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.

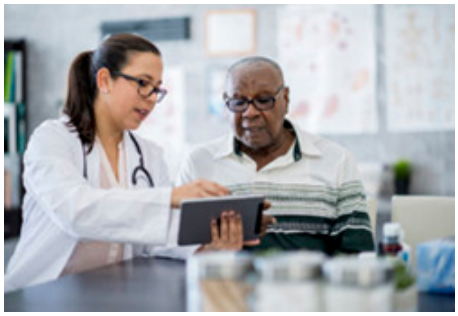
For more information see the **Meeting Notice on the Federal Register**.

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**.

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.

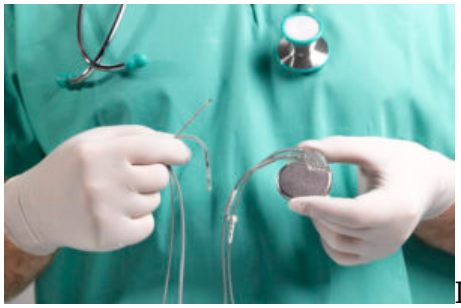
Since receiving FDA approval, Biogen has faced tough scrutiny about Aduhelm's efficacy and cost. Aduhelm's initial annual price of $56,000 elicited widespread criticism. In December 2021, Biogen **announced** that it would reduce the drug's price to $28,200 for some patients. Biogen most likely reduced 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

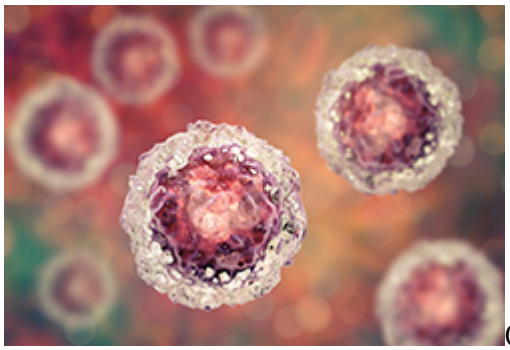
Public Health Emergency

 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**

FDA Issues Guidance for Cell and Gene Therapy Manufacturers to Minimize Potential Transmission of SARS-CoV-2

 On January 19, 2021, the FDA issued **guidance** for licensed and investigational cellular and gene therapy (CGT) manufacturers during the COVID-19 pandemic. This new guidance supplements the recommendations provided in FDA's **June 2020 guidance** regarding manufacturing controls to prevent contamination in drugs, risk assessment of SARS-CoV-2

as it relates to drug safety and quality, and continuity of manufacturing operations as applied to all drug and biological product manufacturers.

The new guidance provides risk-based recommendations to minimize potential transmission of SARS-CoV-2 to patients and facility personnel with specific considerations relating to, among other things, the assessment of donors, cellular and tissue source materials, manufacturing processes, manufacturing facility control, material testing, and the number of patients that can be treated with the product. While FDA acknowledges in the guidance that is not aware of any CGT products that have been contaminated with SARS-CoV-2 or of information indicating transmission of SARS-CoV-2 via CGT products, FDA notes that "CGT manufacturers are expected to evaluate whether [the virus] poses new risks in the context of their specific products, facilities, processes, and manufacturing controls."

FDA recommends that CGT manufacturers review the current good manufacturing practice requirements and recommendations and perform a risk assessment that identifies, evaluates, and mitigates factors that may allow for transmission of SARS-CoV-2 to patients and facility personnel and include a description of the risk assessment and mitigation strategies in any investigational new drug application (IND), biologics license application (BLA), or master file. Since this is an evolving area, manufacturers should look to scientific literature to provide justification and support for their risk assessment and mitigation strategies.

CGT manufacturers should evaluate their manufacturing operations for SARS-CoV-2 risks and be sure that all risk assessments of production controls, including any follow-up and changes, are approved by their quality unit and appropriately documented within their quality management system.

Orange Book Listable?

 When submitting a new drug application ("NDA") with the FDA, an applicant (or branded company) is required to file a list of patents that cover the drug product. These patents will be listed in the FDA's Orange Book upon approval of the drug for commercial sale. Patents that are eligible to be listed in the Orange Book are patents that have claims that cover the drug substance (active ingredient), the drug product (formulation and composition), or the approved method of use.

What patents can't be listed in the Orange Book?

Patents that have claims directed to the process or manufacture of the drug substance, to the packaging of the drug product, or to metabolites or intermediates of the drug substance are not

eligible to be listed in the Orange Book.

Why pursue patents that are Orange Book listable?

Competitors seeking to market a generic version of the drug must certify for each patent claiming the drug or the approved use of the drug that (i) such patent information has not been filed; (ii) the patent has expired; (iii) the date the patent will expire; or *(iv) the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.* Filing a paragraph IV certification can constitute an act of patent infringement and the generic company can be sued before even selling the generic version of the drug. If the branded company files the suit within 45 days of the notice of filing the certification, the FDA will postpone the generic drug approval for 30 months. During this 30 month period, the branded company and the generic competitor can litigate the patent dispute while the generic drug is barred from entering the market. If all patents are held invalid or not infringed, the FDA can proceed to approve the generic drug even if the 30 month period has not yet concluded.

