July 13, 2009

Department of Health and Human Services
Office of MaineCare Services
Office of the Attorney General
State House Station 6
Attn: Anthony Marple, Director, Office of MaineCare Service and Linda Conti, Assistant Attorney General

RE: Comments in Response to Notice of Proposed Rulemaking: Department of Health and Human Services, 10-144, Chapter 275 – Reporting Requirements for Pharmaceutical Manufacturers and Labelers, and Office of the Attorney General, 26-239, Chapter 111 – Reporting Requirements for Pharmaceutical Manufacturers and Labelers (June 9, 2009)

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to submit comments to the rule proposed on June 9, 2009 by the Department of Health and Human Services ("Department") and the Office of the Attorney General ("AG"), "Reporting Requirements for Pharmaceutical Manufacturers and Labelers." The statutory authorities cited are 22 M.R.S.A. § 2700-A (7) and 5 M.R.S.A. § 207 (2). Final rules implementing prescription drug clinical trial reporting were originally issued on February 22, 2007 and manufacturers have been disclosing clinical trial information on publicly accessible websites to meet these existing regulations since they became effective on March 1, 2007.[1]

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. Our healthcare company members have a significant interest in Maine's clinical trial requirements, as they are dedicated to the discovery and development of new treatments and cures for serious and life-threatening diseases and

[1] Maine Department of Health and Human Services, 10-144, Chapter 275, Section 1, and Office of Attorney General, 26-239, Chapter 111---Prescription Drug Clinical Trial Reporting.

conditions. Biotechnology has created hundreds of new therapies and vaccines, including products to treat cancer, diabetes, HIV/AIDS and autoimmune disorders, and many other rare and unmet medical conditions. In fact, between 1995 and 2005, 160 different medicines were approved to treat rare diseases that affect 200,000 or fewer patients.

I. INTRODUCTION

The Notice of Proposed Rulemaking states that it is intended to clarify Maine requirements for clinical trial registry and results reporting, to be compatible with federal law and the publicly funded website, ClinicalTrials.gov (www.clinicaltrials.gov).[2] Clarification of Maine's requirements and compatibility with federal law are laudable goals that BIO supports. However, BIO believes that, in fact, the proposed rule does not achieve those goals. Rather, it appears to create more confusion regarding Maine requirements, is inconsistent with federal requirements, and would frustrate the ability to achieve the goals of Title VIII of the Food and Drug Administration Amendments Act of 2007 ("FDAAA") to "provide more complete results information and to enhance patient access to and understanding of the results of clinical trials."[3] Moreover, Maine's proposal would require the use of federal resources of the National Institutes of Health (NIH) for the purpose of meeting the state requirements, increasing the workload and burden of federal employees intended to be dedicated to the implementation of FDAAA.

This latest version of Maine's clinical trial disclosure regulations raises significant legal, policy, and practical concerns. We set forth these concerns in detail below, and the attached chart includes section-by-section comments specifying our concerns and setting forth recommended changes to the proposed regulations.

BIO would very much appreciate your serious consideration of our views. We are not raising these issues to be oppositional or to suggest that our member companies would not be willing to agree to meet reasonable requirements that enhance patient safety and care and are in the best interest of public health. However, we believe that the proposed rule would not achieve Maine's stated goals and would waste precious research and governmental resources without a meaningful public benefit. We would very much like the opportunity to meet with you to discuss alternative ways to clarify Maine's requirements, achieve the stated goals, and to address FDAAA compatibility.

II. THE PROPOSED REGULATION IS NOT AUTHORIZED BY MAINE LAW

A. THE STATUTE ONLY DIRECTS COLLECTION OF LIMITED CLINICAL TRIAL INFORMATION

[2] 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 11, Reporting Requirements for Pharmaceutical Manufacturers and Labelers (June 9, 2009).
[3] 42 U.S.C. § 282(j)(3)(D)(i).

BIO has raised concerns previously regarding earlier versions of these Maine regulations.[4] We continue to believe that the current regulations are broader than what was directed by the Maine legislature when it enacted §2700-A.3, Disclosure of clinical trials of prescription drugs, which requires manufacturers of prescription drugs dispensed or promoted in Maine to post information regarding clinical trials of those drugs conducted after October 15, 2002. The Maine legislature clearly identified four requirements: (1) name of the entity that conducted or is conducting the trial; (2) summary of the purpose of the clinical trial; (3) dates during which the trial has taken place; and (4) information concerning the results of the clinical trial, including potential or actual adverse effects of the drug.[5] The Maine legislature listed these specific four requirements, with no directive to the Department to expand the list. The statute clearly states that the Department may "adopt rules to implement this section [of the Maine statute]," and goes no further.[6]

