DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

DuVal Client Alert – June 2015

Your Foreign Clinical Data: Does FDA Love It? Or does it not?

EXECUTIVE SUMMARY

Clients often come to our firm asking, "Will FDA accept our foreign clinical data?" In years past, our answer was an equivocal "yes" which required explanation. Today, FDA has unequivocally opened up to foreign data, but will not drop its expectation that the data be developed, monitored and reported in a robust, American-like fashion. FDA has, after all, been skeptical of foreign data due to the lack of rigor it has seen in foreign studies in the past. Our firm certainly has seen its share of foreign data that has not measured up to that typically seen in the United States, but it has gotten much better. This Client Alert addresses FDA's recent guidance on the topic of the acceptance of foreign data by FDA. In late April, 2015, FDA issued a new draft guidance titled "Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States - Draft Guidance for Industry and Food and Drug Administration Staff" (the "Foreign Study Data Guidance").

In this new draft guidance document, FDA acknowledges that as clinical research becomes more and more globalized, certain challenges arise when using foreign clinical study data to support a device premarket application. Differences in study populations, clinical care, and treatment options are just a few of these challenges. FDA could find such differences render the data inapplicable to the intended US

populations and ultimately reject it. To avoid that result, FDA has issued this guidance to describe how it evaluates whether certain aspects of foreign study data are adequate for a premarket application. This **Client Alert** highlights these aspects and discusses what sponsors can do to ensure their foreign study data is applicable.

Scope of the Draft Guidance

The Foreign Study Data Guidance applies to **medical device** manufacturers when **initiating** a foreign study for data or **relying** on previously collected data from a foreign study to support an ("**IDE")**, **premarket notification ("510(k)")**, **de novo petition ("de novo")**, **Humanitarian Device Exemption** ("**HDE")**, or **premarket approval application ("PMA")**.

Framework for FDA's Acceptance of Clinical Trial Data

FDA regulation requires that most premarket applications be supported by **valid scientific evidence**.[1] The Foreign Study Data Guidance echoes this same standards in regards to foreign data. According to the regulation, valid scientific evidence is:

> "*evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use*."[2]

It is important to note that current FDA regulations addressing foreign study data only apply to PMA applications; there are no current regulations addressing IDEs, 510(k)s, de novos or HDEs. Despite the absence of such regulation, FDA has had a longstanding approach of accepting scientifically valid data, regardless of where the study was conducted. Moreover, the Food and Drug Administration Safety and Innovation Act of 2012 ("FDASIA") codified this position regarding the use of foreign clinical study data.[3]

The current regulation regarding foreign study data for PMA applications is outlined below, followed by the most recent FDASIA provision that covers any device application.

Regulation on Acceptance of Foreign Study Data

[1] 21 CFR 860.7 Determination of safety and effectiveness.
[2] See 21 CFR 860.7(c)(2).
[3] Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012).

The current regulation is old and addresses data on a pre-November 19, 1986 basis and a post-November 19, 1986 basis, which means it is quite outdated. It provides that FDA's acceptance of foreign study data only covers foreign studies conducted in support of a Premarket Approval.[4] The requirements under this regulation depends in part on whether the study is conducted under an IDE.[5]

For studies commenced after November 19, 1986 and not conducted under an IDE, the study data must be scientifically valid and the investigator must have conducted study in conformance with the Declaration of Helsinki (1983 version) or the laws and regulations of the country in which the research was conducted, which ever accords greater protection to the human subjects.[6]

In addition, if the data for the PMA is based solely on foreign clinical data, the study must also satisfy the following:

- Generate data that is applicable to the U.S. population and U.S. medical practice;
- Be performed by clinical investigators of recognized competence; and
- Generate data that is considered valid without the need for an on-site inspection by FDA or if questionable, be validated by FDA through an on-site inspection or other appropriate means.[7]

Most Recent Legislation on Use of Foreign Study Data

The FDASIA legislation of 2012 added a section requiring FDA to accept data from foreign studies, provided that the applicant demonstrates that the data are adequate under FDA's applicable standards for supporting clearance or approval of the device. If FDA finds that such data are inadequate under the applicable standards for supporting clearance or approval, then FDA must provide the sponsor with written notice of the finding along with the Agency's rationale for the finding. The main purpose of the Foreign Study Data Guidance is to provide FDA's current thinking on what that rationale might be (see section below on "Considerations When Relying on Foreign Data").

In light of the FDASIA provision, FDA has currently proposed a rule that will require foreign studies to be conducted in accordance with good clinical practice (GCP), or else provide a justification for not complying with GCP.[8]

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[4] 21 CFR 814.15 Research conducted outside the United States.
[5] Studies conducted under an IDE must comply with IDE Regulations. For studies not conducted under an IDE, the requirements of the regulation depends on whether the study began before or after November 19, 1986.
[6] For studies started before November 19, 1986 and not conducted under an IDE, FDA must be satisfied that the data are scientifically valid and that the rights, safety, and welfare of human subjects have not been violated in order for the study data to be accepted.
[7] 21 CFR 814.15 Research conducted outside the United States.
[8] 78 Fed. Reg. 12664 (Feb. 25, 2013).