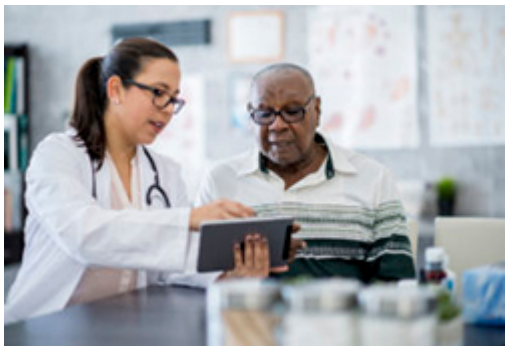
The Continuing Saga of Lab Developed Tests, Including for COVID-19 Testing

In August, the U.S. Department of Health & Human Services (HHS) **announced** that the FDA will not require premarket review of laboratory developed tests (LDTs), whether COVID-19 related or not, absent notice-and-comment rulemaking. Labs may voluntarily seek a premarket approval, 510(k) clearance, or an emergency use authorization (EUA) for their LDTs. Importantly, labs that do not obtain such FDA approval, clearance, or authorization would not be eligible for **PREP Act** coverage.

This announcement may have come as a surprise to FDA, which historically has asserted its medical device regulatory authority over LDTs while often subjecting them to enforcement discretion. Despite this HHS announcement, FDA's May 11, 2020 **Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency** remains in effect and has not been revised since the announcement. Importantly, this guidance offers two pathways for COVID-19 related LDTs – an EUA submission to FDA and the development of an LDT under the authorities of the State in which the laboratory resides, where the State takes responsibility for COVID-19 testing by labs in its State.

For FDA's latest statements on COVID-19 testing, see the **opinion piece** authored by CDRH Director Dr. Jeffrey Shuren and Dr. Timothy Stenzel, Director of the Office of Health Technology 7, In Vitro Diagnostics and Radiological Health, in the Hill.

What are Clinical Outcome Assessments (COAs) and Can They be Used to Support Approval and/or Labeling Claims?



The patient voice is recognized as one of the most critical sources of data in drug development, and patients play an increasingly important role in these efforts by teaching us about their experience with their condition and its impact. A common way sponsors can leverage the patient experience is by utilizing a clinical outcome assessment (COA). A COA is an assessment that describes or reflects how a patient feels, functions, or survives. Such an assessment can be a patient-reported outcome (PRO) measure, observer-reported outcome (ObsRO) measure, clinician-reported outcome (ClinRO) measure, or a performance outcome (PerfO) measure. **Alexander Varond** chaired a session on this topic in June 2020 at the Drug Information Association's Annual Meeting. Slides from his presentation can be found **here**.

FDA plans to issue a guidance that will provide patient-focused approaches and methods to consider in the selection and/or development of COAs. This future guidance, known as Patient-Focused Drug Development (PFDD) Guidance 3, is one piece of FDA's plan to develop a series of four PFDD-specific guidances for stakeholders on how to collect and utilize patient experience data in drug development. We initially discussed this plan and background on patient experience data **here**. In the meantime, FDA has described a "roadmap to COA selection/development for clinical trials" **here**. This roadmap sets forth how to obtain an understanding of the disease or condition, conceptualize clinical benefit (i.e., how a patient feels, functions and survives), and how to select, develop and modify a COA. In Guidance 4, FDA will discuss how to incorporate COAs into endpoints for regulatory decision-making. FDA issued a discussion document related to the forthcoming Guidance 4 **here**.

As background, a COA may support approval of a product if it is a "well-defined and reliable" assessment (21 CFR § 314.126). FDA interprets this to mean that the COA must have content validity, construct validity, reliability, and the ability to detect change. But COAs can do much more. For example, COAs can be included in labeling claims, as with CRYSVITA (burosumab-twza) for X-linked hypophosphatemia linked **here**, which incorporates both PRO and ClinRO measures. COAs can even lead to a regulatory change in thinking about a particular disease or condition. For example, just over two months after hearing directly from patients with epidermolysis bullosa (EB), a rare disorder that results in serious cutaneous manifestations, at an externally-led PFDD meeting, FDA published a draft guidance for sponsors developing therapies for EB that outlined specific examples of efficacy endpoints that would show the drug provides a clinically meaningful improvement. The finalized guidance can be found **here**.

If you are considering developing or utilizing in your clinical development program a COA, or if have questions about other PFDD initiatives such as PFDD meetings, we encourage you to contact your Goodwin life sciences lawyer for assistance on how to incorporate the patient voice–the real experts on their disease or condition—in drug development.

Q&A on FDA's Requirements Related to Financial Disclosure by Clinical Investigators

What financial arrangements between clinical trial sponsors and clinical investigators must be disclosed in a drug, biologic or device marketing application?

In a marketing application, FDA requires that four types of financial arrangements be disclosed: (1) any financial arrangement between the sponsor and the investigator whereby the value of the compensation to the investigator for conducting the study could be influenced by the outcome of the study; (2) any significant payments of other sorts from the sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, a retainer for ongoing consultation, or honoraria, which are greater than $25,000 in cumulative value and given to the investigator or the investigator's institution to support the investigator's activities, exclusive of the costs of conducting the study, for the duration of the study and for one year following the study's completion; (3) any proprietary interest in the tested product held by the investigator; and (4) any significant equity interest in the sponsor held by the investigator, which is any amount for a non-publicly traded company or an equity interest in a public company valued over $50,000 for the duration of the study and for one year following the study's completion.

How is a clinical investigator defined in the context of FDA financial disclosure regulations?

In FDA's financial disclosure regulations, the agency defines a clinical investigator as a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.

What does FDA look for with regard to financial interest?

FDA looks at several factors with regard to financial interest, including the size and nature of the disclosed financial interest, the steps taken to minimize the potential for bias, and the study design. For example, FDA will evaluate whether the study has been designed with multiple investigators (most without a disclosable interest), blinding, objective endpoints, or measurement of endpoints by someone other than the investigator. FDA may initiate audits of the data from the investigator at

issue, request that the applicant submit further analyses of the data or conduct additional independent studies to confirm the results. The agency could also refuse to treat the study as providing data that can be the basis for an agency action. We recommend you contact your Goodwin life sciences or FDA lawyer for further explanation of the agency’s financial disclosure regulations.