In contrast to the clear categories of information to be posted, set forth explicitly in section 2700-A.3 of Maine's law, the proposed regulation lists 26 categories of data, A through Z – many of which are not encompassed by the four statutory categories. For example, recruitment status; status of availability of drug; extended description of the protocol; investigative techniques; strategy for participant identification and follow-up; arms, groups, and interventions; participant eligibility; names, degrees, roles, and affiliations of the principal investigator; and citations to publications related to the protocol – to name a few – are not encompassed by the statutory categories listed above, *i.e.*, "name of entity, summary of purpose, dates, or results of the clinical trial."[7] As BIO has stated in previous comments, none of this detail is required by the statute itself, and it seems flatly at odds with the simple and direct summary in the statute.[8] Also, as BIO has noted previously, this position is buttressed by the fact that the original version of this statute, as introduced in the Maine House of Representatives by Representative Lerman, contained an additional category of disclosures that could be required as "determined by the Commissioner to be relevant"[9] – a paragraph that was deleted by the Legislature prior to final enactment. This deletion makes clear its intent that the information disclosure requirements were to be limited to the summary information specifically requested by the statute itself.

While we have continued to be concerned that the current regulations exceed this statutory authority, this new proposal would be a massive expansion of Maine's statute, well beyond what the Maine legislature authorized when it enacted the law.

Courts in Maine have recognized that rules adopted by a state administrative agency must be "consistent with the terms and purposes of (the statutory scheme which the agency

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[4] See BIO comments to the Office of MaineCare Services and the Office of Attorney General, dated June 1, 2006 and November 13, 2006.
[5] 22 M.R.S.A. § 2700-A.3.
[6] 22 M.R.S.A. § 2700-A.7.
[7] Proposed Rule: Department of Health and Human Services, 10-144, Chapter 275-Reporting Requirements for Pharmaceutical Manufacturers and Labelers and Office of the Attorney General, 26-239, Chapter 111-Reporting Requirements for Pharmaceutical Manufacturers and Labelers (June 9, 2009) (proposed §§ 1.03 H, J, L, M, N, Q, X and Y). Thirteen of the 26 categories in the proposed rule are new in that they are not included in the current (2007) rule.
[8] See BIO June 1, 2006 comments, at p. 3.
[9] *Id.*, citing ME H.B. 1141A.

administers)."[10] While administrative agencies are entitled to some deference in interpreting a statute, "such deference 'must yield to the fundamental approach of determining the legislative intent, particularly as manifest in the language of the statute itself . . .'"[11] Otherwise, a rule that contravenes the provisions of controlling law is of no effect and will be "declared invalid."[12]

Clearly, the Maine legislature wanted disclosure of certain clinical trial information regarding prescription drugs distributed in Maine. However, the legislature did not authorize the submission of detailed, technical information that is beyond the scope of the specific Maine requirements and so expansive that it would require a major new undertaking by manufacturers and the federal government, nor did the legislature authorize the submission of information that is unlikely to benefit prescribing physicians. Clinical trial information is extremely complex, and collecting the amount and type of information called for in the proposed rules would be a tremendous undertaking for each company distributing products to treat patients in Maine.[13] It is critical that Maine take these facts into consideration before finalizing the proposed rules. To avoid being considered as arbitrary and capricious, actions by an administrative agency may not be taken "without consideration of facts or circumstances."[14]

The statutory authority and purpose of the Maine clinical trials disclosure law and regulations is to establish public posting of clinical trial information regarding FDA-approved drugs and biologics *to protect consumers and inform prescribers, to enhance Maine's role as guardian of the public interest*.[15] BIO supports the transparency and availability of useful clinical trial information that can enhance patient care and inform medical decision-making. However, much of the information that would be required under the proposed regulation is extremely detailed, technical scientific information that would not be useful to patients or consumers. In fact, it is our understanding that the additional information in the proposal would not be useful to prescribing physicians. Physicians often work extremely long hours and rely upon services and clinical support tools to synthesize data, addressing the need of busy doctors to consume data in a format that can be practically applied.[16] It is simply impractical to expect physicians to scroll through and interpret the many pages (for a single trial) of data tables, which would be required under the proposed rule.

Further, the results of a single clinical trial would likely not be used by a physician to make prescribing decisions. It is unlikely that a physician would pull results from ClinicalTrials.gov and read through all of the data tables to determine the overall compound profile (efficacy,

