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When FDA Comes Knocking and What to Do About It: FDA Regulatory and Enforcement Risks Relevant to Academic Medical Centers, Health Systems, and Research Institutions

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Practice Resource

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FDA Regulatory and Enforcement Risks

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INTRODUCTION

General counsels at universities, academic medical centers (AMCs), health systems, and research institutions have many legal risks to consider, but the prospect of a visit from a U.S. Food and Drug Administration (FDA) Office of Regulatory Affairs investigator or FDA Office of Criminal Investigations agent is not typically top of mind. However, such visits do occur, and the risks of non-compliance with potentially unfamiliar FDA regulatory obligations and follow-on litigation risks can be serious. New risks have emerged as the rise of artificial intelligence in health care has led to an increase in the number of universities and health systems that produce technologies such as algorithms that may, depending on their intended uses, be regulated by FDA as medical devices.

It may be surprising how many aspects of FDA regulation can apply to work that is conducted at universities, health systems, and other research institutions. FDA has regulations that govern good laboratory practices[1] that are applicable to:

- Preclinical testing conducted to support drug and device research and marketing applications;
- Current good manufacturing practice regulations[2] that apply to drug and device quality assurance testing;
- Good clinical practice regulations[3] that govern drug and device clinical research; and
- Statutory and regulatory provisions that define when products and tools used in medical practice and research may be regulated as drugs or medical devices and thus, may require research or marketing submissions to FDA.

FDA's regulatory framework is complex and broadly applicable to medical products.

This Practice Resource addresses the scope of FDA jurisdiction and the enforcement process; the ways that an institution may find itself on FDA's radar; requirements associated with various types of activities conducted at AMCs, health systems and research institutions; and best practices that can keep such institutions in FDA's good graces. FDA counsel can be critical in helping institutions maintain compliance in a rapidly evolving regulatory environment. They can also assist institutions in navigating their interactions with FDA during FDA inspections and their aftermath to help prevent regulatory issues from spiraling into significant regulatory and litigation risks.

1 21 C.F.R. pt. 58.
2 *Id*. pt. 211 (for drugs) & pt. 820 (for devices).
3 *See, e.g.,* 21 C.F.R. pt. 312, subpt. D (describing sponsor and investigator responsibilities); *id.* pt. 50 (regarding human subject protection).

OVERVIEW OF FDA ENFORCEMENT PROCESSES

FDA Jurisdiction: FDA, sitting within the U.S. Department of Health and Human Services (HHS), has responsibility for protecting the public health by ensuring the safety and efficacy of human and veterinary drugs, biological products, and medical devices; ensuring the safety of foods, cosmetics, and radiation-emitting products; and regulating tobacco products.[4] For drugs, biological products that are regulated as drugs or medical devices,[5] and medical devices, the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations govern the product development phase, including pre-clinical and clinical research intended ultimately to support product clearance or approval; the clearance and approval process; and post-market research and reporting obligations, as well as ongoing manufacturing and product promotion. While occasionally AMCs and health systems are involved with the development of drugs or devices—like the algorithms mentioned earlier that may be used to identify specific risks or optimize patient care or other customized, patient specific treatment tools—it is much more common for the laboratory and research practices at such institutions that involve FDA-regulated products manufactured by other entities to attract FDA scrutiny.

FDA Inspections and Form 483 Observations: FDA conducts routine surveillance inspections of regulated product manufacturers to assess compliance with current good manufacturing practices.[6] The agency also has a bioresearch monitoring inspection program (BIMO) through which the agency assesses the compliance of research sponsors, clinical investigators, and laboratories with applicable clinical practice and laboratory regulations that aim to ensure that clinical and preclinical data used to support marketing applications is of sufficient quality to support the safety and efficacy of medical products. FDA can also inspect any regulated site on a "for cause" basis when the agency has reason to believe, due to a complaint or otherwise, that the site is not operating in compliance with applicable law. Where potential noncompliance with FDA requirements is identified during an FDA inspection, the FDA investigator will present a Form 483 Notice of Inspectional Observations (Form 483) at the end of the inspection during a final close-out meeting. Form 483 lays out the investigator's "observations" regarding objectional conditions that may reflect a violation of applicable legal requirements. Clarifications or objections regarding the observed conditions underlying the Form 483 can and should be raised orally with the FDA investigator in the close-out meeting, but the site that receives the Form 483 will have 15 business days to respond in writing to the observations,

4 21 U.S.C. § 393(b) (2024).

5 Depending on their form, function, and intended use, biological products can be regulated by FDA as drugs or medical devices, wholly exempt from regulation, or lightly regulated as human cells, tissues and cellular and tissue-based products subject only to registration, listing and current good tissue practice requirements. *See* 21 C.F.R. pt. 1271. For purposes of this article, references to drugs and devices include any biological products that are regulated as drugs or devices.

6 21 U.S.C. § 374 sets out FDA's authority to conduct inspections of regulated sites. FDA describes the types of inspections it conducts in more detail on its website: *Types of FDA Inspections*, FDA, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-basics/types-fda-inspections (last visited July 12, 2024).

including by describing any proposed remedial actions that the site will take to address the observations. If FDA is dissatisfied with the proposed remedial steps, the agency can issue a warning letter, which FDA will post publicly on its website.[7]

A highly publicized warning letter can lead to reputational harm and undermine a laboratory, investigator, or sponsor's scientific credibility just like it can undermine consumer confidence in the quality of drugs, devices, foods, and other products produced at manufacturing sites. Additionally, concerns about the quality or integrity of preclinical data used to support the safety of an experimental product for study in humans can lead to a hold on clinical studies or the exclusion of data needed to support the product's clearance or approval. In cases where a testing facility has failed to comply with FDA good laboratory practices (GLPs) in a way that impacts the validity of a nonclinical study, and where FDA does not believe that lesser actions such as a warning letter have been or would likely be adequate to achieve the facility's compliance with GLPs, FDA may "disqualify" the testing facility. If a facility is disqualified under FDA's GLP regulations, FDA will not consider any studies completed at that facility after the date of disqualification. Investigators can also be disqualified for repeated or deliberate failures to comply with FDA's good clinical practice regulations (GCPs).[8] Disqualification prevents an investigator from receiving investigational products, thus precluding clinical trial oversight during the disqualification period and inviting increased FDA scrutiny of data submitted from the disqualified investigator prior to disqualification.

