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Client Alert

FDA & Life Sciences Practice Group

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FDA Issues Final Rule and Guidance Creating New Standards for the Acceptance of Data Obtained from Clinical Investigations Conducted Outside of the United States in Support of IDE and Device Marketing Applications

On February 21, 2018, the Food and Drug Administration (FDA) issued a final rule[i] amending the Agency's regulations on acceptance of data from clinical investigations for medical devices. The final rule amends requirements for data submitted from clinical investigations conducted outside of the United States (OUS) that is intended to support an investigational device exemption (IDE) application, a premarket notification (510(k)) submission, a request for De Novo classification, a premarket approval (PMA) application, a product development protocol (PDP) application, or a humanitarian device exemption (HDE) application. The effective date for the final rule will require compliance for all studies in which enrollment begins on or after February 21, 2019. In addition to this final rule, FDA issued a new guidance document for industry that is intended to help sponsors comply with the new requirements under the final rule.[ii]

The preamble to the final rule notes that the amended regulations are intended to help ensure the quality and integrity of data obtained from OUS investigations and the protection of human subjects. In addition, FDA believes that the amendments made by the final rule create consistency in the Agency's requirements for acceptance of data from clinical investigations for all medical device application and submission types whether conducted inside or outside of the United States. The major change made by the final rule requires that clinical investigations conducted inside and outside of the United States conform to good clinical practices (GCP), if the data from those investigations will be used to support an IDE or device marketing application or submission.

While the final rule is beneficial to medical device sponsors and applicants in that it provides greater clarity about FDA's standards for accepting data from clinical investigations conducted OUS, the rule also adds an additional burden on sponsors who are now required to affirmatively demonstrate that the data submitted is adequate. The rule also reduces the Agency's flexibility to accept data that do not meet the standards outlined in the amended regulations, which increases the importance of ensuring that data collected from investigations OUS is compliant prior to submission of device applications and submissions. Overall, the final rule is a positive development

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for sponsors who are well-positioned to comply with FDA's standards as of the February 21, 2019 compliance date.

For clinical investigations conducted within the United States, IDE and device marketing applications and submissions must now include a statement that investigations were conducted in compliance with the GCP requirements of 21 C.F.R. part 50 (human subject protection regulations), 21 C.F.R. part 56 (institutional review boards regulations), and 21 C.F.R. part 812 (investigational device exemptions regulations). IDE and device marketing applications that rely for support on data from investigations OUS must include a similar statement that the investigations were conducted in accordance with GCP as described in 21 C.F.R. § 812.28(a)(1). In addition to this statement, sponsors and applicants submitting clinical data from investigations conducted OUS that support an IDE or marketing application or submission for a medical device must provide supporting information that describes the actions that were taken to ensure that the investigation conformed to GCP. The guidance document clarifies that "[f]or a multi-center investigation with sites both inside and outside the US, each site would need to comply with the local requirements."[iii] This client alert focuses on the supporting information that applicants must provide to verify conformance with GCP when submitting data from investigations conducted OUS to support IDE or device marketing applications and submissions.

KEY PROVISIONS

STATEMENTS REGARDING THE CONDUCT OF CLINICAL INVESTIGATIONS

As noted above, there are two new required statements that must be included in IDE and device marketing applications and submissions. The statements certify that investigations relied upon by those applications and submissions comply with GCP requirements. For investigations that are conducted within the United States, the statement certifies conformance with the Agency's GCP requirements in 21 C.F.R. parts 50, 56, and 812. For investigations conducted OUS, the applicant or sponsor must certify that the investigations relied upon conform to GCP as defined in 21 C.F.R. § 812.28(a)(1).

Section 812.28(a)(1) describes GCP as "a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are credible and accurate and the rights, safety, and well-being of subjects are protected." GCP requires "review and approval or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating an investigation, continuing review of an ongoing investigation by an IEC, and obtaining and documenting the freely given informed consent of the subjects (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating an investigation."[iv] FDA notes that international standards that the Agency has previously recognized may be used to satisfy the GCP requirement, but sponsors and applicants may choose to meet those requirements through other appropriate means as well. The two international standards referenced in the final rule and guidance are the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Good Clinical Practice: Consolidated Guidance" (ICH E6) and "Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice," ISO 14155:2011.

FDA notes that full conformance with GCP may not always be possible and that, while non-conformance may raise questions of credibility and accuracy of the data submitted in the application, the final rule provides the opportunity for an applicant or sponsor to provide a statement of the reason for non-conformance and a description of the steps that were taken to ensure that the data submitted are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected. In addition, the final rule allows sponsors and applicants to request a waiver of certain GCP requirements so long as it can justify why the requirement is "unnecessary, cannot be achieved, or can be satisfied through an alternative course of action."[v] Such a waiver may be requested with the IDE or medical device application or submission or, alternatively, may be requested prior to submission. Finally, FDA reminds sponsors and

applicants that data from all investigations, including those that do not comply with GCP requirements, must be submitted, as required under applicable medical device regulations.