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[10] *Ingalls v. State of Maine*, 1988 WL 163951(Me.Work.Comp.Com) (1988), citing *Normand v. Baxter State Park Authority*, 509 A.2d 640, 647 (Me. 1986).
[11] *Central Maine Power Company v. Public Utilities Commission*, 458 A. 2d 739, 741 (Me. 1983).
[12] *Joyce v. Webber*, 170 A. 2d 705, 708 (Me. 1961), citing *McKenney v. Farnsworth*, 118 A. 237, 238 9Me. 1922).
[13] See section IV, discussion of the specific nature and complexity of the tasks that would be involved in compliance, and assessment of time and resources that would be involved.
[14] See, *Kroeger v. Department of Environmental Protection*, 870 A.2d 566, 2005 ME 50, citing *Cent. Me Power Co. v. Waterville Urban Renewal Auth*., 281 A.2d 233 (Me 1971).
[15] Proposed Rule: Department of Health and Human Services, 10-144, Chapter 275-Reporting Requirements for Pharmaceutical Manufacturers and Labelers and Office of the Attorney General, 26-239, Chapter 111-Reporting Requirements for Pharmaceutical Manufacturers and Labelers (June 9, 2009) (proposed §1.01)(emphasis added).
[16] Many physicians and surgeons work long, irregular hours; more than one-third of full-time physicians worked 60 hours or more a week in 2006. http://www.bls.gov/oco/ocos074.htm (United States Department of Labor, Occupational Outlook Handbook, 2008-09 Edition); See also http://www.soft32.com/download_159919.html.

safety, patient populations, etc); rather, the physician would read the labeling, *i.e.*, the package insert intended for doctors, that is continually updated to include clinical trial results and has the benefit of review by FDA experts.

Maine's law and regulations only apply to drugs and biologicals that have been approved by FDA and are dispensed, administered, delivered or promoted in Maine, *i.e.*, drugs that are approved and marketed.[17] Unlike the clinical trials registry requirement established by FDAAA and implemented by NIH, the Maine law is not directed at presenting information regarding clinical trials for the purpose of subject recruitment and enrollment (nor does it need to be – the NIH site covers this nationally). Rather, it is directed to marketed drugs, for which initial clinical trials will have been completed. While information from post-market trials may provide some use to prescribing physicians, the key information from pre-approval clinical trials will have already been incorporated into drug labeling for the purpose of providing physicians the information that is necessary and most useful in providing patient care. Accordingly, posting of the additional clinical trial information required by the proposed regulation is unlikely to provide a meaningful benefit, if it is utilized by physicians at all.

Additionally, the proposed expanded requirements may not provide a meaningful benefit for patients. It is likely that most patients would not be trained to read the type of highly clinical information that would be posted on the web site and, therefore, much of the safety information may not be understandable to that population.

In addition to these concerns regarding the expansiveness and questionable utility of the highly detailed, technical clinical trial registry data, we note several inconsistencies between the proposed regulation and the authorizing statute:

- Clinical trial definition: The proposed regulation defines "clinical trial" more broadly than the statute. While the current Maine regulation is consistent with FDA regulations that define "clinical trial" as a hypothesis-testing investigation intended to test safety or effectiveness of a drug or biologic in human subjects, for submission to, or inspection by FDA, the proposed regulation would add "observational (non-interventional)" studies.[18] This exceeds the statutory authority. Further, it presents practical concerns because the terms "observational (non-interventional)" are unclear. For example, it is not clear whether the phrase "observational (non-interventional)" refers to studies in which there are no specific study-mandated interventions, or no interventions at all. It is also not clear whether the regulation would cover retrospective analyses of existing data sets or patient records.
- Website for posting: Maine's statute provides that manufacturers shall post the required information on the publicly accessible website of NIH "or another publicly accessible website." The proposed regulations are at odds with this statutory mandate in that only postings on the NIH website would be considered compliant. While we understand that notices issued by Maine in the fall of 2008 also stated that only posting on the NIH

[17] 5 M.R.S.A. §2698-A; Proposed Rule at §1.01.
[18] Proposed Rule at §1.02-2.

website would be acceptable,[19] we remain concerned that narrowing this option is not authorized by the Maine law. Further, this proposed change presents considerable practical concerns because while some of the newly requested information in the proposed rule is publicly available on alternate websites, it will be enormously time-consuming and resource-intensive to identify, reanalyze, reformat, re-post and/or supplement the information on the NIH website. This substantial undertaking is not only unauthorized by Maine's law, but provides minimal extra benefit to patients in that it is unlikely that there would be much utility to moving the information from one publicly accessible website to another.

B. ISSUANCE OF THE PROPOSED REGULATIONS IS NOT SUPPORTED BY THE MAINE UNFAIR TRADE PRACTICES ACT

In addition to reliance on the specific clinical disclosure statutory provision,[20] the proposed regulations state that a separate basis for their adoption is the Maine Unfair Trade Practices (UTP) Act.[21] The state cannot, however, derive any support for promulgation of the requirements for information disclosure set out in the proposed regulations from the UTP Act or the Federal Trade Commission (FTC) Act,[22] on which the UTP Act is modeled and the interpretation of which is followed as a matter of law by the state.[23] The state cannot simply refer to the broad prohibition of unfair trade practices set out in section 207 (2).[24] Rather, those standards developed by the judicial decisions of Maine under the UTP Act, and by federal courts and the FTC under the FTC Act, must be applied in determining whether a practice or omission constitutes a violation of the UTP Act.

