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**Maine Adopts Revised Regulations
Governing Clinical Trial Registration and Results Reporting**

The Maine Department of Health and Human Services ("DHHS") and the Maine Office of Attorney General ("AG") recently adopted final regulations that significantly revise the existing joint rule governing the disclosure of clinical trial information. These revisions, which became effective on November 2, 2009, differ significantly from both the proposed regulations issued in June 2009 and the existing joint rule in effect prior to November 2, 2009. Of particular importance, the final regulations were revised in response to industry comments to remove some of the most significant burdens sought to be imposed by the proposed rule, including the requirement to re-post on ClinicalTrials.gov ("CT.gov") studies that are currently posted only on non-governmental websites, such as ClinicalStudyResults.org.

While the final regulations are much less onerous than the original proposal, they still impose meaningful additional burdens on clinical trial reporting that, in some cases, exceed the federal requirements under the Food and Drug Administration Amendments Act of 2007 ("FDAAA"). For example, the new Maine regulations require manufacturers to post additional information in registry submissions, such as detailed information about each arm of a study, the identity of principal investigators, and the identity of entities providing financial support for the study. Likewise, the newly revised regulations require the submission of information on a wider range of studies and analyses, including observational studies and *post hoc* analyses, neither of which is required under FDAAA.

For the most part, these new requirements apply prospectively only. In particular, the following compliance dates and timelines apply to the new requirements:

- **Registry Information:**
 - Investigations for which information is posted prior to January 1, 2010 are exempt from the new data element requirements;
 - For studies not previously subject to reporting requirements (e.g., ongoing observational studies), manufacturers have until March 2, 2010 (i.e., 120 days from November 2, 2009) to post registry information;

- Results Information
 - Results information that is submitted for posting *prior to* January 1, 2010 is exempt from the new data element requirements, except the requirement to submit *post hoc* analyses;
 - *Post hoc* analyses must be submitted for previously posted studies if the *post hoc* analysis was completed *after* January 1, 2010;
 - New deadlines apply immediately to certain studies as a result of revisions to the definition of “completion date” to mirror the federal definition of “primary completion date”

- Observational studies completed prior to January 1, 2010 are exempt for the new regulatory requirements.

This memorandum provides a brief summary of the final regulations, highlighting differences from both the proposal and the existing joint rule.

I. Significant New Requirements

The revised regulations impose significant new reporting requirements on companies that, in some cases, exceed federal reporting requirements under FDAAA.

Observational Studies. The final regulations for the first time require manufacturers to submit registration and results information for observational studies, which now are encompassed within the definition of “clinical trial.” 10-144 CMR 275 §1.02-2 (Nov. 2, 2009). This requirement goes beyond federal clinical trial reporting requirements, which do not define observational studies as “clinical investigations” subject to FDAAA reporting requirements, and arguably go beyond the Maine governing statute as well.¹ As mentioned above, under the final, revised Maine regulations, observational studies completed prior to January 1, 2010 are exempt from the new reporting requirements. *Id.* §1.03-6. Ongoing observational studies must be registered within 120 days of adoption of the new rules – i.e., by March 2, 2010 – and results information for observational studies completed after January 1, 2010 must be submitted in accordance with otherwise applicable deadlines (generally one year after study completion). *Id.* §§1.04-1(B), 1.04-2(A).

¹ The governing Maine statute defines a “clinical trial” as a “clinical investigation as defined by FDA” that is intended to be held for inspection or submitted to FDA in support of a research or marketing application. 22 M.R.S.A. §2700-A(1)(A). FDA regulations, in turn, define a “clinical investigation” as “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects,” and explicitly exclude the “use of a marketed drug in the course of medical practice.” 21 C.F.R. §312.3(b). Observational (non-interventional) studies typically involve the use of a particular marketed drug in the course of normal clinical practice and thus are not considered to be “clinical investigations” as defined by FDA. Accordingly, they are not “clinical trials” under Maine’s governing statute and should not be subject to the regulatory reporting requirements. The Maine DHHS and AG rejected industry comments arguing that they lack authority to require the reporting of observational studies but provided no reason for this position. We thus believe there are solid grounds for challenging the Maine regulations as applied to observational studies as inconsistent with the governing statute.

Expanded Registry Information. The final regulations, like the proposal, substantially expand the amount of information that must be submitted for registration purposes. *Id.* §1.03-1. For example, the final regulations now require submission of detailed information regarding each arm of a study, the principal investigator, and any biospecimen retention policies. *Id.* §1.03-1(M)(2), (P), and (V). The final regulations seek to track the data elements required by FDAAA and ClinicalTrials.gov (“CT.gov”) but, in some cases, may go beyond the federal requirements.

