King & Spalding
Client Alert

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For more information, contact:

Christina M. Markus
+1 202 626 2926
cmarkus@kslaw.com

Beverly H. Lorell, M.D.
+1 202 383 8937
blorell@kslaw.com

Ashley C. Parrish
+1 202 626 2627
aparrish@kslaw.com

Elaine H. Tseng
+1 415 318 1240
etseng@kslaw.com

King & Spalding

Washington, D.C.
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 202 737 0500

San Francisco
101 Second Street
Suite 1000
San Francisco, CA 94105
Tel: +1 415 318 1200

Federal Government Takes Steps Toward Enforcement of ClinicalTrials.gov Requirements

Time Is Ripe To Update SOPs And To Ensure Compliance with Results Submission Requirements

In recent days, the federal Department of Health and Human Services ("HHS") clarified the requirements for submission of certain clinical trial results to ClinicalTrials.gov. The Food and Drug Administration ("FDA") separately elaborated how it intends to enforce related legal requirements. After the enactment of the Food and Drug Administration Amendments Act in 2007 and the implementation of detailed regulations in 2017, there has been limited government policing of ClinicalTrials.gov compliance. The two recent pronouncements, however – which come after both administrative litigation to clarify applicable requirements[1] and public watchdog criticism about compliance[2] – could signal increased scrutiny and government enforcement in the near future.

HHS DID NOT APPEAL COURT DECISION: RESPONSIBLE PARTIES MUST SUBMIT "BASIC RESULTS" FOR PAST APPLICABLE CLINICAL TRIALS OF APPROVED DRUG, BIOLOGICAL, AND MEDICAL DEVICE PRODUCTS

In February 2020, the U.S. District Court for the Southern District of New York invalidated HHS' interpretation of 42 U.S.C. § 282(j), a statutory provision that was amended in 2007 to require that sponsors of "applicable clinical trials"[3] ("ACTs") register those trials and later submit "basic results"[4] for public posting to the ClinicalTrials.gov data bank. In general, the statute required the submission of results not later than 30 days after a relevant drug, biological, or medical device product has been approved, licensed, or cleared by FDA.

Pursuant to rulemaking authority, HHS in 2016 promulgated the Clinical Trials Registration and Results Information Submission rule ("Rule"),[5] which took effect on January 18, 2017 and expanded the disclosure requirements. In the Rule's preamble, HHS stated that it would not read its

Rule as imposing a retroactive obligation on sponsors to disclose publicly the basic results of ACTs for trials of products that were approved, licensed, or cleared *after* the trials' completion date but *before* January 18, 2017 (referred to as "pre-Rule, pre-approval ACTs"). The Court rejected HHS' interpretation as contrary to 42 U.S.C. § 282(j), and enjoined HHS to require responsible parties to submit – and ClinicalTrials.gov to post – basic results for pre-Rule, pre-approval ACTs.[6]

HHS did not appeal the District Court decision, and the case was dismissed on July 28, 2020. On that date, HHS amended the ClinicalTrials.gov website to clarify current requirements:

1. **For ACTs that were required to be registered and with a Primary Completion Date *before* January 18, 2017:**
   - If the ACT studied a drug, biological, or device product that *was* approved, licensed or cleared as of the Primary Completion Date, then the responsible party is required to submit the results information, including adverse events, specified in 42 U.S.C. § 282(j)(3)(C) and (j)(3)(I). Generally, this submission deadline is *not later than 1 year after the study's Primary Completion Date*; however, results submission for these ACTs may be delayed under certain circumstances with certifications (e.g., seeking approval, licensing, or clearance of a new use for the drug, biological, or device product; requesting an extension for good cause).
   - If the ACT studied a drug, biological, or device product that *was not* approved, licensed, or cleared as of the Primary Completion Date *but is* subsequently approved, licensed, or cleared, then the responsible party is required to submit the results information specified in 42 U.S.C. § 282(j)(3)(C) and (j)(3)(I) *not later than 30 days after the product is approved, licensed, or cleared* by FDA.
   - If the ACT studied a drug, biological, or device product that *was not* approved, licensed, or cleared as of the Primary Completion Date and *remains* unapproved, unlicensed, or uncleared, then results submission is not required.
2. **For ACTs that are required to be registered and with a Primary Completion Date on or *after* January 18, 2017:**
   - If the ACT studies a drug, biological, or device product that *is* approved, licensed or cleared as of the Primary Completion Date, then the responsible party is required to submit the results information specified in 42 C.F.R. § 11.48. (42 C.F.R. § 11.42(a)(2); note that the content of the submission is more expansive than "basic results" and must include the protocol and statistical plan)
   - If the ACT studies a drug, biological, or device product that *is not* approved, licensed, or cleared as of the Primary Completion Date, then the responsible party is required to submit the results information, including the protocol and statistical plan, specified in 42 C.F.R. § 11.48. (42 C.F.R. § 11.42(b))

