CenterWatch Weekly

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Califf Calls for Major Evidence Generation Revamp, Experts' Opinions Differ

By James Miessler

FDA Commissioner Robert Califf has called for major reform of the clinical research enterprise, particularly in how clinical evidence is gathered, to reduce health disparities between scientific advancement and actual U.S. life expectancy, a huge undertaking that some clinical trial experts question.

Writing in *Clinical Trials* this month, the agency chief and veteran clinical researcher urged an overhaul of the U.S. system for generating clinical evidence, proposing a deep overhaul of the postmarket setting, which he claimed is currently "disaggregated" and struggles to provide sufficient evidence critical to delivering optimal clinical care and treatments to American patients.

Califf's proposed overhaul lays out three priorities that he believes are critical to bring about significant change:

- Improving the integration of and access to high-quality data from traditional clinical trials, electronic health records, and personal devices and wearable sensors;
- Restructuring clinical research operations to support and incentivize the involvement of patients and frontline clinicians; and
- Enabling responsible data-sharing that will help make implementing changes easier.

In addition to these focal points, Califf writes that it's important to address "the

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Ask the Experts: Managing Investigational Products

The FDA's Office of Good Clinical Practice responds to inquiries on a variety of trial-related subjects, providing answers on the agency's official regulations as well as best practices. The following is a selection of questions and answers excerpted from the CenterWatch publication *GCP Questions, FDA Answers*.

Question: *If a patient withdraws consent in a clinical study, is the study coordinator/site allowed to contact the patient for return of the study drug to the site even if the participant has not responded to the site via phone calls and a registered letter?*

Answer: Every effort should be made to have the subject return the investigational product (IP). If the product is not returned, documentation of your efforts to have the IP returned is important. Sponsors and investigators should have internal standard operating procedures in place to address this issue. It is appropriate for the site/sponsor to contact the subject that has withdrawn from a study to obtain the unused IP.

Under FDA's regulations, both the sponsor and the investigator have responsibility for accounting for investigational drugs that are shipped for a clinical trial.

During an FDA bioresearch monitoring inspection, FDA investigators review records to determine compliance with FDA's regulations. This would include compliance with requirements for accounting for IP and compliance with the protocol/investigational plan.

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Upcoming Events

16 FEB — WEBINAR
Fundamentals of FDA Inspection Management: *Reduce Anxiety, Increase Inspection Success*

21 MAY — CONFERENCE
WCG MAGI Clinical Research Conference – 2023 East

[VIEW ALL EVENTS]

Industry Briefs

Dozens of Pediatric Trials Failed to Properly Report Results, Study Finds

Nearly four dozen pediatric clinical trials involving more than 3,600 children failed to publish their findings on ClinicalTrials.gov or in scientific literature, according to a new analysis by U.K.-based trial transparency advocacy group TranspariMED and other non-U.S. researchers.

The analysis, posted on the preprint publication *medRxiv*, began in September 2022 and looked at 81 trials that were in violation of FDA reporting requirements, having neglected to upload results to CT.gov within a year of completion.

The researchers concluded that 43 pediatric trials within that group (encompassing 3,627 children) were completely unreported as of December 2022, despite the continued push by the FDA and other regulators for greater reporting compliance and enforcement of requirements.

Once again, transparency watchdogs are calling for the agency to step up its game and hold sponsors truly accountable for failing to be compliant.

"Our findings highlight the urgent need for FDA and the NIH to systematically enforce reporting requirements in order to curb research waste, reduce publication bias, and accelerate medical progress," wrote Till Bruckner, founder of TranspariMED, and his coauthors.

The analysis was confined to trials exclusively involving patients who could be identified as U.S. children by registry data, meaning it left out trials lacking maximum participant age registry data and trials that aimed to enroll adults and children.

The FDA has been called out for failing to penalize noncompliant sponsors despite having this authority and to date has not issued a single fine. At the same time, it has received praise for its use of noncompliance letters, which have had success in pushing sponsors to share trial findings. It sent its first noncompliance letter in 2021 to Acceleron Pharma and has issued three more since then, according to the agency's website (*CenterWatch Weekly*, May 3, 2021).