Results Information. The final regulations, like the proposed rule, require manufacturers to submit results information in the tabular format required by CT.gov rather than in summary format, such as the ICH E3 synopsis. *Id.* §1.03-2. Moreover, the final regulations require manufacturers to submit not just the “mandatory” data elements required by CT.gov but also all other relevant “optional” data elements for which information is available. *Id.*

Post Hoc Analyses. The final regulations for the first time require manufacturers to submit *post hoc* analyses of previously submitted studies to CT.gov. *Id.* §1.03-2. The final regulations, however, revise and clarify the standard for submitting such analyses. Under the proposed rule, a *post hoc* analysis was required to be submitted if it represented a “meaningful or substantial deviation or correction from previously reported results or is relied upon for claims made in marketing, promotional or educational efforts or materials to prescribers or consumers.”² Industry comments argued that this standard was vague and wide-ranging. In response to these comments, the Maine DHHS and AG revised the final regulations to clarify that a *post hoc* analysis must be submitted only if: (1) it represents a “deviation or correction from previously reported results of an interventional study on the safety or efficacy of the drug,” and (2) the “deviation or correction will be objectively significant to a prudent prescriber of the drug.” *Id.* While still somewhat vague, the standard for submitting a *post hoc* analysis arguably is stricter than under the proposed regulation and should require the posting of fewer *post hoc* analyses. The new reporting requirements apply only to *post hoc* analyses completed after January 1, 2010, regardless of the date of the previously reported results. *Id.* §1.03-6.

Requirement to Post Results on CT.gov. The final regulations recognize CT.gov as the only “acceptable” publicly available database for posting clinical trial results information. *Id.* §1.03-2. As a result, companies can no longer meet the regulatory requirements by posting results information on other publicly available websites, such as ClinicalStudyResults.org or a company’s own website. This provision implements by regulation the policy announced in a September 2008 letter and

² Maine Department of Health and Human Services, Office of MaineCare Services; Maine Office of the Attorney General, Notice of Agency Rule-making Proposal, Department of Health and Human Services, 10-144, Chapter 275, and Office of the Attorney General, 26-239, Chapter 111, *Reporting Requirements for Pharmaceutical Manufacturers and Labelers*, Proposed Rule No. 2009-P136, §1.03-2 (June 9, 2009).

subsequent October 2008 advisory issued by the Maine Office of the Governor, which mandated use of a single website, CT.gov, for the public disclosure of clinical trial results.³ Although industry comments argued persuasively that this “single site” policy is inconsistent with the governing statute, the Maine DHHS and AG refused to revise the regulation.

Completion Date. The definition of “completion date” has been revised to align with the federal definition of “primary completion date” (“PCD”). Under the final regulations, the term “completion date” is now defined as “the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome . . .” *Id.* §1.02-5. If there is more than one primary outcome measure, the collection of data for the last primary outcome controls for purposes of the PCD. *Id.* The definition of “completion date” is important because it is used to establish the deadline for posting results information. Because the PCD can be much different than last-patient-last-visit (“LPLV”) or other common conceptions of “completion date,” this revision may require companies to make immediate changes to their standard operating procedures to ensure that deadlines are not missed for trials subject to the Maine regulations but not FDAAA (which already should be using PCD). It is interesting to note that this revision was prompted by a comment from a generic drug manufacturer.

II. Major Revisions to the Proposed Rule

Based upon industry comments and concerns, the Maine authorities made substantial revisions to the proposed regulations on several controversial issues, such as retroactive application of the new requirements.

Re-Posting of Results Information. In a significant reversal from the position announced in its proposed rule, the final regulations do not require manufacturers to re-post clinical trial results information on CT.gov if such information previously was posted only on a different publicly-accessible website, such as ClinicalStudyResults.org or a company website. Instead, the regulations explicitly state that if registration or results information has been submitted for posting prior to January 1, 2010 in accordance with existing Maine regulations, then the new results posting requirements do not apply (other than the requirement to submit *post hoc* analyses, discussed further below). *Id.* §1.03-6. The new regulations attempt to capture results information posted on websites other than CT.gov by requiring manufacturers to include links from the registry posting for a drug to the publicly accessible Internet website on which results information is posted. *Id.* §1.03-1(X)(1). The re-posting requirement contained in the proposed

³ See Letter dated September 15, 2008, from Trish Riley, Director, Governor’s Office of Health Policy and Finance, available at http://www.maine.gov/dhhs/boh/documents/clinical_trials/JW%20-%20Clinical%20Trials%20-%2009-11-08.pdf; Advisory re: Clinical Drug Trial Reporting (Oct. 24, 2008), available at [http://www.maine.gov/dhhs/boh/documents/clinical_trials/October%2008%20drug%20trial%20advisory%20final\(10-24-08\)%20\(4\)%20\(2\).pdf](http://www.maine.gov/dhhs/boh/documents/clinical_trials/October%2008%20drug%20trial%20advisory%20final(10-24-08)%20(4)%20(2).pdf).

regulation was perhaps the most controversial issue raised during the rule-making process because of the enormous and unnecessary burdens it would have imposed on the regulated industry. The decision by the Maine DHHS and AG to drop this requirement thus represents one of the most important revisions made to the proposed regulation.