FDA CLARIFIES AGENCY PROCEDURES FOR THE ASSESSMENT OF CIVIL MONEY PENALTIES AGAINST DRUG, BIOLOGICAL, AND MEDICAL DEVICE PRODUCT RESPONSIBLE PARTIES AND/OR SUBMITTERS[7]

Noncompliance with ClinicalTrials.gov requirements – such as a failure to submit required clinical trial registration or results information; submission of false or misleading information; or the failure to submit (or to accurately submit) certifications of conformance to FDA[8] -- can lead to traditional FDA administrative, civil, or criminal judicial actions (e.g., Warning Letter, injunction, criminal fine or prosecution). In addition, applicable law provides for the assessment of civil money penalties ("CMPs") of $10,000 for all violations adjudicated in a single proceeding, followed by an additional CMP of up to $10,000 per day for continuing violations not corrected after 30 days. Noncompliance also may result in a loss or delay of National Institutes of Health ("NIH") grant funding.

On August 17, 2020, FDA announced in the Federal Register the publication of a final guidance document that clarifies the agency's intention to enable voluntary compliance efforts before the agency will invoke public findings of noncompliance and/or CMPs.[9] Nevertheless, FDA advises: "If a [responsible party or submitter] does not remedy

noncompliance within 30 days after receiving a Notice of Noncompliance, the Center generally intends to seek civil money penalties, taking into account the type of noncompliance and the circumstances associated with the lack of remediation."

Oversight Approach. FDA plans to review compliance using evidence collected during Bioresearch Monitoring Program ("BIMO") inspections.[10] BIMO inspections of clinical trial sites commonly occur when FDA reviews marketing application submissions. Inspections also can be triggered by clinical trial participant or practitioner complaints.

Notably with regard to inspections, FDA does *not* intend to include on its List of Inspectional Observations (Form FDA-483) information about potential violations concerning ClinicalTrials.gov. This is because FDA investigators may not be able to assess whether required information has been submitted to the ClinicalTrials.gov data bank at the time of an inspection. FDA will, however, include pertinent information collected by an investigator in the later Establishment Inspection Report ("EIR") and will provide that information to the relevant FDA Center for consideration.

When an FDA Center perceives noncompliance with ClinicalTrials.gov-related obligations, the agency intends generally to follow a sequence of steps --

1. **FDA will send a Preliminary Notice of Non-Compliance ("Pre-Notice Letter") to the responsible party or submitter.** The Pre-Notice Letter will describe the potential violation -- which may relate to ClinicalTrials.gov information and/or certifications of conformance that are required to be filed with FDA -- and request that the addressee take any necessary actions to address the potential violation within *30 calendar days after receipt* of the letter. Pre-Notice Letters will include an FDA contact to whom a response may be submitted and who can address questions or concerns of the responsible party or submitter. After a Pre-Notice Letter has been received and the 30-day period for action has passed, FDA will conduct further assessment (using information from any source) to determine whether a violation exists.
2. If FDA determines that a responsible party failed to submit required information to ClinicalTrials.gov and/or submitted false or misleading information, the agency "will issue" a Notice of Noncompliance. If FDA determines that a submitter failed to submit a required certification to FDA, or knowingly submitted a false certification, the agency "intends to issue" a Notice of Noncompliance. **A Notice of Noncompliance will notify the recipient of the Center's determination and give the recipient an opportunity to remedy** noncompliance not later than *30 calendar days after the notification*. FDA intends to post Notices of Noncompliance on the FDA website, and also to transmit Notices of Noncompliance to NIH so the latter can include such notices in the ClinicalTrials.gov data bank, as required under 42 U.S.C. § 282(j)(5)(E).
3. If a responsible party/submitter does not remedy noncompliance within 30 calendar days after receiving a Notice of Noncompliance, FDA generally intends to seek civil money penalties, taking into account the type of noncompliance, corrective action taken by a responsible party or submitter after receiving the Notice of Noncompliance, and the circumstances associated with the lack of remediation.

Civil money penalties may not be the only penalties that FDA seeks. As noted, traditional remedies are available under the Federal Food, Drug, and Cosmetic Act. In addition, the 2016 preamble to the Rule states that 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.

Risk-Based Assessments. FDA expects its evaluation of potential violations to be risk-based, with a focus on:

- Responsible parties who have failed to submit required clinical trial registration and/or results information for applicable clinical trials of products that potentially may pose a higher risk to human subjects, or applicable clinical trials of products intended to address significant public health need. Examples may include trials of a drug, biological, or medical device product not previously approved, licensed, or cleared and intended to treat a serious and/or life-

threatening disease or condition; or applicable clinical trials involving vulnerable populations (such as pediatrics), rare diseases, or emergency research conducted without informed consent under 21 C.F.R. § 50.24;

- Responsible parties or submitters who have a pattern of previous noncompliance with requirements for the submission of clinical trial information and/or required certifications; and
- Applicable clinical trials for which noncompliance exists in conjunction with other noncompliance pertaining to conduct of the trial (e.g., failure to retain clinical trial records, failure to obtain informed consent).