Access the preprint publication here: https://bit.ly/3WDNuqb.

FDA Issues Final Guidance on Cannabis Clinical Research

The FDA has finalized guidance on trials of human drugs containing cannabis and cannabis-derived compounds, offering updated direction on federally authorized sources for cannabis and providing references to relevant quality considerations.

The National Institute on Drug Abuse's (NIDA) Drug Supply Program (DSP), which provides cannabis grown under contract by the University of Mississippi, was formerly the only domestic, federally legal source for cannabis containing more than 0.3 percent delta-9 THC for use in clinical research. But this has changed since the agency's 2020 draft guidance, and sponsors and investigators now have multiple sourcing options beyond the program.

According to the final guidance, researchers may now use non-NIDA DSP sources of cannabis that contain more than 0.3 percent delta-9 THC on a dry weight basis (a THC level that renders the cannabis a Schedule I controlled substance), as well as non-NIDA DSP sources for cannabis at or under the 0.3 percent threshold, so long as FDA deems the source(s) to be of adequate quality during its IND review. They may also still use the NIDA DSP for sourcing cannabis stronger than the 0.3 percent delta-9 THC threshold, the guidance says.

A list of Drug Enforcement Administration (DEA)-cleared growers of Schedule I cannabis is located online and can be accessed through the guidance. The FDA advises that sponsors and investigators with questions about cannabis production and sources for research direct their inquiries to the DEA.

The guidance also includes a section with resources for quality considerations that are especially relevant to trials of drugs containing cannabis and cannabis-derived compounds.

The third and final section, "considerations of control status under the Controlled Substances Act (CSA)," addresses loosened regulatory requirements for cannabis and cannabis-derived compounds following passage of the 2018 Farm Bill, which created the definition of "hemp," cannabis that does not exceed 0.3 percent delta-9 THC by dry weight.

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systemic tendency to optimize individual components of the clinical research enterprise" without thinking about the impact these changes will have on the healthcare system in its entirety.

The article also includes a table that lists the issues, needs and actions potentially facing stakeholders that operate within the clinical research sphere, including sites, sponsors, health systems/hospitals, regulators and clinicians, among others.

Califf claims that postmarket systems in their current state frequently fail to provide the data needed to confirm/refute accelerated approvals and understand the benefits and risks of therapies in the real world, their comparative benefits and risks, and the resources needed to estimate their value as therapies.

Conversely, the article characterizes premarket systems for generating and assessing evidence as working "reasonably well" — and it's this point that has drawn some commentary.

Mark Opler, chief research officer for WCG Clinical Endpoint Solutions, believes Califf's article is on target with its identification of flaws, risks and disparities in postmarketing systems. And while he agrees with Califf's description of the premarket setting to an extent, he believes this area is in dire need of sweeping change in many respects as well.

Opler cites the strikingly low success rates of most therapeutic development programs — which Califf acknowledges as well — but contends that their high rates of failure are not solely caused by limited technologies or limited biological understanding, but also by "systematic inefficiencies and misaligned incentives." This rings particularly true in the realm of neuroscience, which sees some of the lowest levels of success and transition between phases of any therapeutic area, he says.

"Though this can be attributed in part to the tremendous complexity of finding 'druggable targets' in the brain that work as expected, the unacceptably high rate of failure is also due to elevated placebo response, inaccurate outcome measures and an industrial ecology that continues to favor quantity over quality," Opler told *CenterWatch Weekly*.

He also recommends the FDA and other regulators focus more heavily on paving a responsible path forward for the use of novel assessment tools, such as remote automated tools for monitoring treatment efficacy, and a regulatory environment that allows for their safe, thoughtful use in both premarket and postmarket settings. Califf's calls for the use of decentralized trials (DCT) and technologies to reduce access disparities will be more likely to be successful if this is done, Opler believes.