Enforcement: While FDA hopes for voluntary compliance, violations of the FDCA and its implementing regulation can lead to regulatory enforcement by FDA, as described in various places throughout this article. They can also lead to civil injunction or seizure actions or criminal prosecution by the Department of Justice (DOJ).[9] Use of violative FDA-regulated products in appropriate factual circumstances can also lead to tort and professional negligence lawsuits, federal False Claims Act investigations pursuant to 31 U.S.C. § 3729 and state analogs, and criminal prosecutions based on various fraud and conspiracy provisions in Title 18 of the United States Criminal Code.

WHAT PROMPTS AN FDA VISIT?

So how does a university, health system, AMC, or investigator get on FDA's radar in the first place? There are many ways.

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7 FDA outlines various advisory, administrative and judicial enforcement actions in addition to warning letters that FDA can pursue when violations are identified, including but not limited to warning and untitled letters; administrative detentions; recalls; disqualification of investigators; civil money penalties; injunction; seizure; and criminal prosecution, *Regulatory Procedures Manual*, FDA, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual#_top (last updated Mar. 18, 2024).

8 *See* 21 C.F.R. §§ 312.70, 812.119 (2024).

9 *See generally* 21 U.S.C. §§ 331–34.

Study sponsors, investigators and sponsor-investigators are listed in research applications submitted to FDA, as are sites where research is being conducted. Study site inspections are a routine part of the drug and device approval process and can also be initiated in response to an adverse event reported to the agency. Concerns about compliance with good laboratory practices, good clinical practices, or human subject protection requirements may also lead concerned employees or study subjects to file a complaint with FDA. Such complaints can prompt a for-cause inspection.

Laboratories that are involved in testing that supports an investigational new drug (IND) or investigational device exemption (IDE) submission must be listed in an IND or IDE application. Laboratories that are involved with in-process or finished process testing as a manufacturing step in the production of a pharmaceutical or device must be listed in a product's marketing submission. Thus, if a university laboratory is conducting testing that will support drug or biologics submissions, information regarding the laboratory will be submitted to FDA, and the laboratory will be subject to inspection under FDA's BIMO program.

Research findings that are published may come to the attention of FDA through review of the publication. If a published study has no records of an IND or IDE when FDA thinks an IND or IDE should be in effect for such a study, that could also lead to an inspection. While FDA routinely inspects laboratories and clinical study sites as part of its review of a product marketing application, there are other ways for FDA to become aware of concerns about laboratory data or clinical research practices. Anyone who participates in a clinical study or becomes aware of concerns about research practices or human subject protection can also reach out to HHS or DOJ, which can launch an investigation.

In addition, regulated product safety issues or poor outcomes in clinical practice can lead to whistleblower complaints, tort or class action lawsuits, and resulting media attention that can invite scrutiny from FDA regulators, investigative agents, or DOJ prosecutors. Finally, clinicians, hospitals, and product manufacturers or sponsors may affirmatively tout the benefits of their products and services publicly, which may invite government attention and lead to further scrutiny if there is concern about a potential safety risk or an inappropriate or illegal practice.

RESEARCH

Universities and AMCs conduct significant amounts of research from basic science to drug and device clinical trials. Much of this research may be subject to FDA regulatory requirements. Institutional Review Boards (IRBs) are also tasked with reviewing and approving proposed research involving human subjects and monitoring its conduct. IRBs are required to comply with applicable FDA regulations when they review FDA-regulated clinical investigations. IRBs are often part of a university or AMC, though increasingly, research is being reviewed by external IRBs referred to as "central" IRBs, many of which are operated by independent, for-profit entities. FDA's BIMO program is comprehensive, and it monitors and

ensures compliance of regulated research through on-site inspections, data audits, and remote regulatory assessments.

University and AMC counsel are most likely to be brought in to address FDA concerns during or in the aftermath of an FDA inspection of a laboratory or clinical trial site, or when issues related to FDA-regulated products lead to litigation or, more rarely, prosecution. However, FDA questions may also arise as clinical investigators, laboratory personnel, and IRBs make decisions about research and testing activities that may pose regulatory or litigation risk. Institutions should have policies in place and conduct training to ensure that personnel are able to spot FDA regulatory issues and know when to reach out to the legal department for help.

Preclinical Research: University Laboratories

FDA GLP regulations apply to "nonclinical laboratory studies intended to support FDA research or marketing applications for drugs or devices."[10] The purpose of the regulations is to ensure the quality and integrity of any data submitted to FDA. The GLP regulations establish minimum requirements for:

- Laboratory and study personnel
- Facilities and equipment
- Study conduct
- Animal care
- Recordkeeping
- Reporting
- Standard operating procedures that govern all aspects of how a nonclinical laboratory study is conducted.

FDA inspects laboratories conducting FDA-regulated nonclinical laboratory studies to check whether they are complying with GLPs and to prompt remedial action if non-compliance is observed. Laboratories should have detailed policies and procedures—and detailed work instructions when necessary—that provide laboratory personnel with a detailed roadmap to compliance with GLPs. All employees should receive regular training on such procedures to ensure they know what is required to accomplish their jobs in a compliant fashion. BIMO investigators typically review laboratory standard operating procedures (SOPs) and other records for adequacy. Lack of procedures that should be in place, as well as existing procedures that are inadequate or insufficiently detailed, typically lead to BIMO observations. Further, other non-compliances identified are often rooted in inadequate procedures and training. In addition, it is very important to have robust record keeping procedures and an audit plan for auditing records to ensure that laboratory personnel are fully complying with recordkeeping requirements.

10 21 C.F.R. pt. 58.

