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Ruling In HHS Case May Mean More Drug Trial Reporting

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Section 801 of the U.S. Food and Drug Administration Amendments Act of 2007 (codified at 42 U.S.C. § 282(j)) requires that sponsors of applicable clinical trials, or ACTs, register those trials and submit "basic results" specified in the statute to the public ClinicalTrials.gov data bank.

Although six years past its deadline, in September 2016 the U.S. Department of Health and Human Services promulgated regulations that took effect Jan. 18, 2017, and expanded the disclosure requirements — including now requiring results from ACTs involving never-approved drugs and medical devices to be disclosed publicly.

In the preamble of the rule, when discussing the approved versus unapproved product requirements, HHS stated that it would not read its rule to require sponsors to disclose the basic results of ACTs for trials of drugs or devices that were approved, licensed or cleared after an ACT's primary completion date, but before Jan. 18, 2017. HHS referred to that category of studies as pre-rule, pre-approval ACTs.

In December 2018, the plaintiffs Charles Seife, an investigative journalist, and Dr. Peter Lurie, a former associate FDA commissioner and current president of the Center for Science in the Public Interest, filed suit to contest this interpretation by HHS, and to obtain clinical trial results related to recently FDA-approved products. The defendants were HHS and its secretary, the National Institutes of Health and its director, and the FDA and its commissioner.

On Feb. 24, 2020, the U.S. District Court for the Southern District of New York held, in Seife v. U.S. Department of Health and Human Services, that HHS had improperly exempted pre-rule, pre-approval ACTs from the statute's public disclosure requirements for basic results.[1] The court found that Section 801 "unambiguously" requires that basic results of these clinical trials be publicly disclosed on ClinicalTrials.gov.

It concluded:

> The Court sets aside HHS's interpretation of the Final Rule as contrary to the unambiguous terms of the FDAAA, and enjoins defendants to comply with those

terms, which require responsible parties to submit, and ClinicalTrials.gov to include, Basic Results for pre-Rule, pre-approval ACTs.

Section 801 of FDAAA and the Final Rule

Congress enacted Section 801 to "increase the availability of information to the public" and "communicate the risks and benefits of drugs" for the purpose of "help[ing] patients, providers, and researchers learn new information and make more informed healthcare decisions." In accord with the statute, “responsible parties” have been required to submit registration information for ClinicalTrials.gov since Dec. 26, 2007, basic results since Sept. 27, 2008, and adverse events as an additional component of basic results since Sept. 27, 2009, for ACTs as defined in the statute.

Basic results include: (1) demographic characteristics of the patient sample, including the number who participated, dropped out, and were excluded from analysis; (2) primary and secondary outcomes of a study, including values for outcome measures and the results of statistical significance; (3) the point of contact for scientific information about clinical trial results; and (4) whether agreements exist that restrict the principal investigator in discussing or publishing the trial results. Thus, basic results include the core outcomes on which a trial succeeds or fails as well as whether or not the findings met prespecified statistical significance to show that the results were not the play-of-chance.

Section 801 further directed HHS to expand the registry and results data bank not later than three years after the statute’s enactment. HHS did not issue a final rule until Sept. 21, 2016, and the rule did not take effect until Jan. 18, 2017. HHS’ final rule clarified the existing statutory requirements and provided for the expanded registry and results data bank contemplated by the statute.

The new requirements included the disclosure of results from ACTs of products that are not approved, licensed or cleared by the FDA for any use, as well as a major expansion of the scope of trial results and adverse events that must be disclosed. The additional requirements for disclosure of trial results — what are referred to as the expanded results — are not the subject of the court’s ruling.

The Final Rule’s Preamble: HHS’ Interpretation of Marketing Status

A central issue for the court in Seife was the statutory definition of a product’s marketing status and how HHS interpreted this in the rule’s preamble. The statute requires that basic results be submitted for all applicable clinical trials that study a drug or device “that is approved, licensed, or cleared by FDA.” The final rule expanded this requirement to include ACTs that study a drug or device “that is not approved, licensed, or cleared by FDA.” HHS interpreted the term “is approved, licensed, or cleared” to refer to whether the product was approved, licensed, or cleared on the date on which the ACT reached its completion date. The court, however, found that interpretation to be contrary to the statute.