Overall, he feels that there should be less commentary and more decisive action in bringing transformative change to evidence production. "Dr. Califf outlines a future many of us certainly would love to live in," he said. "What concrete steps can decisionmakers and stakeholders, from top to bottom in every level of organization, take to help get there? That's a conversation worth having next."

Nathaniel Katz, WCG Analgesic Solutions' chief science officer, believes Califf's paper represents leadership and an admirable attempt to drive change, but he agrees that its assertion that premarket systems function "reasonably well" is not an accurate characterization. Like Opler, he believes the premarket space needs significant attention for effective reformation of the clinical research enterprise to occur.

Katz calls Califf's recommendation to merge premarket evidence systems with postmarket systems with the aim of accruing higher quality, more informative data from real-world settings an "interesting and visionary concept." But, as Califf himself admits in the paper, this effort will require a great deal of collaboration among a diverse array of entities and, in Katz's opinion, collaboration isn't those entities' strong suit.

The FDA may be better off focusing elsewhere: addressing deficiencies in the premarket setting, where the agency has more power to drive change. "It would be more productive for him to acknowledge the ways in which the FDA-regulated premarket evidence generation system is broken and fix that," he says.

And overall, Katz says that the paper's overarching argument — that revamping evidence generation for the better will turn around the failing U.S. healthcare system — is incorrect.

"His overall thesis is that if only we had better evidence, we could have better and more equitable healthcare outcomes in our society, like those of other wealthy nations who are doing much better than us. It's immediately obvious that this thesis refutes itself: These other nations have exactly the

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same evidence we do and access to the same treatments yet have better health outcomes," Katz says. "It's due to a broken [U.S.] healthcare system, which remains broken due to perverse financial incentives that continue to dampen political will to create meaningful change. Evidence will not change that."

But Kevin Potgieter, Medable's vice president of regulatory affairs, believes that there are significant opportunities for the FDA to beef up its postmarket oversight and vigilance. As it stands now, the U.S.' postmarket system primarily involves a "passive approach" of waiting for adverse event reports and other safety signals to roll in, he says, though certain products will require confirmatory studies, such as those granted accelerated approval.

Other markets, such as the EU, for instance, have enacted stronger postmarket vigilance approaches, requiring routine postmarket clinical follow up activities of manufacturers, something the FDA could consider attempting to emulate.

To Mohammed Ali, Medable's chief domain expert, one of the most pressing demands in healthcare overall is the need for a harmonized way to identify the data most relevant for care, treatment and prevention as it pertains to patients, providers and health networks. Achieving this will come down to making data interoperable and interconnected across the healthcare system's array of stakeholders, he says.

"Healthcare is a team sport. Understanding and managing disease and its impact on patients is a combined effort from multiple stakeholders across the patient ecosystem and care circle," Ali said. "Within this ecosystem, information is not often connected and can reside in disparate locations, so the ability to connect the dots between lab data, healthcare system data, wearable data, payor data and even clinical trial data is critical to ensure the best and most practical solutions possible."

Read Califf's article here: https://bit.ly/40hdzi2.

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"If the cannabis does not meet the definition of hemp … activities related to growing and manufacturing cannabis for use as an investigational drug for research must still comply with applicable CSA and DEA requirements," the guidance notes. "Sponsors and investigators proposing drug development activities involving controlled substances should consult DEA about the applicable requirements."

This section contains information on how to calculate delta-9 THC content early on in the development process "to gain insight into … potential abuse liability and control status" and how this information should be included in an IND.

Access the final guidance here: https://bit.ly/3iUlvns.

WCG MAGI Calls for Second Innovation Challenge Submissions

With this year's WCG MAGI East conference in Philadelphia just a few months away, WCG is now calling for site, sponsor and CRO representatives to submit innovative approaches from their organizations for its Innovation Challenge competition.

Those with interesting, innovative ideas or strategies aimed at increased performance, quality improvement or site efficiency are urged to submit them for consideration, whether they're novel ideas or the fruit of finished projects.