In March 2020, FDA issued a warning letter to a University of Kentucky physician and study director for failure to comply with GLPs at a university laboratory following a poor BIMO inspection in which FDA reviewed a nonclinical laboratory study intended to support a research application for a medical device.[11] The warning letter cited the university physician for having failed to ensure that all experimental data were accurately recorded and verified; applicable GLP regulations were followed; the study protocol was followed; and all required raw data, documentation, and specimens generated by the study were retained. The warning letter also noted that study records were missing required forms and were stored in unsecured areas. Further, study records that were retained memorialized that certain sheep subjects in the study received the wrong protocol-mandated kits. The warning letter noted that "failure to follow the study protocol compromises the quality and reliability of the data generated," though in this case, the investigational device was cleared before the warning letter issued.[12]

When an FDA GLP or other investigation commences, or at the very least upon presentation of a Form 483 at the close of an inspection, it is advisable to call in experienced FDA counsel to help university personnel understand FDA requests and concerns, answer questions, and convey the seriousness with which the university takes compliance. In addition, prior to taking enforcement action, FDA will consider a facility's response to a 483 that provides further context and describes proposed corrective actions if such a response is submitted to the agency within 15 business days of receipt of the 483. Knowledgeable counsel can review the observations, strategize with subject matter experts and study personnel regarding proposed corrective action, and assist with follow-up responses to the agency, as necessary. A robust 483 response often can prevent the issuance of a warning letter or more serious enforcement action.

Clinical Investigations: Hospitals, Research Institutions, and Faculty

FDA regulates clinical research to ensure both the protection of human subjects and the quality and integrity of the scientific data collected. Specifically, FDA oversees clinical investigations, defined as

> any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to [FDA] under the [FDCA], or is not subject to requirements for prior submission . . . but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for research or marketing permit.[13]

11 Letter from Soma Kalb, Dir., Ctr. for Devices & Radiological Health, to Joseph B. Zwischenberger, Univ. of Ky., No. 600258 (Mar. 26, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/university-kentucky-600258-03262020.

12 *Id.*

13 21 C.F.R. § 50.3(c). The prior submission requirements referenced in this definition are those for investigational new drug (IND) submissions under 21 U.S.C. § 355(i) and for investigational device exemption (IDE) applications under *id.* § 360j(g).

Federally funded research involving human subjects is subject to a uniform policy for the protection of human research subjects—the Federal Policy for the Protection of Human Subjects, referred to as the "Common Rule." The policy is implemented by HHS's Office for Human Research Protections (OHRP). Many research studies involving drugs and devices will be subject to both the FDA regulations on clinical investigations and the Common Rule.

FDA regulations govern the following areas relevant to clinical research:

- FDA review of IND and IDE applications prior to commencement of research to ensure there is sufficient evidence that the study will be safe to proceed;
- Good clinical practices specifying how FDA-regulated clinical studies must be conducted and placing obligations on various parties involved in the research;
- Standards for and obligations of IRBs; and
- Informed consent requirements.

FDA also is responsible for enforcing compliance with requirements to submit information on applicable clinical trials to the clinicaltrials.gov database of the National Institute of Health (NIH). Sponsors submitting marketing applications to FDA for human drugs or devices must include a certification of compliance with clinicaltrials.gov requirements.[14]

Through its BIMO program, FDA will regularly inspect and review data from study sites for compliance with IND and IDE requirements as well as GCP and human subject protections. FDA will also inspect IRBs for compliance with regulatory provisions that apply to IRBs. Failure to comply with applicable requirements can lead to warning letters, delays or denial of approval of product applications, exclusion of research from consideration in support of a product application, disqualification of researchers, or even injunctions or criminal prosecution in egregious cases.

Like laboratories, clinical study sites must have detailed policies, procedures, and work instructions in place, as well as robust training to ensure compliance with GCP requirements. SOPs and evidence of training are among the first requests that BIMO investigators make when inspecting a clinical research site. Also, as research protocols are clarified or amended, it is critical that sites have mechanisms in place to inform study personnel to ensure that protocols are strictly followed even as requirements change.

Finally, it is critically important that investigators understand the difference between clinical practice and clinical research, as well as the importance of strict adherence by all clinical research staff, both to clinical study protocols and GCP requirements more generally. Principal investigators (PIs) are themselves fully responsible for compliance with their study protocols, and GCPs more generally as they relate to the studies for which they are serving as PIs. They can also be held responsible for protocol deviations, recordkeeping failures, data integrity problems, and other violations of GCPs that occur in their studies, and for taking corrective and preventive actions so that similar violations do not recur.

14 *See* 42 U.S.C. § 282(j)(5)(B).

GCP violations involving data integrity issues are a particular enforcement priority of FDA and the DOJ currently.[15] Numerous clinical research organizations and individuals working at such organizations have been charged in criminal cases for alleged conduct involving fabrication of research subjects and records, and for misleading FDA personnel in BIMO inspections involving regulated studies.[16] The allegations in these cases have ranged from creating fraudulent records of study subject visits or interactions that never occurred, recording false information in subject case histories, and lying to FDA investigators and study sponsors. It is critical to ensure that any employees supervising a clinical trial as an investigator or sponsor-investigator are well trained in GCPs and take their monitoring role very seriously. Study files should be audited regularly, anomalies investigated and remediated, and legal counsel should be consulted to assist with decisions about whether and how FDA or study sponsors should be notified in the event a data integrity issue or other instance of non-compliance with GCPs is discovered.

Drug Research

Before FDA will allow an unapproved drug or, in many cases an approved drug for an unapproved use, to be tested on human subjects, the sponsor of the research must submit an IND to FDA. If, upon rigorous review of the data submitted in an IND, FDA believes the proposed study assures the safety and rights of subjects and, for Phase 2 and 3 studies, assures that the quality of the scientific evaluation of the drug will be adequate to permit an evaluation of the drug's effectiveness and safety, the agency will permit the research to proceed and an IND will be considered "in effect."[17] Having an IND in effect allows an unapproved drug, or a drug being studied for a new use, to be distributed legally for purposes of the study.[18]

Most research involving investigational drugs must be conducted under an IND. However, researchers can study approved drugs for their approved uses without an IND if certain conditions are met, including that the research is not intended to support a significant labeling

15 *See, e.g.,* Arun G. Rao, Deputy Assistant Att'y Gen., Consumer Prot. Branch, Keynote Address at the Enforcement, Litigation and Compliance Conference: For the Drug, Device, Food and Tobacco Industries (Dec. 6, 2023), https://www.justice.gov/opa/speech/deputy-assistant-attorney-general-arun-g-rao-delivers-keynote-address-enforcement (noting "Clinical researchers who fabricate or falsify clinical trial data can adversely impact critical decisions made by life sciences companies and the FDA related to drug safety and efficacy. And as a result, these highly dangerous fraud schemes can endanger the lives of countless American consumers and erode confidence in FDA's drug approval practice. As such, the investigation and prosecution of clinical trial fraud remains a high priority of the branch.").

