved drug.

Although the agency concedes that the recommendations may not align with safety data expectations in other countries, and that this may lead to implementation difficulties for some trials, it contends the guidance provides sponsors with the flexibility to design and implement trial protocols with selected safety data collections, where suitable.

The guidance states that selective data collection may be fitting during late-stage trials if the following conditions are met:

- The number of patients and their characteristics, as well as the duration of exposure and dose range, used in previous trials are adequate to characterize the safety profile and nonserious adverse events of a drug;
- The occurrence of common, nonserious adverse events has been relatively alike across multiple trials; and
- The compound's safety profile is established enough that it's reasonable to conclude the occurrence of common, nonserious adverse events in the study population will be comparable to rates seen in previous trials.

The FDA outlines several types of clinical trials that may be considered for selective data collection, such as investigations of new indications, postapproval trials conducted as part of postmarketing commitments or requirements, and outcome clinical trials. The agency

notes that some premarket clinical investigations for original applications may be considered for selective data collection, if adequate comprehensive safety data becomes available prior to completion of clinical development. Selective data collection may also be permitted in certain circumstances for postapproval investigations in a different population or with a different dose or condition of use. Specifically, it may be appropriate to collect some adverse event data in only a subset of the overall study population, or selective data collection may be permitted in cases where a lower or shorter dose is being studied.

The guidance also outlines what data collection may be stopped or limited in cases of selective data collection. This includes nonserious adverse events not linked to dose modification, drug discontinuation or trial withdrawal; routine laboratory monitoring; and information on concomitant medications, as well as patient history and physical exams. Means of selective safety data collection include reducing collection to a pre-identified subset of the study population or decreasing the frequency of collection.

Dr. Robert Califf to lead FDA following confirmation as commissioner

A majority of the Senate voted to approve Califf's nomination as head of the FDA, although four continued to oppose his leadership. Califf, who joined the FDA last year as deputy commissioner, hopes to boost the FDA's workforce and improve safety surveillance systems.

Former Duke University researcher and cardiologist Dr. Robert Califf was confirmed as the new head of the FDA as a Senate majority voted in favor of his nomination. Four senators continued to oppose Califf's nomination — Edward Market, D-Mass.; Joe Manchin, D-W.Va.; Kelly Ayotte, R-N.H.; and Richard Blumenthal, D-Conn. Presidential candidate Bernie Sanders, D-Vt., was among those who opposed Califf's nomination, but he did not vote. Califf was serving as deputy commissioner and replaces interim commissioner Dr. Stephen Ostroff, who was filling the vacancy left by Dr. Margaret Hamburg.

Califf outlined several priorities for the agency going forward, with a particular focus on bolstering its workforce. He plans to fortify the regulatory body's workforce by working with academic and other centers to attract new talent. He also plans to establish what he calls professional "homes" for FDA researchers. For example, Califf said the agency is working toward "a coordinated effort to have all [the FDA's] statisticians have an identity and support services that they need." He hopes this move will reduce researchers' administrative burdens, such as maintaining medical licenses.

A second priority Califf identified is to enhance safety surveillance systems. He conceded that the agency's current system "is not enough." However, he said the agency isn't proposing to shed the current system. In particular, he pointed to the need to modernize the existing tools to monitor the safety of medical devices, and the need for medical professionals to "step up" to be part of that process.

Califf takes over the agency amid lawmakers' mounting pressure for change. The 21st Century Cures Act, which would require the agency to consider more flexible clinical trials, recently passed the House of Representatives. The Senate is mulling similar legislation. For his part, Califf, who has worked on high-profile clinical studies in the past, said he's keen to make the clinical trial process more efficient.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

Loeb & Loeb's FDA Regulatory and Compliance Practice comprises an interdisciplinary team of regulatory, corporate, capital markets, patent and litigation attorneys who advise clients on the full spectrum of legal and business issues related to the distribution and commercialization, including marketing and promotion, of FDA-regulated products. Focusing on the health and life sciences industries, including pharmaceuticals, biologics, medical devices, wellness products, dietary supplements and organics, the practice counsels clients on regulatory issues, compliance-related matters and risk management strategies; advises on laws and regulations related to product advertising and labeling; counsels on FDA exclusivity policies and related Hatch-Waxman issues; and provides representation in licensing transactions and regulatory enforcement actions.