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PROPOSED CHANGES TO MAINE'S CLINICAL TRIAL REPORTING REGULATIONS

On June 9, 2009, the State of Maine Department of Health and Human Services (the "Department") proposed revisions to the State's regulations regarding clinical trial registration and results reporting.[1] The proposed revisions would broaden the scope of clinical trials that are subject to the reporting requirement and would significantly increase the number of data elements required for registration and results reporting. The Department's Notice of Proposed Rulemaking (the "Notice") states that the revised regulations "clarif[y] Maine (sic) requirements for clinical trial registration and results reporting, compatible with Federal reporting requirements and with the capabilities of the publicly funded website www.ClinicalTrials.gov."[2]

This e-alert provides an overview of the proposed revisions and discusses some of the implications for companies engaged in clinical trials.

I. BACKGROUND

In 2003, the State of Maine enacted legislation that requires a manufacturer or labeler of prescription drugs that "employs, directs or utilizes marketing representatives" in Maine to disclose to the Department the costs associated with marketing drugs dispensed within the state.[3] In 2005, Maine enacted additional legislation requiring these same companies to post certain registration and results information regarding clinical trials of drugs marketed in Maine.[4] The statute applies to any clinical trial initiated on or after October 15, 2002.

In March 2007, the Department issued regulations implementing Maine's clinical trial registry/results provisions. In addition, since 2007, the Department has issued a number of interpretive letters and advisories, which provide further guidance. Nevertheless, several interpretive issues have remained. In addition, Federal law includes its own clinical trials registration and results reporting requirements.[5] Many companies have noted that the Federal requirements and Maine's requirements, though similar, are at times inconsistent. This has further complicated compliance with Maine's provisions. The Department's proposed revisions reflect, in part, an attempt to resolve some of these discrepancies as well as an attempt to codify certain parts of Maine's guidance letters.

[1] *See* Maine Department of Health and Human Services, Office of MaineCare Services, Proposed Rule, available at http://www.maine.gov/dhhs/oms/rules/other_rules.html.
[2] *Id.*
[3] 22 M.R.S.A. § 2698-A.
[4] 22 M.R.S.A. § 2700-A(3).
[5] These requirements were originally established by the Food and Drug Administration Modernization Act of 1997 (FDAMA) and later expanded by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and are codified in sections 402(i) and (j) of the PHSA.

II. KEY CHANGES IN THE PROPOSED REGULATIONS

A. SCOPE

Pursuant to the regulations, Maine's reporting provisions apply only to "covered clinical trials."[6] The proposed revisions attempt to clarify the definitions of the term "clinical trial" and "covered clinical trial."[7] The proposed revisions would clarify the definition of the term "clinical trial" to include:

1. hypothesis-testing clinical investigations, as defined in 21 C.F.R. § 12.3(b), the results of which either have been or are intended to be submitted to, or held for inspection by, FDA as part of an application for a research or marketing permit;

2. post-marketing clinical investigations on the safety or efficacy of an FDA-approved prescription drug or biological, including investigations of off-label uses, observational studies, and any study relied upon for claims made in marketing, promotional, or educational efforts or materials; and

3. bioequivalency studies testing a drug against the innovator drug or biological product or against another drug or biological product.[8]

The proposed revisions would also clarify the definition of the term "covered clinical trial" in two significant respects. First, the revisions would specify that to be a "covered clinical trial" a "clinical trial" must have been initiated on or after October 15, 2002, be conducted or sponsored by the manufacturer or labeler, and be of a drug or biological product (or device delivering either of such products) that is or has been or is subsequently approved for marketing for any use and dispensed, administered, delivered, or promoted in Maine.[9] The current regulations do not make specific reference to drugs that are subsequently approved.

Second, the revisions would clarify that clinical trials conducted outside of the United States would not be subject to the reporting requirement, unless:

- one or more trial sites are within the U.S. or its territories;
- the results either have been or are intended to be submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit; or
- the results are relied upon by a manufacturer or labeler for claims made in marketing, promotional or educational efforts or materials to prescribers or consumers in the U.S. or its territories.[10]

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[6] Code Me. R. §§ 10.144.275.1.03-1; 10.144.275.1.03-2.
[7] The proposed revisions are helpful in that they simplify the sentence structure of the definition to make the meaning more clear. It does not appear, however, that the changes are intended to significantly alter the meaning of the term.
[8] Proposed Rule: Department of Health and Human Services, 10-144, Chapter 275-Reporting Requirements for Pharmaceutical Manufacturers and Labelers; Office of the Attorney General, 26-239, Chapter 111, Reporting Requirements for Pharmaceutical Manufacturers and Labelers ("Proposed Rule"), amending § 10.144.275.1.02-2, *available at* http://www.maine.gov/dhhs/oms/rules/downloads/c_275_p_06_11_09.pdf.
[9] *Id.*, amending § 10.144.275.1.02-6.
[10] *Id.*

B. Required Information and Format

1. Registration

Under the current regulations, to meet Maine's requirements, 13 data elements must be posted on ClinicalTrials.gov (or its successor). The proposed regulations would expand the list of required elements to 26. Many of the added elements are consistent with elements already required to be submitted to ClinicalTrials.gov under the Federal provisions. However, some of the new requirements mandate the submission of elements currently considered optional on ClinicalTrials.gov.[11] Notably, the proposed revisions would require the identification of all organizations "providing support, including funding, design, implementation, data analysis and reporting" for the study.[12] In addition to submitting links to FDA-approved labeling and safety alerts, as required under the current regulations, the proposed regulations would require the submission of "[a]ny link directly relevant to the protocol,"[13] and "[c]itations to publications related to the protocol."[14]