16 *See, e.g.*, Press Release, Off. of Pub. Affairs, U.S. Dep't of Just., Florida Co-Owner of Clinical Trial Company Pleads Guilty to Obstructing FDA Inspection (Jan. 12, 2022), https://www.justice.gov/opa/pr/florida-co-owner-clinical-trial-company-pleads-guilty-obstructing-fda-inspection (Olga Torres Guilty Plea); Press Release, Off. of Pub. Affairs, U.S. Dep't of Just., Doctor, Clinic Owner and Staff Charged with Falsifying Clinical Trial Data (Mar. 8, 2021), https://www.justice.gov/opa/pr/doctor-clinic-owner-and-staff-charged-falsifying-clinical-trial-data (Tellus Clinical Research CEO and other Staff, Indictment).

17 *See* 21 U.S.C. § 355(i); 21 C.F.R. §§ 312.20, 312.22(a).

18 *See* 21 U.S.C. § 355(i); 21 C.F.R. § 312.1(a).

change, does not involve a factor that significantly increases risks with use of the drug, and complies with FDA regulations governing IRB and informed consent requirements. The regulations at 21 C.F.R. Part 312 describe the responsibilities of both study sponsors and study investigators, and generally lay out required GCPs that govern all aspects of how a study must be conducted.

University faculty often wish to sponsor their own research studies and can be both "sponsors" and "investigators" under the regulations.[19] In such cases, those sponsor-investigators will be responsible for both sets of obligations. This type of research is frequently called "investigator-initiated research" and is often supported financially by pharmaceutical manufacturers as a way to increase scientific learning and publications regarding the use of their products without themselves sponsoring a trial. The sponsor-investigator is typically an individual researcher and not an institution, and the individual researcher, as opposed to the institution where that person works, will be in direct contact with FDA regarding the study. This can raise issues where FDA correspondence is not promptly brought to the attention of the institution and its counsel and the sponsor-investigator instead tries to respond to FDA inquiries or an inspection without assistance. Appropriate internal notification requirements can help in such situations. In other cases, university faculty might serve as investigators in a clinical study sponsored by a commercial manufacturer or other institution. In either event, Part 312 lays out the obligations that are applicable.

Key sponsor responsibilities include:

- Ensuring that an IND is in effect and properly maintained;
- Selecting qualified investigators and providing them with the information needed to properly conduct the investigation;
- Monitoring the investigation to ensure compliance with GCPs, applicable FDA regulations, and the study protocol, including through performing of audits;
- Ensuring that the study drug is controlled, shipped, and disposed of appropriately;
- Informing FDA and all participating investigators of significant new adverse effects or risks with the study drug; and
- Maintaining required study records.

Investigators have an independent obligation to adhere to GCPs, protect human subjects, conduct clinical trials in compliance with FDA regulations and the clinical protocol, and control the study drug. Although sponsors often develop an informed consent form for the clinical trial and manage interactions with IRBs, the investigator is responsible for obtaining subjects' informed consent and ensuring IRB review and approval of the study in accordance

19 An investigator who is both the "sponsor" and the "investigator" is referred to under the regulations as a "sponsor-investigator." 21 C.F.R. § 312.3.

with FDA regulations at 21 C.F.R. Parts 50 and 56. Investigators also are responsible for maintaining required site-level study records and reporting study results, safety events, and certain financial information to the study sponsor.

Investigators may wish to study an FDA-approved drug or device for a new use, such as a new indication, patient population, or dosing regimen, that is not included in the FDA-approved labeling. Such a study generally requires an IND. In contrast, as FDA has stated in its Guidance for Clinical Investigators, Sponsors and IRBs, "use of a lawfully marketed drug for an unapproved use in the course of medical practice is not a clinical investigation and does not require an IND because it involves the use in an individual patient where the primary intent is to treat the patient."[20] It can at times be difficult for physicians to determine when they are practicing medicine, and when they are conducting clinical research. Thorough training and access to legal counsel can help them ensure they understand any potential regulatory implications of their work.[21]

In a warning letter issued to a physician sponsor-investigator at a Minnesota health system for failing to file an IND for his study, FDA noted: "[W]hen an investigator limits his choices, his patients' choices, and the choices of the people working for him in the treatment of those patients, then he is conducting a clinical investigation. This is different from the practice of medicine, where the primary intent is to treat the individual patient."[22] Thus, when a physician decides to compare two treatments involving approved drugs and develops a protocol that dictates when patients should get one treatment or another, that factual scenario describes clinical research that must be evaluated to determine whether an IND must be filed, or whether the research is eligible for an exemption from the need for an IND because it meets all of the factors as outlined in 21 C.F.R. § 312.2(b)(1).

Another scenario that can implicate the IND question, and which is often missed by reviewing IRBs, is when items that are generally regulated by FDA as a "food" or a "cosmetic" are used in a research study in a manner that meets the definition of a "drug." For example, consider a clinical trial where the protocol calls for randomizing patients undergoing surgery to consume, prior to surgery, either a specific type of tea alone or the same tea in combination with a specific protein powder. Both the tea and protein powder are ordinarily regulated as foods. However, when the endpoints of the study require assessment of the effect of administering the tea alone or in combination with protein powder on such surgical side effects as nausea, vomiting, dizziness and pain, the tea and powder have "drug" intended uses in the study. Thus, the study involves the administration of unapproved "drugs" to patients, because

20 FDA, U.S. Dep't of Health & Hum. Servs., Guidance for Clinical Investigators, Sponsors and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND 4 (2013), https://www.fda.gov/media/79386/download.

21 *See* FDA, Clinical Research Versus Medical Treatment (Mar. 22, 2018), https://www.fda.gov/patients/clinical-trials-what-patients-need-know/clinical-research-versus-medical-treatment.

22 FDA, Warning Letter to Jon B. Cole, Ref: 21-HFD-45-04-01 (May 5, 2021), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/jon-b-cole-md-611902-05052021.

neither the tea nor the powder is FDA-approved to treat the studied post-surgical side effects. Such a study requires submission of an IND to FDA.

