Common Bioresearch Monitoring Violations: Updates from FY 2021 to Now

The Bioresearch Monitoring Program (BIMO), run by the U.S. Food and Drug Administration (FDA), oversees the conduct of on-site inspections and data audits of FDA-regulated research in support of new product development and marketing approvals. As a follow up to our **July 2021 post**, we highlight here the most common violations FDA's BIMO identified in Fiscal Year (FY) 2021 along with those we have seen so far in FY 2022. Our review focuses on BIMO's clinical investigator, sponsor, and contract research organization (CRO) inspection outcomes across 516 inspections conducted in FY 2021, as these comprised nearly 85 percent of all BIMO inspections.

Amongst these, 81 percent did not result in any findings of noncompliance. Eighteen percent resulted in findings of noncompliance but without recommending regulatory action, and about one percent resulted in findings of noncompliance recommending official regulatory action. In FY 2021, the most common violations leading FDA to issue a Form FDA 483, FDA's official form for documenting noncompliant inspection findings, included:

- **Failure to submit an IND application.** For example, FDA issued several Warning Letters for investigations of dietary supplements or foods determined by the FDA to be drugs. FDA found that the study designs demonstrated the investigational products were intended to cure, mitigate, and/or treat a disease or condition, triggering application of FDA's drug authorities and requiring an Investigational New Drug (IND) application to be in place before conducting the research.

- **Failure to follow the investigational plan and implement corrective or preventive action plans.** For example, in one **Warning Letter** resulting from a BIMO inspection, the FDA noted that the investigator failed to exclude subjects according to the study's exclusion criteria and did not identify any procedures in place to prevent future violations.

- **Inadequate or inaccurate recordkeeping (including case histories, study records, and drug disposition records).** For example, in one recent **Warning Letter** following a BIMO inspection, the FDA noted that a study site failed to retain necessary documents for 2 years following marketing approval when it could not locate informed consent forms and case report forms, amongst others, from a study for which a Biologics License Application was pending.

Of note, these continue to be the most frequently cited violations in BIMO Warning Letters issued to date in 2022. To avoid these missteps and better understand the scope of their respective

responsibilities before, during, and after a clinical trial, sponsors, CROs and investigators should review **FDA's BIMO Compliance Program Guidance Manuals** and ensure adoption of standard operating procedures (SOPs) that provide an infrastructure for regulatory compliance. Sponsors and investigators should also ensure that they understand when an IND application is required, and review the requirements for appropriate recordkeeping during and after a clinical trial. Finally, sponsors and CROs should have mechanisms in place to both promote protocol adherence and promptly respond to any deviations when they inevitably occur. Sponsors receiving BIMO Form FDA 483s should respond with a detailed explanation of their root cause findings, corrective actions, and their plan to prevent similar missteps in the future. The Goodwin FDA team works closely with sponsors to apply FDA's Good Clinical Practice requirements and to resolve BIMO inspection findings when they occur.

Connect with our Goodwin FDA team to learn more.

*Maura Friedlander, a 2022 summer associate in Goodwin's Washington, D.C. office, contributed to this post.

Potential AI/ML Learnings to Come from FDA Public Advisory Committee Meeting on Skin Lesion Analyzer Technology in Late July

 On July 28, 2022, the U.S. Food and Drug Administration (FDA) will hold a public advisory committee meeting to discuss skin lesion analyzer (SLA) technology and its application to detecting skin cancers in various patient care settings. This meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee will focus on algorithm-based SLA devices for adjunctive detection of skin lesions, including skin cancers, and stands to provide industry another layer of thinking on FDA's perspective on artificial intelligence and machine learning (AI/ML) device technologies.

In announcing this meeting, FDA explained that in recent years it has observed an increased interest in SLA devices employing AI/ML. The agency is seeking expert input from the panel on approaches to evaluate the performance of SLA devices, which have a range of technologies and indications.

The committee will discuss and provide recommendations to FDA on: (1) the diagnosing standard, or ground truth, that should be used as a comparison for the performance of diagnostic devices, e.g., histology, consensus opinion of a panel of dermatologists, opinion of a single dermatologist, or other means; (2) acceptable sensitivity and specificity thresholds based on the target diagnosis (melanoma, basal cell carcinoma, squamous cell carcinoma) or intended user (dermatologist,

primary care physician, lay user); (3) patient characteristics, including lower or higher incidence populations, that should be tested before marketing; and (4) the balance of increased access with risk mitigation measures that are appropriate when the devices are used by lay people, by populations with very high or very low incidence of melanoma, by populations with low incidence, but high mortality associated with melanoma, or by the target diagnosis/lesion type.