Organizations Providing Support for a Clinical Trial. In a reversal from the proposed rule, the final regulations do not require manufacturers to provide the names of organizations providing design, implementation, data analysis and reporting or other similar services with respect to a clinical trial, although they continue to require the disclosure of up to ten (10) funding sources. *Id.* §1.03-1(E). Industry comments argued that this information often is considered to be confidential commercial information and may be subject to contractual non-disclosure provisions. The Maine DHHS and AG agreed, except with respect to funding sources.

“Extended” Protocol Information. In another important reversal from the proposed rule, the final regulations do not require manufacturers to provide “extended” protocol information as part of a registration submission. The proposed regulation would have required manufacturers to submit an “extended description of the protocol,”⁴ but industry comments argued that this information was confidential. Industry further asserted that the National Institutes and Health (“NIH”) and the Food and Drug Administration (“FDA”) are tasked with considering whether to require submission of this precise information as part of the ongoing federal rulemaking process to implement FDAAA and that Maine should not short-circuit this federal process. The Maine DHHS and AG accepted these comments and deleted the requirement to submit an extended description of the protocol.

III. Other New Requirements and Revisions to the Proposed Rule

In addition to the major provisions and revisions discussed above, the final rule incorporates a number of other relevant new requirements and revisions to the proposed rule. This section provides a brief summary of these provisions.

Phase I Studies. The definition of “clinical trial” has been revised to clarify that it does not include phase I studies. *Id.* §1.02-2. Accordingly, phase I studies, other than bioequivalence studies, are not subject to the clinical trial reporting requirements under Maine law.

Foreign Clinical Trials. The final regulations clarify that clinical trials conducted outside the United States are not considered to be “covered clinical trials” subject to the Maine reporting requirements unless: (1) one or more trial sites are located within the U.S. or its territories; (2) the results of the trial are intended to be submitted to FDA in

⁴ Proposed Rule No. 2009-P136, §1.03-1(H).

support of a research or marketing application (e.g., Investigation New Drug application (“IND”) or New Drug Application (“NDA”)); or (3) the results are relied upon in marketing, promotional or educational efforts or material to prescribers or consumers in Maine. *Id.* §1.02-6. This treatment of foreign clinical trials differs from the treatment of such trials under FDAAA.⁵

Posting Date and Notification Period. The final regulations, like the proposed rule, provide that the posting date for clinical trial information is deemed to be the date that the information is received by NIH, rather than the date it is accepted and made publicly available. *Id.* §1.03-5. This change will help ensure that companies are not penalized for administrative posting delays at NIH over which they may have little or no control. The final regulations also extend the deadline from 30 to 90 days for manufacturers to provide a notification to Maine authorities if information submitted to CT.gov has not been posted in a timely manner. *Id.* This revision appropriately addresses the routine delays in posting information on CT.gov caused in large part by NIH’s quality control review activities.

Good Cause Delays. The final regulations, like the proposal, treat “good cause” extensions granted by NIH as permissible extensions under Maine law. *Id.* §1.04-2(C)(1).

Updates. In a reversal from the proposed rule, the final regulations do not include a provision requiring updates to be submitted for registry or results information at periodic intervals (e.g., 12 months).⁶ However, other regulations state that a manufacturer is responsible for “maintaining the reliability, accuracy and truthfulness of a posting.” *Id.* §1.03-4. Moreover, with respect to results information, manufacturers must submit any *post hoc* analysis that deviates from or *corrects* previously submitted results information if the deviation or correction will be objectively significant to a prudent prescriber of the drug. *Id.* §1.03-2. Thus, other regulatory provisions should ensure that posted information is updated on a regular basis even in the absence of an explicit update provision.

As discussed above, the revised regulations impose additional burdens on the regulated industry that, in some cases, go beyond federal clinical trial reporting requirements. Although we expect that the Maine requirements will be preempted within the next twelve to eighteen months, there is no guarantee that preemption will occur within this time frame, since preemption is dependent upon promulgation of final regulations implementing FDAAA. Accordingly, companies need to carefully assess

⁵ See Draft NIH Guidance: Elaboration of Definitions of Responsible Party and Applicable Clinical Trial, at 8-9 (March 9, 2009).

⁶ Proposed Rule No. 2009-P136, §1.04-2(F).

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how they will comply with both existing FDAAA reporting requirements and the newly revised Maine regulations.

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