While an IRB may be able to assist with determining when research must be reviewed by FDA before it can be initiated, it can only do so if it is consulted in the first place. Further, IRBs without trained FDA regulatory counsel may miss issues like the "drug" classification for the tea and powder in the example described above. Thus, all university staff that may be involved in clinical research should be properly trained on research-related obligations, including the requirement to consult an IRB before initiating any clinical research. And IRBs should understand the importance of reaching out to the legal department for advice in more complicated cases.

Device Research

FDA regulations governing IDEs apply to all clinical investigations of medical devices intended to "determine safety and effectiveness" unless an exemption applies. These requirements are outlined in 21 C.F.R. Part 812. The regulations in Part 812 dictate when research falls within the scope of Part 812, when a full IDE must be submitted, what information must be included in the IDE, the obligations of sponsors, investigators and IRBs, the records that must be maintained by sponsors and investigators, and the information that must be reported to FDA.

When an IDE is in effect, an unapproved or uncleared device can be distributed and used in a clinical trial to collect safety and effectiveness data required to support a premarket application and will be exempt from certain other regulatory requirements that would otherwise apply. Similar to the drug context where not all studies involving a drug will require an IND, not all device studies will require submission of an IDE. Making the right call as to whether an IDE submission is needed is a critical first step to mitigating regulatory and litigation risk.

As outlined in 21 C.F.R. § 812.2, a full IDE will only need to be submitted and approved for studies involving "significant risk" devices. The comprehensive definition of a significant risk device is outlined in 21 C.F.R. § 812.3 and further described in FDA guidance, but, as the name would suggest, this category includes devices that have the potential to pose a serious risk to health. Some examples of significant risk devices include implantable spinal devices and extended wear contact lenses. Abbreviated requirements apply to devices that are not considered significant risk devices, and these studies do not require an IDE to be submitted to FDA. Examples of non-significant risk devices are described in FDA guidance and include, for example, daily wear contact lenses and catheters.

Certain studies are exempt from FDA's IDE regulations entirely. These include, for example, studies involving an FDA-cleared device used in accordance with its labeled indication, devices undergoing consumer preference testing that do not put patients at risk, custom devices ordered by a physician for a particular patient or practice purpose (no more

than five units per year), and studies involving certain noninvasive diagnostic devices that are not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure. Although these studies are exempt from IDE requirements, they are not exempt from IRB and informed consent requirements, and appropriate policies should be in place to ensure compliance with IRB review and informed consent obligations even for IDE exempt studies and studies subject to abbreviated IDE requirements.

The analysis for when Part 812 governs a device research study and when a full IDE must be submitted is even more complex than the analysis governing drug studies. Sponsors are responsible for making the initial risk determination for a device study and presenting it to an IRB. Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's significant risk/non-significant risk determination and modify the determination if the IRB disagrees with the sponsor. Because both the sponsor and the IRB are ultimately responsible for ensuring that an IDE is in place for any significant risk device study—and both potentially can face FDA enforcement if an erroneous risk determination means an IDE is not submitted when necessary—either the sponsor or IRB may ask FDA to weigh in on whether a study involves a significant risk device or not. FDA's determination is final.

Human Subject Protection

Human subject protection is a critical aspect of FDA-regulated clinical research. 21 C.F.R. Part 50 governs human subject protection, including the requirements for valid informed consent and when exemptions from informed consent requirements apply. As FDA has noted in recent guidance, informed consent requires much more than a signature on a form. Rather, "[i]nformed consent involves providing a prospective subject, or their legally authorized representative (LAR), with adequate information to allow for an informed decision about participation in the clinical investigation prior to enrollment."[23] This begins at the time a subject is recruited into a trial, through the trial's conclusion. The regulations describe the basic elements of any compliant informed consent, how to ensure that an informed consent is voluntarily entered, and how informed consent should be documented. Part 50 also lays out additional safeguards specifically for children in clinical investigations. The obligations in Part 50 apply not just to FDA-regulated drug and device clinical trials, but also to clinical investigations that support applications for research or marketing permits for foods, including dietary supplements and food and color additives.

21 C.F.R. Part 56 outlines standards for the composition, operation, and responsibility of IRBs for the review of FDA-regulated clinical investigations to ensure risks to subjects are minimized and are reasonable in relation to anticipated benefits to the subjects and the importance of the research. IRBs also ensure the selection of subjects is equitable, that

23 FDA, U.S. Dep't of Health & Hum. Servs., Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors 3 (2023), https://www.fda.gov/media/88915/download.

informed consent is sought and appropriately documented, that research data is monitored to ensure subject safety, and that adequate provisions are in place to protect subject privacy and data confidentiality.

Avoiding conflicts of interest by study investigators is another critical element to ensuring the protection of human subjects. 21 C.F.R. Part 54 outlines the information investigators must provide to sponsors and sponsors must maintain regarding potential financial conflicts investigators may have. This part also discusses the types of financial arrangements that investigators must disclose to sponsors and sponsors must disclose to FDA when a marketing submission is made. The purpose of disclosing these financial arrangements is to put sponsors and FDA on notice of potential conflicts of interest so that sponsors, and ultimately FDA, can ensure any potential bias is appropriately mitigated.[24] It is important for potential investigators to know that any financial interests they may have in a product under development or any financial benefit they may receive from industry could impact their ability to serve as an investigator in a study of that product, or in any study where the company from whom they have received financial compensation is a sponsor. FDA's regulations on financial disclosure are separate from the Public Health Service (PHS) regulations on conflict of interest in PHS-funded research with which universities and AMCs may be more familiar.

The federal Common Rule, codified at 45 C.F.R. Part 46, also governs human subject protection in federally funded clinical trials. While the 21st Century Cures Act,[25] passed in December 2016, requires that FDA and HHS harmonize their human subject protection requirements, harmonization has yet to be fully achieved, meaning that much research remains subject to two, slightly different sets of regulations.

Failure to comply with human subject protection requirements can lead both to FDA and HHS enforcement, as well as civil lawsuits brought by study subjects and their families. Thus, research institutions need to be familiar with and ensure researchers and IRB members are appropriately trained on both FDA and Common Rule requirements, and that study records and IRB files are regularly audited to ensure compliance.

