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Federal District Court Holds Clinical Trial Sponsors Must Submit More Data to ClinicalTrials.Gov

A recent federal court ruling may require clinical trial sponsors to report a decade's worth of previously exempted data to the National Institutes of Health ("NIH") for publication on ClinicalTrials.gov. In *Seife v. Department of Health and Human Services*, the U.S. District Court for the Southern District of New York invalidated NIH regulations that exempted certain clinical trials conducted between 2007 and 2017 from results reporting requirements mandated by the Food and Drug Administration Amendments Act ("FDAAA").

If the government allows the ruling to take effect without appealing, or if it is upheld on appeal, this decision could prove onerous for study sponsors who have relied on this exemption in the NIH regulations. There is now a substantial amount of data—nearly ten years' worth of clinical trial results for products that had not received marketing authorization at the time of trial completion—that may ultimately need to be submitted to ClinicalTrials.gov. In this Alert, we provide an overview of relevant clinical trial results disclosure requirements, describe the court's rationale for invalidating the government's interpretation of FDAAA provisions, and discuss implications for industry, academic institutions, and other parties responsible for complying with FDAAA requirements.

Background

In 2007, Congress enacted certain provisions of FDAAA to make clinical trial information more accessible to patients, health care providers, researchers, and the general public. To this end, FDAAA requires sponsors of certain clinical trials to register trials and to report two classes of results—"Basic Results" and "Expanded Results"—to ClinicalTrials.gov, a public database administered by the NIH.

FDAAA requires "Responsible Parties"—sponsors or sponsor-designated principal investigators—to submit to NIH certain information about clinical trial results (referred to in the statute as "Basic Results"[1]) for "each applicable clinical trials [or "ACT"] for a drug that *is approved* under [21 U.S.C. § 355] or licensed under [42 U.S.C. § 262] or a device that is cleared under [21 U.S.C. § 360(k)] or approved under [21 U.S.C. § 360e or § 360j(m)]."[2] The statutory text did not specify the date on which a product's marketing status should be assessed for purposes of triggering the Basic Results reporting requirements. With respect to Expanded Results, FDAAA's reporting requirements are similarly indefinite, though for a different reason: the statute gives HHS discretion to determine when Expanded Results must be reported for products that have not received marketing authorization.[3]

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[1] Responsible Parties submit both "Basic Results" and "Expanded Results." Basic Results include demographic characteristics of the ACT's patient sample, primary and secondary outcomes, a point of contact for information regarding the ACT, and agreements that may limit what a principal investigator may say about an ACT after its completion. Expanded Results include both technical and nontechnical summaries of the ACT and a full protocol. The HHS interpretation discussed in this alert pertains only to the submission of Basic Results.

[2] An "applicable clinical trial" or ACT is defined to include both an applicable device clinical trial and an applicable drug clinical trial. *See* 42 U.S.C. § 282(j)(1)(a)(i). An "applicable device clinical trial" is further defined as "(I) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 360(k), 360e, or 360j(m) of title 21 against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and (II) a pediatric postmarket surveillance as required under section 360l of title 21." 42 U.S.C. § 282(j)(1)(a)(ii). An "applicable drug clinical trial" is defined as "a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to" the new drug approval provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. 42 U.S.C. § 282(j)(1)(a)(iii)(I).

[3] 42 U.S.C. § 282(j)(3)(D)(ii)(II).

In a 2016 rule ("Final Rule") issued under FDAAA, the Department of Health and Human Services ("HHS") took the position that "Basic Results" reporting would not be required for a trial completed after FDAAA's effective date (September 27, 2007) and before the Final Rule's effective date (January 18, 2017), if the product evaluated in the trial was not approved or cleared by FDA at the time of the trial's completion. The Final Rule states that a Responsible Party must submit the Basic Results of pre-Rule ACTs "for which the studied product is approved, licensed or cleared by the FDA," unless a waiver provision applies. In language very similar to that of the statute, the Final Rule defines "approved drug" as "a drug product that is approved for any use under [21 U.S.C. § 355] or a biological product licensed for any use under [42 U.S.C. § 262]," and it defines "approved or cleared device" as "a device that is cleared for any use under [21 U.S.C. § 360(k)] or approved for any use under [21 U.S.C. §§ 360e or 360j(m)]." However, in the *Federal Register* preamble—but not in the regulatory text—NIH provided its interpretation that "the marketing status of a product will be determined based on its marketing status on the primary completion date [of the ACT]." As a result of that interpretation, Responsible Parties have not been required to report Basic Results for any pre-Rule ACT that concluded prior to its studied product's FDA approval or clearance. Because products are typically studied before they receive marketing authorization, NIH's interpretation created a significant exemption from the reporting requirements.