Additionally, on July 29, 2022, the committee will discuss the possible reclassification of two class III, PMA approved computer-aided melanoma detection devices, MelaFind (P090012) and Nevisense (P150046), both of which are intended for use on cutaneous lesions suspicious for melanoma when a dermatologist chooses to obtain additional information when considering biopsy. According to the FDA announcement, "The committee will discuss if there is sufficient information to reclassify computer-aided devices for adjunctive diagnostic information of lesions suspicious for melanoma from class III to class II, and what special controls may be appropriate to provide reasonable assurance of safety and effectiveness" if they are reclassified.

This meeting, and any actions the FDA takes as a result, could offer industry further insight into the FDA's approach to regulating AI/ML diagnostic and screening products more broadly.

The meeting will be held virtually on July 28, 2022, from 9 am to 5:45 pm ET and July 29, 2022, 9 am to 4 pm ET. Comments received on or before July 11, 2022 will be provided to the committee and the public docket will remain open for comment for FDA's consideration until August 29, 2022.

For more information see the **Meeting Notice on the Federal Register**.

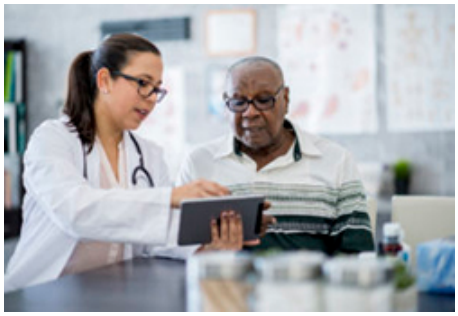
Brian Burgess to Speak on Emerging Legal Issues and Trends for Interchangeable Biosimilars at FDLI Annual Conference

The annual Food & Drug Law (FDLI) conference will be held on June 14-15, bringing together experts from the federal government, industry, the private bar, non-profit, patient and consumer advocates, consulting organizations, and academia to address complex legal, regulatory, compliance, and policy issues facing the FDA-regulated industry. Goodwin is a proud sponsor of the conference and partner **Brian Burgess** is a featured speaker on the panel, ***Interchangeable Biosimilars – Emerging Legal Issues and Trends***. During this session, the speakers will discuss what can be learned from the first interchangeable approvals and what it tells us about FDA's interchangeability framework. The speakers will also address what the competitive landscape for biologics looks like,

how the statutory standard regarding “any given patient” may play out, and whether applicants will be able to use real world evidence to support interchangeable licensure.

Let our Goodwin team **know** if you will be attending the FDLI Annual Conference. For additional information about the conference, please click **here**.

Clinical Trial Diversity Planning for Sponsors: What to Know About FDA’s Recent Draft Guidance



On April 13, 2022, the U.S. Food and Drug Administration (“FDA”) issued a **draft guidance** providing specific recommendations to the industry on how to improve diversity in clinical trials. The FDA’s focus on increasing racial and ethnic diversity in clinical trials is not new, with the agency issuing several guidances since 2016 on this topic.[1] However, the recent draft guidance sets out new expectations for sponsors conducting clinical trials intended to support marketing authorization of drugs, biologics, and medical devices.

Read the **client alert** by FDA Senior Associate **Elizabeth Mulkey** and Partner **Alexander Varond**.

For Clinical Trial Recruiting, Words Matter

In a recent publication we helped co-author, we examined ClinicalTrials.gov entries and their possible impact on informing potential subjects of their eligibility to participate in clinical trials. In

particular, we analyzed certain clinical trials focused on HIV treatment or prevention that allowed entry of pregnant women to assess the use of pregnancy-related terms in each trial's description and inclusion/exclusion criteria, such as those relating to gestational age and trimester. The assessment focused on evaluating the potential utility of ClinicalTrials.gov for pregnant women and their healthcare providers in identifying potential clinical research in which they may be eligible to participate. In brief, we found that descriptors and terminology can play an important role in communicating with providers and prospective subjects about eligibility for participation. While our findings are in the context of HIV research and pregnant women, our takeaways could apply to other disease areas and populations where specific terminology may play a role in successful identification and recruitment of eligible patients, particularly where competition for patients presents an ongoing challenge, such as rare diseases.

Read the full **article** in *Contemporary Clinical Trials Communications*.

