



February 21, 2024

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RE: Docket No. [FDA-2023-P-0660](#)

Dear Mr. Mendoza and Dr. Morten:

This responds to the Citizen Petition (FDA-2023-P-0660) (“Petition”) you submitted on behalf of the Universities Allied for Essential Medicines (UAEM), to the Food and Drug Administration (FDA or Agency) on February 27, 2023. FDA sent an interim response on August 23, 2023. The Petition requests that FDA take the following actions:

1. “Order and organize offices to increase enforcement of 42 U.S.C. § 282(j), issuing more Pre-Notices and Notices of Noncompliance and imposing civil money penalties when appropriate”;
2. “Order the drafting and issuance of a new guidance document which explains how FDA will focus its enforcement efforts. This guidance should clearly outline a prioritization framework for the enforcement of 42 U.S.C. § 282(j)”;
3. “Create a public dashboard of Pre-Notices sent by FDA.”¹

We have carefully considered the issues raised in your Petition. We have also reviewed the comments in the public docket for this Petition. For the reasons stated herein, your Petition is granted in part and denied in part.

I. Regulatory Background on ClinicalTrials.gov

Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires that responsible parties must register and submit summary results information for certain clinical trials to the

¹ Petition at 4.



ClinicalTrials.gov data bank.² The National Institutes of Health (NIH) and the Department of Health and Human Services (HHS) published a final rule,³ codified at 42 CFR part 11, which became effective on January 18, 2017, to implement FDAAA’s provisions. This final rule clarified and expanded the clinical trial registration and results information submission requirements.

FDAAA added section 301(jj)⁴ of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which includes the following prohibited acts:

- Failing to submit the certification required under section 402(j)(5)(B) of the Public Health Service Act or knowingly submitting a false certification to FDA;
- Failing to submit required clinical trial information to the ClinicalTrials.gov data bank; and
- Submitting false or misleading clinical trial information to the data bank.

FDAAA also amended section 303(f) of the FD&C Act by adding a new subparagraph, which authorizes FDA to assess civil money penalties against person(s) committing these prohibited acts.⁵

II. Summary of the Petition

Arguments and relief requested in the Petition include the following:

1. *FDA should improve its efforts to enforce Section 801 of FDAAA*

UAEM asserts that FDA is not upholding its responsibility to enforce FDAAA’s requirements for ClinicalTrials.gov registration and results information submission. UAEM requests that FDA increase its enforcement of responsible parties’ reporting duties, specifically requesting that FDA undertake three steps to increase enforcement, including:

- a. “Increase the number of Pre-Notices it issues, sending out a minimum of 250 such Pre-Notices annually, at least until compliance materially improves”;
- b. “Be more stringent about issuing Notices of Noncompliance to trials sponsors who fail to react to their Pre-Notices”; and
- c. Impose civil money penalties on those trial sponsors that refuse to comply even after receiving a Notice of Noncompliance”.⁶

² Section 801 of the Food and Drug Administration Amendments Act (FDAAA) (Pub. L. 110-85), amending section 402(j) of the Public Health Service Act (Pub. L. 78-410).

³ 81 Fed. Reg. 64,982 (Sept. 21, 2016).

⁴ 21 U.S.C. 331(jj).

⁵ 21 U.S.C. 333(f)(3).

⁶ Petition at 21.



2. FDA should issue new guidance with a new “enforcement prioritization framework”⁷

UAEM requests that FDA rescind its guidance on *Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank* (August 2020)⁸ (hereinafter the CMP Guidance) and issue new guidance that “commit(s) FDA to more vigorous enforcement” and articulates a new “enforcement prioritization framework.”⁹

UAEM proposes a different framework than articulated in FDA’s CMP Guidance, focusing first on NIH-funded trials of FDA-approved products as its highest enforcement priority due to the large number of trials funded by NIH. UAEM also urges FDA to prioritize, among other trials, those upon which FDA relies for product approval decisions, NIH-funded trials of unapproved products, Phase IV trials of FDA-approved products subject to postmarketing commitments and requirements, other trials of FDA-approved products, and trials for unapproved products of “high importance.”¹⁰ Finally, UAEM encourages FDA to address as its highest priority the trials of FDA-approved products that are already being widely used by patients and prescribers.