Public Health Research

Universities often have robust public health programs engaged in research that has nothing to do with facilitating FDA approval of a drug or device. Those engaged in such research may not have even considered the possibility of FDA jurisdiction over their research and may have no familiarity with applicable requirements until they have already violated them. Thus, it is prudent to arm public health researchers with a basic overview of FDA regulations governing research that involves human use of FDA-regulated products, as well as a contact in their university's legal department to call for advice prior to initiating a study that might fall within FDA's jurisdiction.

24 *See, e.g.*, FDA, U.S. Dep't of Health & Hum. Servs., Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators (2013), https://www.fda.gov/media/85293/download.

25 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016), https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.

As an example, there is significant interest among public health researchers on the public health effects of cannabis use that is legal under the laws of some states. However, an "interventional" study of legal cannabis, which is not approved by FDA in most forms, would likely require submission of an IND to FDA, or a request to FDA for a waiver of IND requirements. FDA takes a broad view of what it means for a study to be "interventional" and may even view a study involving subjects self-administering cannabis that they procured themselves as "interventional" if the study protocol places any limitations or restrictions on the subjects' behavior. As another example, during the COVID-19 pandemic, epidemiologists were very interested in evaluating technologies that would facilitate community-based screening for COVID-19 as a public health tool. Such technologies are generally regulated by FDA as medical devices. While some research in this area falls outside of FDA jurisdiction as public health surveillance, drawing the lines between diagnostic, screening and public health use of COVID-19 test products is not always simple.

Reaching the right decision regarding the need for FDA review of research is critically important because failure to comply with FDA research review requirements can render distribution of an experimental, unapproved, or uncleared product illegal during the study. In addition, failure to comply with other FDA research-related obligations can render a product misbranded or can lead to an independent criminal violation of the FDCA. In addition, use of an investigational product in a non-compliant way could undermine potential defenses in litigation that could arise if use of the product leads to patient harm.

CONTRACT TESTING LABORATORIES

Some universities have laboratories that do contract testing of active pharmaceutical ingredients, raw materials, and/or finished drug products for customers who rely on testing to establish compliance with current good manufacturing practices (cGMPs). University laboratories engaged in these activities must comply with applicable cGMP requirements,[26]which focus on ensuring the quality of the products tested. These requirements govern the layout and cleanliness of the facility, the appropriateness and accuracy of the equipment, qualifications of the personnel, recordkeeping requirements, and the written procedures that address all aspects of how the laboratory functions.

FDA has the right to inspect such laboratories for compliance with cGMPs and to take enforcement action when a non-compliance is identified. A university that hosts such a laboratory must be aware of the requirements for such a facility and should ensure audits are conducted regularly to identify gaps and ensure compliance. Failure to do so can lead to FDA action, including, but not limited to, a warning letter.

26 While cGMPs and GLPs can seem similar in many ways, their ultimate purpose is different. The purpose of laboratory testing of finished products is for quality assurance purposes, to ensure the products tested meet their specifications. For this reason, such testing must be conducted in compliance with cGMPs. The purpose of GLPs is to ensure the quality of the pre-clinical laboratory data, in the research and development phase, that will ultimately be relied on to support a product's approval.

As an example, FDA inspected a contract testing laboratory run by a university laboratory over the course of four days in late 2021, during which agency investigators identified serious deficiencies that resulted in an FDA warning letter.[27] Among the identified deficiencies were insufficient controls over computerized systems to prevent unauthorized access to or changes to data. A customer audit had identified falsification of data over the course of three years, which involved entering arbitrary values in computerized systems for sample, spike, and correlation. The FDA investigators identified additional data integrity concerns that undermined test results obtained supporting the quality of drug product and drug ingredients tested. FDA also found that laboratory personnel were not adequately trained, and that the laboratory lacked an adequate quality unit or quality system to provide appropriate oversight over the laboratory operations. Such noncompliance raises both FDA enforcement risk, as well as the risk of litigation brought by customers who have contracted for cGMP-compliant testing.

As with research-focused inspections, it is useful to call in experienced FDA counsel to assist during and immediately following an inspection, especially if a Form 483 is issued at the end of the inspection. An appropriate remediation plan and well-written response may prevent the issuance of a warning letter. If a warning letter is issued, the letter will be public, and manufacturers may be hesitant to rely on the laboratory for further testing. Notice of noncompliant testing and potentially inaccurate results could trigger regulatory requirements for the manufacturer and could impact whether the manufacturer's product meets its specifications. Thus, for a testing laboratory to keep cGMP-testing contract work, it must ensure the laboratory is compliant with cGMPs.

CLINICAL LABORATORY TESTING

Laboratory tests are often critical to patient care, assisting with diagnosis and with identifying genetic factors that can make a particular treatment more or less likely to be effective. Clinical laboratories are regulated in all states, with two exceptions, under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).[28] FDA views most tests performed in such laboratories as medical devices subject to its jurisdiction. Historically, however, FDA took the position that it would not regulate, and would exercise enforcement discretion over, a category of tests referred to as laboratory developed tests (LDTs), which FDA considered to include in vitro diagnostic tests that are "designed, manufactured, and used within a single site laboratory certified under CLIA that meets the requirements to perform tests of high complexity." In May 2024, FDA published a final rule ("the Final Rule") that phases out historic enforcement discretion for LDTs over the course of four years and brings LDTs

27 *See* FDA, Warning Letter to David L. Tierney, Principal Investigator, Miami Univ. Dep't of Chemistry & Biochemistry, No. 623494 (Apr. 20, 2022), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/miami-university-department-chemistry-and-biochemistry-623494-04202022.

28 The exceptions are New York and Washington State, both of which are "CLIA-exempt" states because they maintain laws governing clinical laboratories that are at least as stringent as CLIA.

clearly within the definition of "medical device." The rule would subject these tests to FDA regulatory requirements, including the requirement that laboratories register and list the tests with FDA, as well as premarket review, quality, research, and adverse event and recall reporting obligations. However, the LDT Final Rule also exempts in vitro diagnostics marketed as LDTs at the time of issuance of the Final Rule from certain of the device regulations that will be phased in over time—namely premarket review and most quality system requirements—so long as the tests are not significantly modified. The Final Rule preamble also includes an exemption from premarket review and quality system requirements for LDTs that are provided by a laboratory integrated within a health care system for the unmet needs of patients receiving care in the same health care system.