Medicare Agrees to Limited Payment for New Alzheimer's Drug

On January 11, 2022, the Centers for Medicare and Medicaid Services (CMS) **released** a proposed National Coverage Determination (NCD) decision memo limiting Medicare coverage for Biogen's new Alzheimer's drug, Aduhelm. Under the terms of the NCD – despite FDA's 2021 approval of the drug – CMS will only pay for Aduhelm for Medicare beneficiaries who are enrolled in a qualifying clinical trial to assess the drug's safety and its effectiveness in slowing the progression of Alzheimer's. CMS **stated**, "[B]ased on the public comments submitted previously and evidence CMS reviewed, the potential for harm, and important questions that remain, we have determined that coverage with evidence development through clinical trials is the right decision for Medicare patients, clinicians, and caregivers, and we look forward to receiving feedback on the proposal." The proposed NCD is **open** to public comment for thirty (30) days, and a final decision from CMS is expected **on April 11**. If the proposed NCD is finalized, CMS must evaluate each submitted clinical trial to verify that it meets the qualifying criteria specified in the proposed NCD.

Aduhelm has been approved by FDA for the treatment of Alzheimer's since June 2021. This is the first drug approved by FDA for the treatment of Alzheimer's in almost 20 years. In 2019, two clinical trials for Aduhelm were **paused** due to data showing the drug was of no benefit to patients' cognitive function. However, after Biogen re-analyzed one of its trials, it decided to apply to the FDA for approval. The FDA used the accelerated approval process but can withdraw Aduhelm from the market if Biogen's new clinical trial demonstrates that the drug is ineffective. The FDA **pivoted** on the approval itself, later **recommending** Aduhelm only in patients with mild cognitive impairment

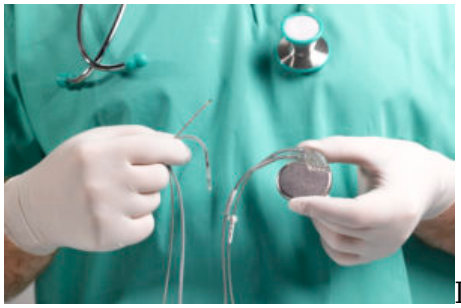
or mild dementia. Patient advocacy groups such as the Alzheimer's Association **played** an important role in pressuring FDA to approve Aduhelm, given the minimal advancements in drug treatment in the space.

Since receiving FDA approval, Biogen has faced tough scrutiny about Aduhelm's efficacy and cost. Aduhelm's initial annual price of $56,000 elicited widespread criticism. In December 2021, Biogen **announced** that it would reduce the drug's price to $28,200 for some patients. Biogen most likely reduced the price in response to slower than anticipated sales and CMS's announcement it would increase Medicare's monthly Part B premium for outpatient care in anticipation of the Aduhelm's price impact. Adding to Biogen's challenges, an FDA advisory committee agreed almost **unanimously** that the clinical trials did not provide strong enough evidence to corroborate Aduhelm's efficacy data. However, based on the clinical trials it did review, FDA **claimed** that Aduhelm could reduce clumps of plaque in the brain, which is likely to slow dementia. The discrepancy between the advisory committee's and FDA's findings coupled with broad criticism of the FDA led the Department of Health and Human Services Office of Inspector General to conduct a **probe** into the FDA's approval process for Aduhelm.

Adding to the complexity, State Medicaid programs have also been vocal in protesting CMS's decision. Unlike Medicare, Medicaid is required to cover all FDA-approved drugs regardless of a drug's clinical efficacy. Therefore, had Medicare determined not to cover Aduhelm, all costs would **shift** to the state Medicaid programs. Though some states and insurers have already **declined** to cover Aduhelm, CMS's ruling is likely to influence other payors to refuse coverage.

While some commenters and industry observers have questioned whether CMS's decision with respect to Aduhelm somehow creates a new, default secondary clinical testing and approval threshold for drug makers, it is more likely that the Medicare agency's decision on Aduhelm reflects the unique circumstances posed by the drug (*i.e.* unclear efficacy concerns, conflicting FDA guidance, and an unusually high price point). Whether CMS will make a habit of limiting coverage for innovative drugs only to beneficiaries participating in additional clinical trials remains to be seen, but is not likely. We will continue to monitor trends and developments at CMS with respect to coverage and payment decisions on new therapeutics and treatments, including additional research and testing requirements that the agency may impose.

Planning For The End: Goodwin FDA attorneys Steve Tjoe and Susan Lee highlight key takeaways From FDA's draft guidances proposing transition plans for medical devices marketed under EUAs or enforcement policies during the COVID-19 Public Health Emergency

 During the COVID-19 public health emergency, the United States Food and Drug Administration (FDA) has issued hundreds of Emergency Use Authorizations (EUAs) and numerous enforcement policies to facilitate the availability of important medical devices. On December 23, 2021, FDA published two draft guidances setting forth the Agency's proposed process for transitioning the multitude of devices brought to market under these circumstances to full compliance with FDA requirements:

- Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (the "EUA Transition Draft Guidance"); and
- Transition Plan for Medical Devices That Fall Within Enforcement Policies Issued During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (the "Enforcement Policies Transition Draft Guidance").