3. FDA should make Pre-Notice of Noncompliance Letters public via a public dashboard

UAEM asks FDA to publish information about Pre-Notice of Noncompliance Letters (hereafter, “Pre-Notice letters”) on its website, on the page where FDA already provides information about Notices of Noncompliance and civil money penalties. UAEM states that making Pre-Notice letters publicly available will also serve to bring public attention to responsible parties of noncompliant trials and “may also help FDA’s enforcement actions be more effective.”¹¹

III. Discussion

FDA takes seriously its role in enforcing the ClinicalTrials.gov registration and results information submission requirements for the subset of interventional clinical trials that study FDA-regulated drug products, biological products, or device products and that meet the statutory definition of “applicable clinical trials”¹² set forth in section 801 of FDAAA, including its implementing regulations at 42 CFR part 11. The requirements for submission of clinical trial information to ClinicalTrials.gov are important to our mission of protecting and promoting the public health. Providing transparency in the clinical trial process may benefit patients looking for trials in which to participate, and it may benefit clinicians, academic researchers, and the public by identifying what clinical research has been done, potentially avoiding duplication of effort and supporting prioritization of research funding.

The transparency afforded by the ClinicalTrials.gov data bank is important for FDA and interested parties, although FDA notes that the summary results information available on the ClinicalTrials.gov data bank is

⁷ Petition at 22.

⁸ The CMP Guidance, Docket No. [FDA-2018-D-0787](https://www.fda.gov/media/113361/download), is available at <https://www.fda.gov/media/113361/download>.

⁹ Petition at 22.

¹⁰ Petition at 24.

¹¹ Petition at 28.

¹² The term “applicable clinical trial” means an applicable device clinical trial or an applicable drug clinical trial as defined in 42 CFR 11.10(a).



only a portion of the extensive and comprehensive safety and efficacy data that may be submitted to and reviewed by FDA with a marketing application. It is generally not possible to draw conclusions about the safety or efficacy of FDA-regulated medical products based solely on the limited amount of public information on ClinicalTrials.gov for any specific trial, nor is this the intent of the data bank.

Finally, a large majority of clinical studies registered on ClinicalTrials.gov appear not to be applicable clinical trials subject to the ClinicalTrials.gov results information submission requirements.¹³ The data bank includes a substantial number of non-applicable clinical trials, such as observational studies, behavioral intervention studies, phase 1 drug trials, and feasibility studies of medical devices. Although parties conducting clinical research should have an ethical imperative to share research results publicly, parties conducting clinical trials that do not meet the legal definition of “applicable clinical trial” are not required under FDAAA, including its implementing regulations in 42 CFR part 11, to submit summary results information to the ClinicalTrials.gov data bank.¹⁴

We address your specific requests herein.

1. Petition request #1: FDA’s Enforcement Efforts to Address Section 801 of FDAAA

FDA’s compliance and enforcement activities relating to the ClinicalTrials.gov registration and summary results submission requirements are incorporated into FDA’s Bioresearch Monitoring (BIMO) programs in each medical product center, as a component of the BIMO program’s existing compliance portfolio related to FDA-regulated trials.¹⁵ At present, FDA identifies potential noncompliance with the ClinicalTrials.gov registration and results information submission requirements for applicable clinical trials primarily through risk-based surveillance strategies that use an internal analytics platform with data from ClinicalTrials.gov and from FDA systems. In addition, FDA assesses compliance with the ClinicalTrials.gov registration and results information submission requirements during sponsor and sponsor-investigator inspections;¹⁶ these inspections have found a high degree of compliance with the legal requirements.¹⁷ FDA also follows up on

¹³ Califf RM, The importance of clinical trial transparency and FDA oversight. Dec. 4, 2023. <https://www.fda.gov/news-events/fda-voices/importance-clinical-trial-transparency-and-fda-oversight>. (Last visited Dec. 4, 2023). Further, results information is not required to be submitted where the applicable clinical trial concluded prior to January 18, 2017, and the studied product has not been approved, cleared, or licensed by FDA.

¹⁴ FDA’s authority under section 303(f)(3) (21 U.S.C. 333(f)(3)) of the Act extends to the submission of clinical trial information required under section 402(j) of the PHS Act, including its implementing regulations. Therefore, if a trial is not an applicable clinical trial, or the submission of clinical trial information is not required under section 402(j) of the PHS Act, including its implementing regulations (e.g., if the submission is solely due to a term and condition of a grant award), the submission of information to ClinicalTrials.gov, or any alleged failure to so submit, is not subject to FDA enforcement under either the FD&C Act or section 402(j) of the PHS Act.