Seife v. HHS arose from concern that this interpretation impermissibly narrowed the scope of studies for which Basic Results must be reported and was contrary to the intent of FDAAA. In December 2018, the plaintiffs—investigative journalist Charles Seife and physician Dr. Peter Lurie (also the President of the Center for Science and the Public Interest and a former FDA Associate Commissioner)—sued HHS under the Administrative Procedure Act, seeking to invalidate the exemption from Basic Results data reporting requirements for pre-Rule ACTs. Plaintiffs argued that HHS's interpretation of the FDAAA reporting requirements deprived them "as well as other researchers and advocates, of the data necessary to ensure transparency in research, promote better decision-making by clinicians and policymakers, eliminate bias in the medical literature, and to make patients, clinicians, and regulators aware of medical product safety and effectiveness."[4] Plaintiffs also sought to force HHS to start taking enforcement action against any Responsible Parties not in compliance with their reporting obligations.

HHS Interpretation of 2016 Final Rule

Judge Naomi Reice Buchwald ruled in favor of plaintiffs on the first issue, finding that HHS's interpretation in the Final Rule's preamble, that the marketing status of a product "will be determined based on its marketing status on the primary completion date [of the ACT]," was not entitled to deference and conflicted with the unambiguous language of FDAAA. Agreeing with the parties that the question was one of statutory rather than regulatory construction, the court considered whether the *Chevron* doctrine might require deference to HHS's interpretation of the statutory provision.[5] Ultimately, the court determined that *Chevron* did not apply because HHS announced its interpretation in the Final Rule's *Federal Register* preamble rather than in binding regulatory text.

Even if HHS's interpretation had carried the force of law, it would not have been entitled to deference because, in the court's view, FDAAA's text is *not* ambiguous.[6] The relevant statutory language requires the HHS Secretary to include Basic Results in ClinicalTrials.gov "for each [ACT] for a drug that *is approved…or licensed* or a device that *is cleared…or approved*,"[7] and Judge Buchwald reasoned that "is" indicates a present state. That is, Basic Results reporting applies to any ACT of "a drug or device that is presently approved, licensed or cleared" so long as other statutory criteria are satisfied.[8]

Judge Buchwald found confirmation for this reading in another provision of the statute, which provides:

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[4] Complaint at 25, *Seife et al v. HHS et al*, 1:18-cv-11462 (S.D.N.Y. 2020) (paragraph 109).

[5] *Chevron U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984).

[6] *Id*. at 32-33.

[7] 42 U.S.C. § 282(j)(3)(C) (emphasis added).

[8] *Seife*, at 33.

> "[w]ith respect to an applicable clinical trial that is completed before the drug is initially approved…or initially licensed…or the device is initially cleared…or initially approved, the responsible party shall submit to the Director of NIH for inclusion in [Clinicaltrials.gov] the clinical trial information described in subparagraphs (C) [i.e., Basic Results] and (D) not later than 30 days after" the product's approval."[9]

Judge Buchwald expressly rejected HHS's arguments that the provision cited above merely "prescribes the deadline" for the submission of Basic Results for pre-approval ACTs in the event HHS decided to exercise its statutorily provided discretion to mandate the reporting of Basic Results for pre-approval ACTs. She held that FDAAA mandated the reporting of Basic Results for pre-approval ACTs and that the discretion that HHS claimed the statute provided applied only to the reporting of Expanded Results.