In our **recent Alert**, we summarize some key takeaways from FDA's proposed transition plan for manufacturers of devices marketed under a COVID-19 EUA ("EUA Devices") and devices marketed under one of more than 15 COVID-19 enforcement policies listed in the guidance ("Enforcement Policy Devices"). **Read More**

Review of FDA's 2021 Drug Approvals – Small Molecules Dominate

 The FDA's Center for Drug Evaluation and Research (CDER) approved 50 new drugs and biological products in 2021 (not including the vaccines, cellular and gene therapy products, or other products approved in 2021 by the Center for Biologics Evaluation and Research). As in past years, small molecule drug approvals dominated the list.

Of the 50 approved new drugs and biological products, 33 were small molecule drugs and 17 were monoclonal antibodies and other big molecules drugs. A new ADC (antibody drug conjugate) was approved, Tivdak®, and a bispecific antibody was also approved, Rybrevant®. Notably, a small interfering RNA drug was approved, Leqvio®, for the treatment of atherosclerotic cardiovascular disease.

As small and big molecule drugs enter the clinic, Goodwin's patent attorneys focus on securing not only composition of matter patent protection, but additional patent protection derived from clinical data. Learn more about additional patent protection secured from the clinic in **Goodwin's Patent Savvy Executive video**.

Each new drug and biological product can be found in the FDA's **Orange Book** or the FDA's **Purple Book**. To learn more about the Orange Book and how to determine patent terms on approved drugs, visit **Goodwin's Patent Savvy Executive video**.

See the full list **here**.

On Remote Control: FDA Issues Draft Guidance to Facilitate Use of Digital Health Technologies for Remote Data Acquisition in Clinical Trials

 During the COVID-19 pandemic, decentralized clinical trials and remote patient monitoring and data acquisition became a necessity, accelerating the use of digital health technologies in clinical trials. Acknowledging that technological advances "have revolutionized the ability to remotely obtain and analyze clinically relevant information from individuals" and that "DHTs [ ] are playing a growing role in health care and offer important opportunities in clinical research," the FDA issued during the last week of December 2021 a draft guidance, ***Digital Health Technologies for Remote Data Acquisition in Clinical Investigations***, which provides recommendations for sponsors, investigators and other stakeholders to facilitate the use of DHTs for remote data acquisition in clinical trials, including clinical trials that will be submitted to the FDA in a marketing application for a medical product.

The draft guidance defines a digital health technology (DHT) as a system that uses computing platforms (such as a mobile phone, tablet, or smart watch), connectivity, software, and/or sensors for healthcare and related uses. Some DHTs may meet the definition of "device" under the Federal Food, Drug and Cosmetic Act, but the draft guidance specifically does not address the circumstances under which a DHT would meet the statutory definition of a device and notes that DHTs used in clinical investigations generally are exempt from premarket clearance or approval requirements, as long as the clinical investigation is compliant with 21 CFR Part 812.

The draft guidance explains that sponsors must foremost ensure that a DHT is "**fit-for-purpose**" for

its proposed use in a specific clinical investigation. In essence, the level of verification and validation associated with the DHT must be sufficient to support its use and interpretability in the clinical investigation. This may require sponsors to work with the developer or manufacturer of the DHT, patients, caregivers, and other technical and clinical experts to assure that the DHT is suitable for its intended purpose in the clinical investigation. The draft guidance advises sponsors to select a DHT that corresponds to the clinical outcome to be assessed, and that considers the clinical trial population and the design/operating characteristics of the DHT that may affect trial participants' use of the DHT.

Sponsors should also be prepared to describe how they will analyze data collected from DHTs in their statistical analysis plan, including prespecifying "**intercurrent events**" (defined as events that occur after treatment initiation that result in missing or erroneous data associated with the clinical outcome of interest) that may be related to the DHT and/or the general purpose computing platform, and how these events will be accounted for in the analysis. To maintain data integrity, FDA recommends that the output of the DHT and associated metadata be transmitted to a **durable electronic data repository** that is protected from alterations and maintained until the end of the record retention period. FDA generally will consider data in such a repository to constitute the source data and should be made available for inspection and to reconstruct and evaluate the clinical investigation.