Considerations when Relying on Foreign Data

FDA acknowledges that certain challenges exist in using data derived from foreign studies to support an FDA marketing application. In particular, the Foreign Study Data Guidance notes three special considerations that premarket applicants should think about when relying foreign study data.

> **"Differences in clinical conditions**: Differences between the clinical conditions in an OUS country and those in the US can affect the relevance of the data to the intended US population. OUS countries may have different standards of care, which can affect the analysis of the benefits and risks of the studied device relative to standard practice. Differences in clinical facilities and levels of clinical skill can also affect OUS study data to the extent that such data may not be generalized to US clinical practice and the differences could impact the data's usefulness in supporting the safety and/or effectiveness of the device."
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> "**Differences in Study Populations**: To the extent a device has disparate safety effects or benefits in different demographic groups, differences in the race, ethnicity, age, gender and sex of a foreign population can affect the applicability of the study to the intended US population. Reporting of the representation of such groups in the device submission becomes particularly important to allow appropriate sub-group analyses. The OUS studied population and the intended US patient population may also differ in the prevalence of confounding clinical factors that can affect risks of an intervention as well as clinical response. For example, populations vary widely in the prevalence of smoking, diabetes, and obesity, and rare or regionalized co-morbidities occur in certain populations that can confound study results. Cultural, educational and language differences can also affect the interpretation of and applicability of study results, and the ability to pool OUS data with US data."
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> "**Differences in regulatory requirements**: When studies conducted OUS are initiated to satisfy the requirements of foreign countries, rather than, or in addition to FDA, the studies may not be designed to address the questions necessary to satisfy FDA requirements. For example, an OUS regulatory entity may require demonstration of safety and *performance* to support approval, while the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that for PMA approval, the data must provide a reasonable assurance of safety and effectiveness. If an OUS study is designed to show a device meets an endpoint related to performance, the data may be inadequate to show that the probable benefits outweigh the probable risks."

What Sponsors Can Do

The Foreign Study Data Guidance wisely suggests that addressing these considerations early on in the development process can increase the likelihood that FDA will accept the data, i.e., the data can support the premarket application. One key way that sponsors can address these considerations is by engaging with FDA through the Pre-Submission process and developing a position of advocacy on how their foreign data will meet the three criteria discussed in the section above.[9] For a thoughtful analysis of the Pre-Submission process, see our **Client Alert**, "The Pre-Sub Meeting and Gilligan's Island: When a Three Hour Tour Can Turn Into a Shipwreck."[10]

It is important to remember that the regulatory pathway will influence the data to be generated. For example, the 510(k) program does not require a demonstration that the benefits outweigh the risks (as part the third criterion above). That is because with a 510(k), the subject device enjoys the underlying regulatory presumption that the predicate has already established that the benefits outweigh the risks of a device, the device is safe and effective, and the device has a clinical utility. The sponsor need only demonstrate that the subject device does not diminish safety and effectiveness in comparison to the predicate, i.e., it is substantially equivalent. Please see our **Client Alert**, "AdvaMed and MDMA Should Oppose FDA's 510(k) Benefit-Risk Guidance."[11]

Sponsors have a strategic opportunity to engage with FDA to understand what is needed before commencing foreign clinical studies. The Foreign Study Data Guidance highlights a few important examples where Pre-Submission interactions can spare valuable time and effort for sponsors, as well as mitigate and set expectations for post-approval plans. Failure to engage with FDA can potentially result in data reanalysis, additional confirmatory studies, and generally additional time spent for the review of the premarket application. Taking the opportunity to engage with FDA through Pre-Submission helps sponsors make the most of their data, which rings true regardless of whether the study is conducted in the United States or abroad.

Our firm routinely engages with our clients in Pre-Submission meetings with FDA. Watch for additional **Client Alerts** regarding this topic as well as others relating to clinical trials and FDA interactions. If you have any questions regarding this, please contact us at duval@duvafdalaw.com or by phone at (612) 338-7170 x1.

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[9] See "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

[10] See "The Pre-Sub Meeting and Gilligan's Island: When a Three Hour Tour Can Turn Into a Shipwreck" at http://duvalfdalaw.com/docs/DuVal_Client_Alert_The_PreSub_Meeting-Gilligans-Island.pdf.

[11] See "AdvaMed and MDMA Should Oppose FDA's 510(k) Benefit-Risk Guidance" at http://duvalfdalaw.com/docs/DuVal_Client_Alert_FDA_510k_Benefit_Risk_FINAL.pdf.

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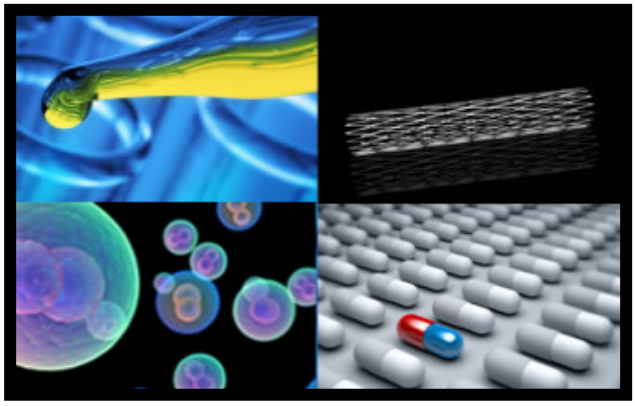

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