2. Results

The current regulations specify that results information must be posted on ClinicalTrials.gov (or its successor website) "or, if not available for such posting, a publicly accessible Internet website."[15] In a letter guidance issued on September 15, 2008, the Department specified that results information must be posted on ClinicalTrials.gov.[16] The proposed revisions codify this guidance by removing the current reference to "a publicly accessible Internet website" as an alternative.[17]

The proposed revisions would substantially revise the content submission requirements for the results database. The current regulations set out specific data elements and format requirements, including "a summary of the clinical trial that is compliant in format and content with the Synopsis in the ICH E3 Structure and Content of Clinical Study Reports."[18] The proposed revisions delete these specific content and format requirements and, instead, require manufacturers and labelers to submit results information to ClinicalTrials.gov in accordance with the fields and formatting requirements currently supported by that database. Specifically, the proposed revisions would require the manufacturer or labeler to complete each of the following reporting categories on ClinicalTrials.gov:

- Results Point of Contact
- Certain Agreements
- Participant Flow
- Baseline Characteristics
- Outcome Measures
- Adverse Events

[11] For example, the revised regulations would require the submission of an extended description of the protocol, citations to related publications, and relevant links, including links to FDA medical product safety alerts; whereas the ClinicalTrials.gov website denotes these data elements as optional.
[12] Proposed Rule, *supra* note 8, amending § 10.144.275.1.03-1(E).
[13] *Id.*, amending § 10.144.275.1.03-1(Z)(1).
[14] *Id.*, amending § 10.144.275.1.03-1(Y).
[15] *Id.*, amending § 10.144.275.1.03-2.
[16] Letter from Trish Riley, Director, State of Maine Governor's Office of Health Policy and Finance, at 2 (Sept. 15, 2008), *available at* http://www.maine.gov/dhhs/boh/documents/clinical_trials/JW%20-%20Clinical%20Trials%20-%209-11-08.pdf.
[17] Proposed Rule, *supra* note 8, amending § 10.144.275.1.03-2.
[18] Code Me. R. § 10.144.275.1.03-2(A).

All mandatory data elements and all other relevant ("optional") data elements would be required to be completed (provided the data are available for the optional data element).[19]

3. Post Hoc Analysis and Updates

The revised regulations would add new requirements for submission of information stemming from post hoc updates. Specifically, manufacturers or labelers would have a "continuing duty" to post information from "any post hoc analysis that represents a meaningful or substantial deviation or correction from previously reported results."[20] Similarly, if post hoc analysis is relied upon for "claims made in marketing, promotional or educational efforts or materials to prescribers or consumers," the revisions would require the posting of information necessary "so as to always maintain consistency with such claims."[21] The proposed revisions would require that updates to "clinical trial information previously posted" be submitted at least once every 12 months, unless there was no change to the "clinical trial results information" in the preceding 12 months.[22]

C. TIMING OF SUBMISSIONS

The proposed revisions would maintain the timing of submission requirements largely unchanged, except to delete provisions that were applicable only to trials that were completed prior to the adoption of the original rules. The revisions would, however, impose significant requirements relating to trial information previously posted on "publicly accessible" websites in compliance with the current rules. All results information posted prior to December 8, 2008, on a "publicly accessible" website, in accordance with the current regulations, would have to be posted on ClinicalTrials.gov within 180 days.[23] For clinical trial registration, results, and identification information posted on or after December 8, 2008, manufacturers and labelers would have 120 days after the adoption of the revised regulation to "post or repost information necessary to comply with the revisions."[24]

D. POSTING DATE

Under the revised regulations, information submitted to ClinicalTrials.gov would be deemed posted on the date that it is "received" by the NIH (as opposed to "accepted" under the current regulations). The current regulations require manufacturers to notify the Department in writing if submitted information has not appeared on ClinicalTrials.gov within 30 days after submission. Due to a backlog of submissions, NIH has frequently failed to post information within 30 days of submission. As a result, the revised regulations would increase the time period before notice must be submitted to the Department from 30 days to 90 days.[25]

E. EXTENSIONS

The current regulations provide, subject to certain limitations, for up to two six-month extensions on the results submission deadline in the event that compilation and analysis of the data are not sufficiently complete. The proposed regulations would retain

[19] Proposed Rule, *supra* note 8, amending § 10.144.275.1.03-2.
[20] *Id.*, amending § 10.144.275.1.04-2(E).
[21] *Id.*
[22] *Id.*, amending § 10.144.275.1.04-2(F).
[23] *Id.*, amending § 10.144.275.1.04-2(A)(iii).
[24] *Id.*, amending §§ 10.144275.1.04-1(B);10.144275.1.04-2(B); 10.144275.1.04-3(B). Despite the requirement that information currently posted on publicly accessible websites be posted on ClinicalTrials.gov, the revised regulations retain a provision requiring manufacturers and labelers to report publicly accessible websites where results data are posted.
[25] *Id.*, amending § 10.144275.1.03-5.

this provision and add a new provision requiring the Department to recognize extensions for "good cause" granted under the FDAAA.[26]

F. CONTACT INFORMATION

The proposed regulations identify the following contact address within the Department where manufacturers should direct any communications: OMS Pharmacy Unit, Clinical Trials Reporting, Maine Department of Health and Human Services, 442 Civic Center Drive, 11 State House Station, Augusta, Maine 04333.[27]

III. PROCEDURES

The Notice indicates that there will be a public hearing on the proposed changes to the regulation on July 1, 2009. Comments on the proposed changes from interested third parties are due by midnight Monday, July 13, 2009.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:

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[26] *Id.*, amending § 10.144275.1.04-2(D).
[27] *Id.*, amending § 10.144275.1.05-3.