Furthermore, Judge Buchwald summarily dismissed HHS's argument against applying FDAAA retroactively, noting that "responsible parties knew since the FDAAA's enactment in 2007 that the statute required them to submit Basic Results for each ACT of a product that is approved."[10] Put another way, because Judge Buchwald determined that the statutory requirements were clear from the start, she concluded that HHS and industry cannot complain that they lacked notice. To have held otherwise, Judge Buchwald wrote in closing, would have left in place an exemption "utterly contrary to the FDAAA's aims."[11]

Seife v. HHS thus invalidated HHS's attempt to limit Basic Results reporting when studies involve products that were not approved, licensed or cleared for marketing by the time of a study's completion date. In practice, this means that Responsible Parties who did not report Basic Results information for ACTs completed before a product was approved, cleared or licensed, when approval, licensing or clearance has since been granted, may ultimately be required to report Basic Results data for those ACTs.

NIH's Failure to Post Non-Compliance Notices, Create ClinicalTrials.gov Search Function

Plaintiffs also argued that HHS is required to take enforcement action against Responsible Parties who have not fulfilled their FDAAA reporting obligations. On this issue, the court held that the government's determinations of whether to enforce compliance were not subject to judicial review.

FDAAA directs HHS to issue a notice of noncompliance to a Responsible Party that fails to submit required clinical trial data, or submits data that are false and misleading in any respect. FDA, to which HHS delegated this enforcement authority in 2012, must notify the Responsible Party of the alleged deficiency and allow the Responsible Party thirty days to remedy data defects. If the responsible party fails to do so, FDA may impose civil monetary penalties.[12]

FDAAA further requires HHS to post a "notice" on ClinicalTrials.gov if "the responsible party for an [ACT] fails to submit clinical trial information for such clinical trial as required [by the statute]."[13] The notice must state that the Responsible Party is out of compliance, whether penalties have been imposed, and whether the party has submitted corrected data to ClinicalTrials.gov. Importantly, NIH cannot satisfy this posting requirement until FDA has first notified the Responsible Party and given it 30 days to correct the problem. In addition, under a related provision, the NIH director must ensure that "the public may easily search [ClinicalTrials.gov] for entries that include [notices of noncompliance.]"[14]

Judge Buchwald invoked longstanding Supreme Court doctrine to rule against the plaintiff on this issue, holding that "an agency's decision not to prosecute or enforce" is generally unreviewable because such decisions are typically

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[9] Quoting 42 U.S.C. § 282(j)(3)(E)(iv).
[10] *Seife*, at 38.
[11] *Seife*, at 39.
[12] 42 U.S.C. § 282(j)(5)(C).
[13] 42 U.S.C. § 282(j)(5)(E)(i).
[14] 42 U.S.C. § 282(j)(5)(E)(vi).

"committed to an agency's absolute discretion."[15] Judge Buchwald reasoned that, because NIH's ability to post noncompliance notices depends on FDA's first making an unreviewable discretionary decision, NIH's failure to satisfy the requirements of FDAAA is likewise unreviewable.

Implications

Since clinical trial registration and results information was first required to be reported to ClinicalTrials.gov, few issues have been more confusing than whether and what type of clinical trial results must be reported for ACTs completed before the studied product was approved for marketing. For nearly ten years, HHS's interpretation of FDAAA's reporting requirements made it seem that Responsible Parties need not report Basic Results for pre-Rule, pre-approval ACTs. The *Seife* decision has upended that understanding.

HHS has not announced whether it will appeal the *Seife* decision, nor has it offered any reporting guidance in light of the decision. Given the competing priorities at HHS, and the historical lack of enforcement related to ClinicalTrials.gov, it remains to be seen whether and how HHS will take any action to require reporting in line with the court's decision. For now, Responsible Parties should recognize that Basic Results for Pre-Rule ACTs of products that were not yet approved or cleared at the time of completion of the trial may need to be reported in the future. In the meantime, it would be prudent for Responsible Parties to take an inventory of clinical trials potentially impacted by the *Seife* decision so that Basic Results reporting, if ultimately required, could begin without significant delay.

[15] *Heckler v. Chaney*, 470 U.S. 821 (1985).