¹⁵ See FDA Compliance Program [7348.811](#), Clinical Investigators and Sponsor-Investigators and FDA Compliance Program [7348.810](#), Sponsors, Contract Research Organizations and Monitors.

¹⁶ *Id.*

¹⁷ As of October 30, 2023, FDA has conducted more than 430 inspections of sponsors and sponsor-investigators for the medical product centers since the ClinicalTrials.gov regulations (42 CFR part 11) became effective in 2017. These inspections found few instances of noncompliance with the ClinicalTrials.gov requirements. In general, as evidenced by the relatively small number of Pre-Notice letters that result from inspections, most potential violations are quickly addressed by responsible parties without need for further follow-up.



complaints it receives alleging potential noncompliance with the ClinicalTrials.gov registration and results information submission requirements. To date, fewer than five percent of the Preliminary Notices of Noncompliance (Pre-Notice letters) that the Agency has issued have resulted from inspections and complaints.

FDA uses a risk-based approach to evaluate potential noncompliance and, when necessary, the Agency issues Pre-Notice letters and Notices of Noncompliance and will take any other regulatory or enforcement action available under section 402(j) of the PHS Act, including its implementing regulations, and the FD&C Act. When examining cases of potential noncompliance, FDA staff evaluate whether a specific trial appears to meet the definition of an applicable clinical trial¹⁸ and, if so, whether the required registration or results information submission for the trial may be overdue.¹⁹ As part of this assessment, staff may access non-public information submitted to FDA for review as part of an investigational or marketing application, as well as review public information such as journal publications with trial results and public statements about a trial on the responsible party's website or in the trade press. Additionally, staff assess whether the same responsible party may have other applicable clinical trials that are potentially noncompliant with the ClinicalTrials.gov requirements.

If a responsible party appears to be noncompliant with ClinicalTrials.gov registration and results information submission requirements, FDA will generally send a responsible party a Pre-Notice letter to encourage voluntary compliance.

The law requires FDA to issue a Notice of Noncompliance if it determines that a responsible party has failed to comply with the ClinicalTrials.gov registration or results information submission requirements. FDA also has the authority to pursue enforcement action—such as filing an administrative complaint seeking civil money penalties or seeking a judicial injunction and/or criminal prosecution—against a responsible party for its failure to comply with the ClinicalTrials.gov registration and results information submission requirements.

a. Increasing the Number of Pre-Notice Letters

While FDA agrees that Pre-Notice letters are very effective in providing responsible parties with opportunities to address potential noncompliance, FDA denies the Petitioners' specific request to commit to "sending out a minimum of 250 such Pre-Notices annually, at least until compliance materially improves,"²⁰ for the reasons stated below.

FDA's approach to compliance and enforcement of the ClinicalTrials.gov requirements is consistent with other FDA compliance programs, which generally prioritize activities following a risk-based approach.

¹⁸ We note that NIH has developed a checklist that can help responsible parties determine whether a particular trial meets the definition of an applicable clinical trial. The checklist is available at https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf.

¹⁹ Registration information must be submitted within 21 days of the first subject's enrollment. 42 CFR 11.24. Also, summary results information generally must be submitted within one year of the trial's primary completion date, but may be delayed in certain circumstances (e.g., with an extension for good cause). See 42 CFR 11.44.

²⁰ Petition at 21.



When deciding where to focus limited compliance resources, FDA considers which activities are likely to have the greatest and most direct public health impact and balances resource allocation to ClinicalTrials.gov with resource needs for other compliance programs, such as evaluating inspection reports of sponsors, clinical investigators, and other establishments to determine whether there have been violations of the law. Second, although FDA’s internal analytics platform has made it easier to identify potential noncompliance, there is no software algorithm to evaluate the complexities and reliably identify applicable clinical trials, and therefore, staff must still manually review non-public documents to verify whether the ClinicalTrials.gov requirements appear to apply to a specific trial.