Many laboratories, including those within universities and AMCs, have historically viewed their provision of testing services as outside of FDA's jurisdiction and have significant concerns about FDA enforcing medical device requirements against LDTs. While the rule is likely to be challenged in litigation—assuming it survives such challenges and is not preempted by potential Congressional legislation—it could have significant implications for AMCs and other institutions that offer testing services that use LDTs.[29] The agency sought public comment on a proposed definition for AMCs and on a number of specific questions related to the possible public health rationale and evidence that might support an enforcement dissection policy for LDTs manufactured by AMCs.[30] However, the LDT Final Rule does not include an enforcement discretion policy directed at AMCs, though certain LDTs currently offered by AMCs and those covered by the narrow "unmet needs" exemption will fall within enforcement discretion policies contemplated by the rule.[31]

CLINICAL USE OF UNAPPROVED OR UNCLEARED MEDICAL PRODUCTS

Research and testing are not the only contexts in which universities and AMCs may interact with FDA-regulated products. Practitioners at university-affiliated hospitals also use FDA-regulated products, including drugs, biological products, and medical devices to treat and diagnose patients in a clinical setting. FDA does not regulate the practice of medicine, and physicians are generally free to prescribe and use FDA-cleared or approved medications and devices to treat their patients as they see fit. However, when a physician or hospital treats patients with a drug or medical device that has not been approved or cleared by FDA (or has

29 Medical Devices; Laboratory Developed Tests, 88 Fed. Reg. 68,006, 68,023 (proposed Oct. 3, 2023) (to be codified at 21 C.F.R. pt. 809).

30 *Id.* at 68,024.

31 For a summary of key takeaways from the Final Rule, *see* Gregory H. Levine et al., *A Test of Patience: FDA Moves Forward with Controversial Final Rule on Laboratory Developed Tests* (May 12, 2024), https://www.ropesgray.com/en/insights/alerts/2024/05/a-test-of-patience-fda-moves-forward-with-controversial-final-rule-on-laboratory-developed-tests.

been modified from its approved or cleared form), they may run afoul of legal prohibitions that are subject to enforcement.[32]

These issues most frequently come up in the device context, and institutions should have procedures in place to (1) ensure that devices developed at the university or in university hospitals have appropriate FDA clearance or approval,[33] and (2) ensure that appropriate due diligence is conducted on third-party devices considered for use at the institution. It is important to have confidence that the manufacturers selling devices for use in the institution are complying with their own regulatory obligations. Any injury that is associated with use of a device in clinical practice that requires but lacks FDA clearance or approval could subject the institution and practitioner to lawsuits alleging medical malpractice or negligence causes of action, could subject the physician to a disciplinary action or could impact the institution's license. Further, any attempt to obtain reimbursement for use of unapproved or uncleared medical devices in clinical practice could also subject the practitioner and the hospital to False Claims Act liability.

Software as a Medical Device

One type of FDA-regulated device that is often overlooked in clinical and research settings is medical software. Some examples of medical software include diagnostic algorithms that analyze medical images, symptom checkers, applications for tracking and sharing wearable device data, triaging functions that use a patient's medical information to predict deterioration, and allergy/drug-drug interaction checkers. Many medical software products are subject to FDA medical device requirements, and use of these software without appropriate clearance or approval, compliance with device quality system and post-marketing requirements, and (when applicable) compliance with clinical trials-related regulations can expose institutions to FDA enforcement risk and other legal and reputational risks described above.

As digital health tools become an increasingly important part of health care, FDA has worked to develop a framework to appropriately regulate these tools while encouraging

32 Causing the distribution of unapproved drugs violates 21 U.S.C. § 331(d). Causing the distribution of adulterated or misbranded drugs or devices violates *id*. § 331(a). Receiving adulterated or misbranded drugs or devices in interstate commerce and then proffering them for delivery or sale violates *id*. § 331(c). Adulterating or misbranding a device while held for sale after shipment in interstate commerce violates *id*. § 331(k). Devices that require an FDA premarket approval but lack it are considered adulterated. *Id.* § 351(f)(1)(b). Devices that require a 510(k) clearance but lack it are considered misbranded. *Id*. § 352(o). Modifying an approved or cleared device or drug can also render that product adulterated or misbranded. *See generally id*. §§ 351 and 352. *See also* Overview of FDA Enforcement Processes, on page 137, regarding enforcement authorities and risks.

33 We note that there is a limited exemption for licensed medical practitioners who manufacture or otherwise alter medical devices solely for use in their own professional practice, from the need to register as device manufacturers and obtain premarket clearance to use such devices in their practice. *See* 21 C.F.R.§ 807.65(d). However, the limits of the licensed practitioner exemption are not clearly defined, and it is critical to conduct a careful assessment and consider the risks with relying on this exemption in any particular circumstance.

innovation.[34] FDA takes a tiered, risk-based approach to the regulation of software, whereby, depending on its intended use and level of risk, a software function is either (1) a medical device subject to regulation; (2) a medical device subject to "enforcement discretion" for which FDA has announced its policy not to enforce regulations that would otherwise apply to certain devices; or (3) not a medical device and therefore not subject to FDA regulation.[35] Software that is regulated by FDA as a medical device is referred to as software as a medical device, or "SaMD." Determining whether a particular software tool is subject to FDA regulation requires a detailed and fact-specific analysis under an ever-evolving and expanding patchwork of FDA guidance documents.

For example, FDA has issued guidance on Clinical Decision Support Software, which interprets a statutory exclusion from the definition of device for clinical decision support (CDS) software that meets certain criteria.[36] Prior to issuing the final guidance on CDS in 2022, FDA issued two drafts of the guidance, and in each case the guidance has substantially changed from the prior version. Under the statute, clinical decision support software is not a medical device if it meets all of the following four criteria:

1. Is **not** intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system;
2. Is intended to display, analyze, or print medical information about a patient or other medical information, like clinical practice guidelines;
3. Is intended to support or provide recommendations to a health care provider (HCP) about prevention, diagnosis, or treatment of a disease or condition; and
4. Is intended to enable HCPs to independently review the basis for the software's recommendations so HCPs do not primarily rely on the recommendations when making a clinical diagnosis or treatment decision.