The Decisions of the Court

Defendants’ Motion for Dismissal: Standards of Review and Standing

The defendants moved for lack of subject matter jurisdiction under Federal Rule of Civil Procedure 12(b)(1), arguing that the plaintiffs lacked standing under Article III of the Constitution. The court concluded that the plaintiffs suffered a concrete, particularized injury sufficient to establish standing under Article III because they were denied access to information that, in the court’s view, HHS had an obligation to disclose and the plaintiffs had a right to obtain.

The court's decision reflects an aggressive application of the doctrine of informational standing and will likely be challenged by the government on appeal. Although Congress undoubtedly intended to make information available to the public, it is not at all clear that the plaintiffs' inability to access this information gives rise to an injury sufficient to confer Article III standing.

The Plaintiffs' First Cause of Action

The court addressed two causes of action asserted by the plaintiffs in their complaint. The first contended that HHS' interpretation in the preamble of the final rule is contrary to the unambiguous terms of Section 801. The court agreed that a key provision in the statute defines the obligations of HHS regarding basic results:

> Not later than 1 year after September 27, 2007, the Secretary [of HHS] shall include in the registry and results data bank for each applicable clinical trial for a drug that is approved under section 355 of Title 21 or licensed under section 262 of this title or a device that is cleared under section 360(k) of Title 21 or approved under section 360e or 360j(m) of Title 21, the following elements [of Basic Results].

The court observed that an additional statutory provision specifically addresses the situation where an ACT studied a product that was approved after the ACT's estimated or actual completion date. It rejected the defendants' position that the latter applies only if HHS were to exercise its discretion to require the submission of basic results for preapproval ACTs by rulemaking.

The court disagreed with the defendants' separate argument that the statute should not be construed to apply retroactively. The court determined that the obligation to submit basic results for pre-rule, pre-approval ACTs is not retroactive because "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[,licensed, or cleared]."

The court observed that its opinion is consistent with Congress' purpose in enacting Section 801. It concluded that Congress was concerned negative trial results may not be released by sponsors, and the public could not assess the safety and efficacy of drugs and devices. The court stated:

> Plainly, requiring ClinicalTrials.gov to include Basic Results for pre-Rule, pre-approval ACTs ameliorates that concern and furthers those broader goals. Doing the opposite, by contrast, would exempt the responsible parties for every pre-approval ACT completed soon after September 27, 2007 and [before] January 18, 2017 from disclosing negative results regardless of whether thousands of Americans use the product, which would be utterly contrary to the FDAAA's aims.

The court reached this final judgment:

> The Court accordingly finds that the FDAAA unambiguously requires responsible parties to submit, and defendants to include on ClinicalTrials.gov, Basic Results for pre-Rule, pre-approval ACTs.

The Plaintiffs' Second Cause of Action

The plaintiffs' second cause of action asserted that the NIH's failure, to date, to post notices of noncompliance pursuant to the statute's NIH public notice provision, and to create a search function for

such notices on ClinicalTrials.gov, was unlawfully withheld or unreasonably delayed. For several statutory interpretation and enforcement discretion-related reasons, the court granted the defendants' motion and dismissed this claim.

What's Next

HHS has not yet announced whether it will appeal the district court's finding. If the district court's decision is not overturned, drug and device companies and other organizations that sponsor ACTs will have to determine if they submitted all required results to ClinicalTrials.gov for trials that (1) were completed on or after Sept. 27, 2007, and before Jan. 18, 2017, and (2) studied a product that the FDA approved, licensed or cleared at any time after the ACT completion date. If basic results of these trials were not previously submitted, the basic results must be submitted by sponsors for public disclosure and posting by HHS on ClinicalTrials.gov.

Under the rules of appellate procedure, the government defendants have 60 days to file an appeal with the U.S. Court of Appeals for the Second Circuit. If they file an appeal, the case will be briefed and argued through 2020, and likely decided in 2021. Interested parties may be able to participate in the appeal, either by seeking leave to intervene or by filing an amicus brief in support of either side.

Implications of an Appeal

The district court's decision puts companies and other organizations that are responsible parties of ACTs and that have not submitted basic results in a difficult position; until any appeal is resolved, it is unclear what the likely impact of the decision will be.