Although we decline to commit to issuing a specific number of Pre-Notice letters annually, FDA encourages voluntary compliance with the ClinicalTrials.gov registration and results information submission requirements in a number of ways. For example, FDA has presented on how it undertakes compliance and enforcement for ClinicalTrials.gov registration and results information submission requirements at conferences and meetings, including the Clinical Trials Registration and Results Reporting Taskforce (a national consortium of members from academic medical centers, universities, hospitals, and non-profit organizations), provided information on FDA’s compliance role to federal agencies, regularly responded to public and media inquiries, and posted compliance and enforcement training videos on its website.²¹ FDA also is taking steps to enhance its internal analytics platform in order to support FDA’s surveillance activities related to ClinicalTrials.gov. FDA’s platform relies in part on review of non-public information that has been submitted to FDA in investigational and marketing applications. Further, FDA is assessing ways to increase awareness of a responsible party’s institution, where feasible, by alerting organizational leadership of a Pre-Notice letter in order to correct deficient processes when multiple trials are potentially noncompliant, among other possible improvements.

b. Issuing Notices of Noncompliance

FDA denies the Petitioners’ request that we “be more stringent about issuing Notices of Noncompliance”²² to those responsible parties who fail to take action in response to Pre-Notice letters. FDA believes that our current approach following issuance of a Pre-Notice letter is appropriate. After a responsible party receives a Pre-Notice letter, FDA must further review and assess the clinical trial record as well as other relevant information (including, for example, results information that may have been submitted to the ClinicalTrials.gov data bank but has not yet been posted in accordance with the regulations) to determine whether the responsible party has failed to submit required clinical trial information to the ClinicalTrials.gov data bank.²³ In evaluating a responsible party’s actions in response to a Pre-Notice letter, FDA considers whether the responsible party is promptly and diligently taking action to address any potential noncompliance; if the responsible party is doing so, we believe it is appropriate to allow sufficient time for them to complete this work. Thus, in many instances there is likely to be a delay between issuance

²¹ ClinicalTrials.gov – A Three Part Series, Aug. 9, 2023, <https://www.fda.gov/drugs/news-events-human-drugs/clinicaltrialsgov-three-part-series> (last accessed Dec. 3, 2023).

²² Petition at 21.

²³ Pre-Notice letters generally indicate that FDA intends to further review and assess the relevant clinical trial beginning 30 calendar days after the responsible party receives the letter.



of a Pre-Notice letter and issuance of any subsequent Notice of Noncompliance. When FDA makes a final determination that a responsible party is in fact noncompliant with the information submission requirements for applicable clinical trials, FDA will issue a Notice of Noncompliance.

c. Imposing Civil Money Penalties

The Petitioners request that FDA impose civil money penalties on responsible parties who fail to comply with the ClinicalTrials.gov registration and/or results information submission requirements after receiving a Notice of Noncompliance. Civil money penalties are a civil enforcement tool available to FDA for, among other things, certain violations relating to ClinicalTrials.gov.²⁴ To the extent your Petition requests that FDA take enforcement action, FDA denies such request, because the decision whether to pursue an enforcement action is “generally committed to an agency’s absolute discretion.” *Heckler v. Chaney*, 470 U.S. 821, 821 (1985).²⁵

As in all areas that FDA regulates, the Agency’s goal is to achieve timely voluntary compliance with the law without having to resort to legal action, which can be resource intensive and time-consuming. In any civil enforcement action, FDA bears the burden of proving by a preponderance of the evidence the violations alleged, specifically here, the responsible party’s noncompliance with the registration and/or results information submission requirements. Building an enforcement case requires identifying all of the evidence and determining which witnesses will testify regarding the noncompliance before FDA can file an administrative civil money penalty action under section 303(f)(3) of the FD&C Act.²⁶ Civil money penalty proceedings are governed by FDA regulations in 21 CFR part 17, which provide for limited discovery and the right to a hearing before an administrative law judge before a civil money penalty is assessed. These initial proceedings can be lengthy, and the regulations provide for either party to appeal an administrative law judge’s initial decision to HHS’s Departmental Appeals Board (Board). If a responsible party is displeased with the Board’s decision, the statute provides that they may appeal to the federal Court of Appeals.

As of December 4, 2023, FDA has issued five Notices of Noncompliance to responsible parties for failure to respond or adequately respond to a Pre-Notice letter, all of which have been resolved, and FDA has not yet pursued civil money penalties against any responsible party.²⁷

2. Petition Request #2: Revise Guidance and Enforcement Approach

FDA denies the Petitioners’ request to rescind the guidance *Civil Money Penalties Relating to the*

²⁴ See 21 CFR 17.1(c).