FDA's CDS guidance interprets and provides instructive examples addressing each of these four criteria. For example, FDA interprets the third criterion to mean that, in order to qualify as non-device CDS, the software should (i) provide condition-, disease-, and/or patient-specific information and options to an HCP to enhance, inform and/or influence a health care decision; (ii) not provide a specific preventive, diagnostic, or treatment output or directive (i.e., it should provide a list of options rather than a single recommended treatment

34 A list of FDA guidance documents that are relevant to digital health products is available on FDA's website at *Guidances with Digital Health Content*, U.S. Food & Drug Admin. (Nov. 3, 2023), https://www.fda.gov/medical-devices/digital-health-center-excellence/guidances-digital-health-content.

35 *See* FDA, U.S. Dep't of Health & Hum. Servs., Policy for Device Software Functions and Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff (2022), https://www.fda.gov/media/80958/download.

36 *See* FDA, U.S. Dep't of Health & Hum. Servs., Clinical Decision Support Software: Guidance for Industry and Food and Drug Administration Staff (2022), https://www.fda.gov/media/109618/download.

or potential diagnosis); (iii) not be intended to support time-critical decision-making; and (iv) not be intended to replace or direct the HCP's judgment. Whether a particular software product meets this criterion and the other criteria to qualify as non-device CDS requires careful analysis under FDA's guidance.

Whether a particular software tool is an FDA-regulated medical device is oftentimes unclear, and institutions must make a risk-based judgment call and consider potential risk-reducing mitigations. HCPs and others at the institution developing medical software, as well as clinical trial sponsors, sponsor-investigators, and IRBs, should be trained on identifying when the use of digital tools could have regulatory implications and when they should call the legal department for help. Knowledgeable FDA legal counsel that are closely monitoring FDA's regulatory decision-making and enforcement in this area can be a critical resource.

SUMMARY OF BEST PRACTICES

Tone at the Top: Considering the significant FDA regulatory obligations that attach to activities conducted at AMCs, hospitals, and health systems, it behooves these institutions to have a robust compliance infrastructure in place that is appropriately resourced. Such an infrastructure requires a compliance-focused mindset that starts at the highest levels of management. Institutional leadership should communicate the message that patient care, human subject protection, ethical conduct, and high-quality science are paramount, and that these critical commitments require compliance with applicable law and institutional policies. It is also important for clinicians at such institutions who also conduct research to clearly understand the difference between clinical practice and research and ensure that research obligations are strictly adhered to when treating patients as part of a research study.

Policies and Procedures: A robust set of (1) policies that explain the rationale for various categories of compliance obligations and (2) procedures and work instructions that provide step by step instructions for how to comply with established policies provide a necessary framework for compliance. At a minimum, to assure compliance with applicable FDA obligations, institutions should have policies and procedures in place that ensure:

1. Necessary standard operating procedures are established and updated as required by regulations.
2. Personnel are properly qualified for their roles, trained appropriately, maintain appropriate hygiene, and wear appropriate clothing for their tasks, and that such qualifications and training are documented.
3. Responsibilities are clearly defined and assigned.
4. Facilities and equipment are appropriately designed for their function and maintained as required.
5. Proposed research is appropriately reviewed and approved by all necessary parties in compliance with applicable law and institutional policies.

6. Clinical trial agreements are reviewed by the legal department and approved before signed.
7. Clinical research staff understand the role of IRBs and when approvals must be sought or reports made.
8. Clinical investigators, research staff, and laboratory personnel understand how to comply with their research or laboratory-related obligations and who to contact if FDA appears for an inspection, reaches out with questions, issues a 483 at the close of an inspection, or sends a warning letter.
9. Recordkeeping is compliant, conforms with applicable regulations, reflects good documentation practices, and records are appropriately maintained and retained.
10. Records are appropriately reviewed and evaluated to ensure reporting obligations are met.
11. Human and animal research subjects are protected as required by law.
12. Clinical investigator financial conflicts of interest are reported to sponsors and appropriate records of payments are maintained.
13. Investigational products are appropriately handled, stored, and tracked.
14. Non-investigational medical products used in clinical practice are appropriately vetted to ensure FDA approval and appropriate use is understood.
15. Physician or staff developed medical devices, including digital tools used in clinical care, are reviewed by knowledgeable attorneys before being used in clinical practice or marketed by the institution or clinicians.
16. Billing practices comply with applicable law.
17. Employees know who to contact with questions or concerns about compliance.
18. Internal audits are conducted regularly and compliance lapses are investigated and remediated.
19. Internal investigations are comprehensive and identify root cause. Corrective and preventative actions are put in place to ensure identified problems are corrected and do not recur.
20. Employees who unintentionally violate compliance obligations are retrained. Employees who intentionally and persistently violate obligations are sanctioned and terminated when appropriate.

Training and Auditing: Regular training of employees on the rationale for policies and procedures, what they require, and the consequences of non-compliance are critical. Further, good training programs involve more than simply providing relevant employees with policies and procedures to read. High-quality training highlights critical information in an interactive format and includes assessments. In addition, institutions cannot simply trust that once employees are trained on a set library of polices and procedures, compliance necessarily follows. Policies must be updated. Training must be refreshed. A compliance hotline should be established for the purpose of reporting lapses in compliance so they can be investigated and remediated. And institutions should maintain an internal auditing program to ensure that policies and procedures are being followed. If lapses are identified through audits or complaint reporting, an investigation should be conducted that identifies root causes, and corrective and preventive action to be taken, potentially in the form of clarifications to policies and training, reminders as to the importance of compliance, or appropriate sanction of offending employees.

CONCLUSION

This article reviews at a very high level many of the key requirements arising from research, laboratory testing, and clinical use of FDA-regulated drugs and devices, and the related risks that universities, health systems, and research institutions may face in the ordinary course of performing these activities. Suggestions for best practices are offered to serve as a starting point for developing a compliance program. Experienced regulatory consultants and lawyers can assist in the development or assessment of an institution's compliance program to mitigate potential FDA regulatory, litigation, and other enforcement risks arising out of day-to-day research, clinical, and laboratory activities. All involved in these highly regulated activities should also know who in the legal department to call when questions arise, or should FDA come knocking at the door.

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