Finalists will be chosen by a review panel — the MAGI Steering Committee and Jill Johnston, Innovation Challenge moderator and WCG's chief innovation officer — to present their innovations to the conference audience in a special session, with a winner being selected by the crowd through in-person voting.

Finalists will have five minutes each to present their innovations, followed by a five-minute Q&A session led by the steering committee. Innovations will be assessed based on their novelty, resource requirements, ability to move from conception to production, and overall impact on an efficiency, performance or quality outcome, not their complexity.

Bayer and its Kits4Life trial supply donation program was crowned the winner of last year's MAGI West conference in Las Vegas (*CenterWatch Weekly*, Oct. 24, 2022).

Submit your idea(s) here: https://bit.ly/407s0ox.

Ask the Experts

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Additionally, FDA regulations require that a sponsor ensure that unused drugs are returned or otherwise disposed of in a way that does not expose humans to risk and that records be maintained as to disposition of all such drugs (21 CFR 312.59). Allowing individual study sites to dispose of unused investigational drugs would not be inappropriate. You as the core pharmacy/sponsor can specify the conditions for such drug disposal or allow the site(s) to follow their own disposal policy if it is acceptable to you.

The individual sites would need to maintain proper documentation regarding the amounts of drug, identifying codes, date of disposal and actual method of disposal and a copy of such documentation would need to be sent to you for your records. While you might not have the resources to monitor actual drug disposal at each study site, review of drug accountability records, which would include such disposal documentation, is usually part of the final study monitoring or closeout visit for each site.

Question: *In situations where notification is sent to the IRB before emergency administration of the IP (as the manufacturer requires the notification up front to ship the article), do IRBs also need to obtain documentation within five days after the drug is administered or is the one notification prior to administration sufficient?*

Answer: 21 CFR 50.23(a)(3) requires that the documentation be submitted to the IRB within five working days after the use of the IP. However, if there is time for this information to be provided to the IRB before the administration of the IP and the information was sufficient for the IRB's needs, then there would be no expectation that the information would need to be subsequently submitted to the IRB again.

The exception from informed consent described at 21 CFR 50.23(a) is intended for the situation in which a participant with a life-threatening situation is unexpectedly identified and it is thought they might benefit from the IP but consent cannot be obtained in a timely manner because of the clinical need to use the IP quickly, that is, within the therapeutic window. It is not meant to be a prospectively planned method in which to enroll subjects into a clinical trial and should be used judicially.

Question: *ICH E6(R2) section 5.14.5 states that you must maintain sufficient quantities of the IP(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. Additionally, it states that, to the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.*

Does this mean we need to maintain records or need to maintain IP samples?

Answer: Under FDA's regulations, both the sponsor and the investigator have responsibility for accounting for investigational drugs that are shipped for a clinical trial.

Required accountability for a drug used in a clinical trial is the same whether or not the drug is already commercially available. The drug supplied by the sponsor for use in the clinical trial needs to be maintained separately from any purchased for general use at the site. Manufacturers usually allocate a specific lot of the drug for the study so any problems/adverse effects that could possibly be associated with a manufacturing problem can more easily be identified. As far as disposition of the drug, you need to follow the directives in that regard in the study protocol. If no instructions are in the protocol or other documents that are part of the investigational plan, you should ask the sponsor what they want you to do with any drug remaining at the end of the study. Both the sponsor and each clinical trial site is responsible for maintaining detailed accountability for drugs used in a clinical trial.

Please consult your sponsor for specifics on how drug accountability can be maintained at your site. Please remember any study-related documents given to study subjects should be approved by your reviewing IRB. Also, please remember, if you are performing additional procedures for drug accountability, it is best to develop standard operating procedures so that there is consistency among study staff.

For more information on the CenterWatch publication *GCP Questions, FDA Answers*, click here: https://bit.ly/3ylWOpj.

Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status
Trials Authorized			
TScan Therapeutics	T-Plex	Solid tumors	IND for a phase 1 trial approved by the FDA
TScan Therapeutics	TSC-204-A0201	Solid tumors	IND for a phase 1 trial approved by the FDA
TScan Therapeutics	TSC-204-C0702	Solid tumors	IND for a phase 1 trial approved by the FDA
ImmPACT Bio	IMPT-314	Aggressive B-cell lymphoma, including diffuse large B-cell lymphoma	IND for a phase 1/2 trial approved by the FDA
Mirati Therapeutics	MRTX1133	Solid tumors with KRASG12D mutations	IND for a phase 1/2 trial approved by the FDA
Carina Biotech	CNA3103	Advanced colorectal cancer	IND for a phase 1/2a trial approved by the FDA
Decibel Therapeutics	DB-OTO	Congenital hearing loss caused by mutations of the otoferlin gene	Phase 1/2 trial authorized by the UK's regulatory authority
Diamond Therapeutics	Low-dose psilocybin	Generalized anxiety disorder	Phase 2 trial authorized by Canada's regulatory authority
Varian	Cardiac radioablation	High-risk refractory ventricular tachycardia	IDE approved by the FDA
Trials Initiated			
ADARx Pharmaceuticals	ADX-324	Hereditary angioedema	Initiation of a phase 1 trial

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Drug & Device Pipeline News

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Company	Drug/Device	Medical Condition	Status
AltruBio	ALTB-268	Ulcerative colitis	Initiation of a phase 1 trial
Awakn Life Sciences	(S)-ketamine	Alcohol use disorder	Initiation of a phase 1 trial
Dyadic International	DYAI-100, COVID-19 recombinant protein receptor binding domain booster vaccine	COVID-19	Initiation of a phase 1 trial
Illuminare Biotechnologies	Illuminare-1	Fluorescent agent to provide real time visualization and delineation of nerves during surgery	Initiation of a phase 1 trial
Mersana Therapeutics	XMT-2056	Previously treated HER2+ advanced/ recurrent solid tumors	Initiation of a phase 1 trial
Vistagen Therapeutics	PH10 pherine nasal spray	Major depressive disorder	Initiation of a phase 1 trial
VITRAC Therapeutics	VIC-1911 and VIC-1911 plus sotorasib	KRAS G12C-mutant non-small cell lung cancer	Initiation of a phase 1 trial
Immunis	IMM01-STEM	Muscle atrophy associated with knee osteoarthritis	Initiation of a phase 1/2a trial
REGENXBIO	RGX-202	Duchenne muscular dystrophy	Initiation of a phase 1/2 trial
Eloxx Pharmaceuticals	ELX-02	Alport syndrome with nonsense mutations in the COL4 gene	Initiation of a phase 2 trial
Highlightll Pharmaceutical	TLL-018	Moderate-to-severe plaque psoriasis	Initiation of a phase 2 trial
SOTIO Biotech	Nanrilkefusp alfa	Colorectal cancer	Initiation of a phase 2 trial
Teva Pharmaceuticals	TEV-44749 (subcutaneous long-acting injectable formulation of olanzapine)	Schizophrenia	Initiation of a phase 3 trial
Aculys	Pitolisant	Excessive daytime sleepiness associated with obstructive sleep apnea	Initiation of a phase 3 trial in Japan
Approvals			
ALK	Odactra (house dust mite allergen extract) tablet for sublingual use	House dust mite-induced allergic rhinitis in patients age 12 through 17	Approved by the FDA for expanded age indication
BeiGene	Brukinsa (zanubrutinib)	Chronic lymphocytic leukemia or small lymphocytic lymphoma	Approved by the FDA for new indication
Seagen	Tukysa (tucatinib) plus trastuzumab	Previously treated RAS wild-type, HER2-positive unresectable or metastatic colorectal cancer	Accelerated approval granted by the FDA
TheracosBio	Brenzavvy (bexagliflozin)	Type 2 diabetes	Approved by the FDA

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