²⁵ FDA’s regulations make clear that requests to take judicial enforcement action are not properly the subject of a citizen petition under 21 CFR 10.30. See 21 CFR 10.30(k) (the citizen petition regulations do not apply “to the referral of a manner to a United States attorney for the initiation of court enforcement action”).

²⁶ 21 U.S.C. 333(f)(3).

²⁷ See ClinicalTrials.gov – Notices of Noncompliance and Civil Money Penalty Actions. <https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions> (last accessed Dec. 4, 2023).



ClinicalTrials.gov Data Bank (August 2020).²⁸ We believe that, as explained above, the agency's current enforcement policy as articulated in the CMP Guidance has been effective. However, FDA grants the Petitioners' request to consider Petitioners' proposed enforcement framework to the extent FDA decides in the future to revise the CMP Guidance.

FDA notes that the current enforcement approach already considers many of the factors identified in UAEM's proposed enforcement framework. For example, FDA focuses on applicable clinical trials of unapproved products in which the product is intended to address a significant public health need (e.g., COVID-19 and pivotal trials for recently FDA-approved products) and trials that include vulnerable populations (e.g., pediatrics, cognitively impaired participants).

FDA prioritizes enforcement of the ClinicalTrials.gov requirements for applicable clinical trials of unapproved, unlicensed, or uncleared products, in part because information about the safety and effectiveness of FDA-regulated medical products that are approved, licensed, or cleared is available in product labeling and in FDA reviews that are posted on the agency's website. Product labeling is developed based on FDA's review of a sponsor's application or submission, which is more comprehensive than the summary results information required to be submitted to ClinicalTrials.gov. The summary results information that is available on ClinicalTrials.gov, while valuable to patients and providers, does not reflect the fulsome evaluation of safety and effectiveness that occurs as part of the review process.

Similarly, FDA prioritizes potential noncompliance in applicable clinical trials conducted by responsible parties that have frequent noncompliance, whether with the ClinicalTrials.gov registration and/or results information submission requirements or with other FDA statutes and regulations related to clinical trial conduct and reporting.

Also, FDA coordinates with NIH to address applicable clinical trials conducted with NIH grants that are potentially noncompliant with the ClinicalTrials.gov registration and results submission requirements, and the agencies continue to explore ways to increase alignment and improve NIH-funded applicable clinical trial compliance.

3. Petition Request #3: Publicly Available Pre-Notice Letters

FDA grants the Petitioners' request that FDA create a public dashboard of the Pre-Notice letters sent by FDA. On December 4, 2023, FDA posted all previously issued Pre-Notice letters²⁹ regarding potential noncompliance with the registration and results information submission requirements for ClinicalTrials.gov to its website,³⁰ and FDA intends to add newly issued Pre-Notice letters on a quarterly basis. We believe that public availability of Pre-Notice letters will provide greater transparency and awareness of FDA's

²⁸ See footnote 8.

²⁹ Please note that FDA was unable to resolve potential noncompliance issues with certain responsible parties or their successors (e.g., if the responsible party was a defunct company). Such cases have been closed administratively without submission of registration and/or summary results information or further action taken by FDA.

³⁰ Pre-Notices for Potential Noncompliance, <https://www.fda.gov/science-research/fdas-role-clinicaltrials.gov-information/pre-notices-potential-noncompliance> (last accessed Dec. 4, 2023).



compliance actions and may further increase voluntary compliance by responsible parties.

4. Additional Activities

FDA is exploring other ways to identify and address challenges to voluntary compliance with the ClinicalTrials.gov registration and summary results submission requirements, including working with the Clinical Trials Transformation Initiative (CTTI) to identify practices that could help responsible parties improve registration and summary results information submission.³¹ We will work with CTTI to identify potential next steps for suggested actions by responsible parties.

IV. Conclusion

In conclusion, we grant in part and deny in part this Petition, as stated herein.

Sincerely,

Lauren K. Roth
Associate Commissioner for Policy

cc:

The Honorable Xavier Becerra, Secretary
U.S. Department of Health and Human Services

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³¹ See 2024 CTTI report, “Improving Timely, Accurate, and Complete Registration and Reporting of Summary Results Information on ClinicalTrials.gov” https://ctti-clinicaltrials.org/wp-content/uploads/2024/01/CTTI_SuggestedPractices_ClinicalTrials-gov_FINAL.pdf (last accessed Jan. 19, 2024).



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