RECOMMENDATIONS: RESPONSIBLE PARTIES AND SUBMITTERS MUST INVENTORY STUDIES AND SUBMISSIONS AND CONFIRM COMPLIANCE, ADJUST POLICIES AND PROCEDURES AS NECESSARY

Some responsible parties historically submitted basic results for applicable clinical trials of all approved drug, biological, or medical device products. However, entities that relied upon HHS' preamble statements and/or the advice on the ClinicalTrials.gov website and did not submit results for pre-Rule, pre-approval ACTs (i.e., applicable clinical trials with a Primary Completion Date *before* FDA approval was received, and for which FDA approval occurred *before* January 18, 2017) now must prepare and submit that information.

HHS recently updated and corrected the ClinicalTrials.gov website to encourage responsible parties to submit results for trials affected by the *Seife* court decision "as soon as possible."[11] We expect FDA to exercise reasonable discretion if responsible parties are working toward compliance; nevertheless, on the website HHS cited the various remedial and punitive actions that may be available for failure to submit results information.

Fundamentally, based upon the *Seife* decision and FDA's final guidance concerning civil money penalties, we recommend that responsible parties and other persons involved with ClinicalTrials.gov submissions:

1. Review and update their registration, results disclosure, and compliance certification policies and procedures, as needed;
2. Determine whether individual trial records are complete for applicable clinical trials (including the submission of "basic results," including adverse events, for any pre-Rule, pre-approval ACTs); and
3. Consider how other business activities can be informed by this new stage of compliance activity (e.g., reviewing the compliance status of studies of targeted products, reviewing EIRs and requesting copies of Pre-Notice Letters and Notices of Noncompliance in upcoming diligence reviews; reviewing conformance to FDA certification requirements).

King & Spalding has extensive experience with clinical trials and the range of related regulatory requirements. We would be pleased to discuss these with you in greater detail, and to support entity- or product-specific reviews.

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[1] Seife et al. v. HHS, et al., No. 18-cv-11462-NRB, 2020 WL 883478 (S.D.N.Y. February 24, 2020).

[2] E.g., Piller C., "Transparency on Trial," Science, 367:6475, pp. 240-243 (Jan. 17, 2020); DeVito N. et al., "Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study," The Lancet, 39:10021, pp. 361-369 (Jan. 17, 2020).

[3] See generally 42 U.S.C. § 282(j)(1)(A)(i) and 42 C.F.R. § 11.10(a).

[4] See generally 42 U.S.C. § 282(j)(3) and 42 C.F.R. § 11.48.

[5] The Rule is codified at 42 C.F.R. Part 11.

[6] See "U.S. District Court Overturns HHS Interpretation of Final Rule that Permitted Sponsors of Certain Drug and Device Trials to Avoid Disclosure of Results on ClinicalTrials.gov" (March 3, 2020), available at https://www.kslaw.com/news-and-insights/us-district-court-overturns-hhs-interpretation-of-final-rule-that-permitted-sponsors-of-certain-drug-and-device-trials-to-avoid-disclosure-of-results-on-clinicaltrialsgov.

[7] FDA uses the term "submitter" to mean an individual or entity that (i) submits certain applications or submissions to FDA regarding drug, biological, or device products and (ii) provides a certification to FDA under 42 U.S.C. § 282(j)(5)(B) (certifying conformance to ClinicalTrials.gov requirements, as applicable). In some cases, the submitter is someone other than the responsible party for an ACT.

[8] To certify compliance with ClinicalTrials.gov requirements, FDA requires that applicants submit Form FDA-3674 with certain applications, including:

- Investigational New Drug Application ("IND")
- New Clinical Protocol Submitted to an IND
- New Drug Application ("NDA")
- Efficacy Supplement to an Approved NDA
- Biologics License Application ("BLA")
- Efficacy Supplement to an Approved BLA
- Abbreviated New Drug Application
- Premarket Approval Application ("PMA")
- PMA Panel Track Supplement
- Humanitarian Device Exemption
- 510(k) submissions that refer to, relate to, or include information on a clinical trial

FDA does not require the submission of a Form FDA-3674 with an Investigational Device Exemption ("IDE") application, because IDEs were not included in the statutory requirement. See generally FDA, "Guidance for Industry – Form FDA-3674, Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions" (June 2017), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/form-fda-3674-certifications-accompany-drug-biological-product-and-device-applicationssubmissions.

[9] FDA, "Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank; Guidance for Responsible Parties, Submitters of Certain Applications and Submissions to the Food and Drug Administration, and Food and Drug Administration Staff; Availability," 85 Fed. Reg. 50028 (Aug. 17, 2020), available at https://www.federalregister.gov/documents/2020/08/17/2020-17909/civil-money-penalties-relating-to-the-clinicaltrialsgov-data-bank-guidance-for-responsible-parties.

[10] FDA, "Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank – Guidance for Responsible Parties, Submitters of Certain Applications and Submissions to FDA, and FDA Staff" (Aug. 2020), available at https://www.fda.gov/media/113361/download.

[11] See "ClinicalTrials.gov -- Frequently Asked Questions," available at https://clinicaltrials.gov/ct2/manage-recs/faq#fr_6.