FDA further notes that "unique privacy risks" may arise when DHTs are used in a clinical trial. Sponsors are advised to evaluate the risk of potential disclosures of personally identifiable information through breaches of the DHT, the general computing platform on which the DHT runs, and/or the durable electronic repository, assure appropriate security safeguards are in place, and consider including such information in the informed consent documents for the clinical trial.

The draft guidance recommends that sponsors:

- train trial participants and trial personnel on the use of DHTs and develop a plan to provide technical assistance to trial participants and study personnel;
- develop a risk management plan to address potential problems with the DHT (e.g., interference between mobile applications, or loss, damage and replacement);
- develop a safety monitoring plan that addresses how abnormal measurements related to participants' safety measured by DHTs will be reviewed and managed; and
- develop a contingency plan for any changes to the DHT (e.g., discontinuation of a specific model, operating system updates)

The draft guidance includes appendices with specific examples of how different types of DHTs could be incorporated into a clinical investigation. Given the particular circumstances of each DHT and clinical investigation, the draft guidance encourages sponsors to engage early with the appropriate FDA Center responsible for the medical product under development to discuss the proposed use of DHT(s) in a clinical investigation and, for DHTs or DHT-collected endpoints that require qualification, engage with an appropriate FDA qualification program, such as the **Medical Device Development Tool Qualification Program**.

Comments on the draft guidance are due March 23, 2022.

Reality Check: FDA Draft Guidance Outlines Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drugs and Biological Products

Last week the FDA issued another draft guidance in its series of recent guidance documents setting forth the agency's views regarding the generation and use of Real-World Data (RWD) and Real-World Evidence (RWE) for prescription drugs and biological products. (see our **recent post** on FDA's draft guidance relating to registries).

This latest draft guidance, **Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products**, clarifies the agency's expectations for sponsors submitting new drug applications (NDAs) or biologics license applications (BLAs) with studies using Real-World Data (RWD) to support the safety or effectiveness of drugs or biological products, when such studies are not subject to FDA's investigational new drug (IND) application requirements under **21 CFR Part 312**. The draft guidance focuses on non-interventional (*a.k.a.* observational) studies, in which patients receive a drug during routine medical practice, according to a medical provider's clinical judgment and based on patient characteristics, rather than via assignment to a study arm and according to a clinical trial protocol.

Key considerations outlined in the guidance:

- *Sponsors designing a non-interventional study to support a marketing application should engage early with the relevant FDA review division* (e.g., through a Type C meeting) and be prepared to submit draft protocols and SAPs for FDA feedback *before* conducting the study analyses.

- *To assure the FDA that the results of a non-interventional study were not skewed to favor a particular conclusion,* sponsors should provide evidence that the non-interventional study protocol and statistical analysis plan were finalized *prior* to reviewing outcome data and *before* performing prespecified analyses. Sponsors should provide a justification for selecting relevant data sources and generate audit trails in their datasets. FDA also recommends that sponsors post their non-interventional study protocols on a publicly available website, such as **ClinicalTrials.gov**.

- *Sponsors must be able to submit patient-level data from the RWD.* Where a third party owns or controls the RWD, sponsors should have agreements with such parties to ensure that patient-level data and source data to verify the RWD can be provided to the FDA for inspection, as

applicable. Sponsors should have well-documented programming codes and algorithms that would allow the FDA to replicate the study analysis using the same dataset and analytic approach.

- *Non-interventional studies should be monitored*. The FDA advises sponsors to use a risk-based quality management approach, with a focus on preventing or mitigating important and/or likely risks to study quality. If a non-interventional study does not include any activities or procedures involving patients, monitoring can focus on assuring the data integrity of the RWD, from extraction to analysis to reporting of results. When a non-interventional study protocol includes ancillary activities or procedures, sponsors should exercise appropriate oversight of processes critical to human subject protection.

- *Adverse events that a sponsor becomes aware of through a non-interventional study must be submitted in accordance with postmarketing safety reporting regulations*. However, the agency acknowledges that if a sponsor is conducting a non-interventional study that appropriately utilizes only a subset of a larger dataset, the sponsor will not have to search the entirety of the dataset for adverse events.

- *Sponsors should take responsibility for all activities related to the design, conduct and oversight of a non-interventional study that is being submitted for regulatory review*. This includes selecting qualified researchers, ensuring the study is conducted in accordance with the protocol, maintaining and retaining adequate study records, and maintaining an electronic system to manage RWD that complies with **21 CFR Part 11**. Where a sponsor engages third parties to perform certain study-related tasks, the responsibilities of each organization should be documented and made readily available to the FDA upon request.

Comments on the guidance should be submitted to the docket by March 9, 2022.