SUPPORTING INFORMATION FOR STATEMENT OF CONFORMANCE WITH GCP FOR INVESTIGATIONS CONDUCTED OUS

Applicants and sponsors relying on data from clinical investigations conducted OUS must describe the actions that were taken to ensure that the relevant research conformed to GCP. The required supporting information must include the information under 21 C.F.R. § 812.28(b) or the applicant may cross-reference to another section of the application or submission where such information is located. In addition to the required statement, sponsors and applicants submitting data from investigations conducted OUS that are intended to support an IDE or medical device application or submission must provide the following supporting information:

1. Names of investigators and names and addresses of the research facilities and sites where records relating to the investigations are maintained;
2. Investigator qualifications;
3. Description of the research facilities;
4. Detailed summary of the protocol and results of the investigation, and if requested, case records or additional background data;
5. A statement that the device used in the clinical investigation is identical to the one that is the subject of the application or submission, or a detailed description of the device used in the investigation;
6. Discussion demonstrating that the data and information constitute valid scientific evidence;
7. The name and address of the IEC that reviewed the investigation and a statement that the IEC meets the definition in § 812.3(t);
8. Summary of the IEC's decision to approve, or provide a favorable opinion of, the investigation;
9. Description of how informed consent was obtained;
10. Description of incentives provided to subjects to participate;
11. Description of how the sponsor monitored the investigation and ensured that the investigation was carried out consistently with the protocol; and
12. Description of how investigators were trained to comply with GCP and to conduct the investigation in accordance with the protocol.

21 C.F.R. § 812.28(a)(2) details which of the above twelve items of information must be included in an application or submission based on the level of risk involved in the investigation. Significant risk investigations require the most information and investigations that meet 21 C.F.R. § 812.2(c)'s exemption criteria require the least supporting information. As with investigation conducted within the U.S., sponsors and applicants may request a determination by FDA of whether the device investigation is significant or non-significant through the Q-submissions program.[vi] Alternatively, sponsors and applicants may make their own determination; however, if proceeding based on its own determination, a sponsor or applicant should maintain documentation that demonstrates the rationale for the determination as such documentation may be requested by the Agency under 21 C.F.R. § 812.28(a)(2). FDA notes in the guidance document that it "does not intend that foreign IECs provide oversight of [the significant/non-significant risk] determination," because foreign IECs may not be familiar with FDA terminology relating to these categories.[vii]

Once a determination has been made as to whether the investigation poses a significant or non-significant level of risk or is exempt under § 812.2(c), the sponsor or applicant can determine what supporting information is required under 21 C.F.R. § 812.28. Significant risk device investigations are required to submit all twelve items in an IDE or device marketing application or submission. Non-significant risk device investigations are required to submit the information described in numbers 1, 4, 5, 7, 8, 9, and 11, above. Note that FDA may request the information described in number 10

as well as the rationale for determining that the investigation is of a non-significant risk device, but such information does not need to be provided in the application or submission, unless requested. For exempt investigations, FDA may request the information identified in numbers 1, 4, 5, 7, 8, 9, 10, and 11, above, as well as the rationale for determining that the investigation is exempt under § 812.2(c), but such information is not required to be submitted in an application or submission, unless requested.

IMPLICATIONS OF THE FINAL RULE FOR MEDICAL DEVICE COMPANIES

As outlined above, the final rule is somewhat of a double-edged sword for medical device sponsors. The rule provides clarity on the standards that FDA will apply in determining whether data relied upon in IDE and device marketing applications and submissions are acceptable; however, the amended regulations also create a significant risk for medical device sponsors and applicants as the Agency may refuse to accept data that are essential to approval or clearance of a device. The final rule amends the regulations to place the burden on the sponsor or applicant to demonstrate that the data were obtained from investigations that conform to GCP. In addition, the criteria established in the amended regulations decreases the Agency's flexibility in accepting data from investigations that do not comply. In sum, sponsors who are well prepared to comply with the final rule should find the increased clarity beneficial in ensuring FDA's acceptance of data from investigations conducted OUS, while those applicants who may not be in compliance with the final rule will likely be burdened by the Agency's reduced flexibility to accept non-compliant data.

Due to the risk involved in failing to comply with the amended regulations, sponsors and applicants must ensure that investigations beginning on or after February 21, 2019 conform to GCP and other requirements mandated by the final rule. Medical device companies should begin drafting and adopting policies and procedures now for implementation before the effective date. Sponsors that plan to begin an investigation on or after the effective date must review the regulations closely to ensure that the proposed investigation conforms with GCP, that waivers are requested where appropriate, and that the documentation necessary to demonstrate compliance will be collected throughout the investigation. In addition, sponsors should consider beginning the process of revising their IDE and medical device marketing applications and submissions templates to include a new section for the required statement confirming compliance with GCP as well as a section or separate document that may be used for reporting the supporting information required under 21 C.F.R. § 812.28(b).

King & Spalding will continue to monitor developments related to the new final rule, and would be pleased to assist in helping medical device companies understand the rule, update internal procedures, ensure that data collected OUS will be acceptable for submission to FDA, and navigate the premarket approval process under the amended regulations.

[i] 83 Fed. Reg. 7366 (February 21, 2018).
[ii] U.S. FOOD & DRUG ADMIN., ACCEPTANCE OF CLINICAL DATA TO SUPPORT MEDICAL DEVICE APPLICATIONS AND SUBMISSIONS FREQUENTLY ASKED QUESTIONS 1 (2018), *available at* https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM597273.pdf.
[iii] *Id.*at 6.
[iv] *Id.* at 5.

[v] *Id.*
[vi] U.S. FOOD & DRUG ADMIN., REQUESTS FOR FEEDBACK ON MEDICAL DEVICE SUBMISSIONS: THE PRE-SUBMISSION PROGRAM AND MEETING WITH FOOD AND DRUG ADMINISTRATION STAFF 1 (2017), *available at* https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf.
[vii] U.S. FOOD & DRUG ADMIN., ACCEPTANCE OF CLINICAL DATA TO SUPPORT MEDICAL DEVICE APPLICATIONS AND SUBMISSIONS FREQUENTLY ASKED QUESTIONS 5 (2018), *available at* https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM597273.pdf.