Significantly, the district court's decision does not strike down HHS' final rule or conclude that the final rule is invalid. Instead, the district court's decision purports to declare unlawful HHS' interpretation of the rule as set forth in the rule's preamble, and requires the defendants to comply with the court's interpretation of what both the statute and the final rule require.

If the defendants pursue an appeal, it is unlikely that the government will take any enforcement action against responsible parties of ACTs until all appeals are resolved. If the government decides not to appeal or if the district court is affirmed on appeal, there is a risk that responsible parties could face statutory penalties for not having previously submitted basic results for pre-rule, pre-approval ACTs. The defendants' interpretive position appears to be driven by fair-notice concerns and a recognition that there has been general confusion over what information about trial results must be publicly disclosed, including because of the long delay that occurred between the statute's enactment and the effective date of the defendants' final rule.

If the defendants lose on appeal and an appellate court concludes that the statute has always been unambiguous, responsible parties will be put in the potentially challenging position of having to argue that, despite the statute's plain language, they were entitled to rely on the defendants' interpretation in failing to disclose basic results.

Potential Penalties

Section 801 penalizes actions or omissions including the failure to submit required clinical trial registration or results information; the submission of false or misleading information to ClinicalTrials.gov; the failure to submit certifications of conformance with ClinicalTrials.gov requirements

to the FDA in association with certain applications and submissions to the FDA; and knowingly submitting a false certification to the FDA. The statute provides for civil money penalties, notices on ClinicalTrials.gov of noncompliance, and potentially other penalties under the Federal Food, Drug and Cosmetic Act or laws punishing false statements to the government.

In September 2018, the FDA (the agency charged with enforcement of ClinicalTrials.gov requirements) published a draft guidance that describes its planned approach of reviewing compliance and identifying violations of ClinicalTrials.gov provisions. The agency may collect evidence during Bioresearch Monitoring Program inspections — these occur, for example, when the FDA inspects clinical trial sites that generated data for a marketing application.

BIMO inspections also may be triggered by a complaint about activities at a trial site. Complaints might come from site personnel with compliance concerns, from clinical trial participants who look for results of a trial in which they have participated and do not see the results (note that informed consent forms now must include an affirmative statement about the existence of ClinicalTrials.gov and the fact that certain trial-related information may appear there), or from other sources.

In the event of perceived noncompliance, the FDA intends to generally follow a sequence of steps:

- The FDA will send a preliminary notice of noncompliance (pre-notice letter) to the responsible party. The pre-notice letter will describe the potential violation and request that the responsible party review it and make any necessary corrections within 30 days.

- The pre-notice letter will advise that FDA will conduct further review and assessments of information from any available source, and failure to comply with applicable requirements may result in further regulatory action, including the issuance of a notice of noncompliance, civil money penalties, injunction, and/or criminal prosecution.

- A notice of noncompliance will notify the recipient of the FDA's determination and give the recipient an opportunity to remedy noncompliance not later than 30 days after the notification.

- If a responsible party/submitter does not remedy noncompliance within 30 days after receiving a notice of noncompliance, the FDA generally intends to seek civil money penalties, taking into account the type of noncompliance and the circumstances associated with the lack of remediation.

Among available penalties, the law provides for assessment of civil money penalties, even for unintentional or potentially minor failures (e.g., "failure to submit [required] clinical trial information"). Authorized penalties have a maximum of $10,000 (adjustable over time) for all violations adjudicated in a single proceeding, followed by $10,000 per day for continuing violations not corrected after 30 days. Other federal laws may be invoked, such as 18 U.S.C. § 1001, which makes it a crime to make certain false statements to the government.

In its guidance, the FDA stated that enforcement is expected to be risk-based. That said, however, scrutiny from the district court, coupled with recent published articles that raise questions about both compliance and foregone civil money penalty collections, may maintain a focus on ClinicalTrials.gov for some time to come.

Because of the complexities of the district court's ruling, companies should take care in making decisions about how to proceed. At this time, it is unclear whether the government will appeal and to what extent it might exercise enforcement discretion for companies and other organizations that did not submit basic results for pre-rule, pre-approval ACTs.

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[1] See Memorandum and Order, Seife et al. v. U.S. Dep't of Health & Human Services., No. 1:18-cv-11462, 2020 WL 883478 (S.D.N.Y. Feb. 24, 2020).