The Maine Supreme Court has adopted the three-factor analysis of whether a practice or omission is unfair that is set out in the FTC Amendments Act of 1994.[25] This analysis codifies the analytical approach followed by the FTC since issuance of its original Unfairness Policy Statement in 1980.[26] The Maine Supreme Court has stated that, in determining whether an act is unfair under the UTP Act, "the act or practice: (1) must cause, or be likely to cause, substantial injury to consumers; (2) that is not reasonably avoidable by consumers; and (3) that is not outweighed by any countervailing benefits to consumers or competition."[27]

As noted in these comments, the information required to be disclosed under the proposed regulations is extremely detailed, technical scientific information that would likely not be useful to patients or consumers. Further, the requirements would relate only to those drugs and

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[19] See September 15, 2008 letter to manufacturers from Trish Riley, Director, Governor's Office of Health Policy and Finance, and October 24, 2008 "Advisory Re Clinical Trial Drug Reporting".
[20] 22 M.R.S.A. § 2700-A.3.
[21] 5 M.R.S.A. § 207 (2).
[22] 5 U.S.C. § 45 (a).
[23] 5 M.R.S.A. § 207 (1).
[24] 5 M.R.S.A. § 207 (2).
[25] 15 U.S.C. § 45 (n).
[26] 4 Trade Reg. Rep. (CCH) Para. 13, 203.
[27] *State v. Weinshenk*, 868 A.2d 200, 2006 (Me. 2005); *Tungate v. MacLean-Stevens Studios, Inc.*, 714 A.2d 792, 797 (Me. 1998); *Bangor Publishing Co. v. Union St. Market*, 706 A.2d 595, 597 (Me. 1998).

biologicals that are already marketed in Maine, that is, those approved by the FDA. The unavailability of information in the additional categories for disclosure incorporated in the proposed regulations, such as recruitment status of clinical trials, investigative techniques, trial participant eligibility, and the like, cannot reasonably be concluded to "cause, or be likely to cause, substantial injury to consumers," as required by the Maine Supreme Court's interpretation of the standards for application of the UTP Act. Neither can the adverse consequences and burden of supplying such additional information, as set out above in these comments, reasonably be concluded to be "outweighed by any countervailing benefits to consumers or competition," particularly since the "benefits" of this additional information are non-existent for consumers or competition. Indeed, the Maine Supreme Court has clearly stated that the substantial injury to consumer's requirement for application of the UTP Act is designed to exclude "trivial or merely speculative harms."[28]

It could not be more clear that the "harms" for which disclosure of the additional items assertively address is "merely speculative" at best, and properly should be considered non-existent, since the drugs and biologicals have been approved by FDA and because those prescribing the drugs or biologicals, the patients'/consumers' physicians, have access to and can understand all of the information required to be disclosed by FDA for such products.

The proposed regulations also cannot be supported by reference to the deception aspect of the UTP Act. Here also, the Maine Supreme Court has followed the FTC's approach, adopted in its Deception Policy Statement of 1983.[29] The Maine Supreme Court has stated that "an act or practice is deceptive if it is a material representation, omission, act, or practice that is likely to mislead consumers acting reasonably under the circumstances."[30] The Court further stated that, to be material for a consumer, the representation or omission must involve "information that is important to consumers and, hence, likely to affect their choice of, or conduct regarding, a product."[31] There can be no credible argument that the unavailability of information regarding the additional items set out in the proposed regulations to patients/consumers is "likely to mislead" them about the safety or efficacy of an approved drug or biological, or that the information could be considered remotely likely "to affect their choice of" a drug or biological, particularly where that choice is subject to selection and prescription by their attending physicians.

Consequently, the state can derive no authority whatsoever in support of promulgation of the proposed regulations from the Maine UTP Act.

III. THE PROPOSED REGULATION IS NOT CONSISTENT OR COMPATIBLE WITH FEDERAL REQUIREMENTS

The Notice states in the "Concise Summary" that the rulemaking is compatible with federal reporting requirements and with the reporting capabilities of the publicly funded website,

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[28] *Tungate*, 714 A.2d at 797.
[29] 4 Trade Reg. Rep. Para. 13, 205.
[30] *State v. Weinshenk*, 868 A.2d 200, 206 (2005).
[31] *Id.*

ClinicalTrials.gov. BIO applauds Maine for seeking to achieve compatible requirements. Universally, efforts should properly be directed to establishing a system that uses both private and government resources efficiently to achieve the goal of providing accessible, useful information to enhance medical care. However, we are extremely concerned that the proposed Maine requirements will not achieve this goal, and may, in fact be obstructive.

A. PURPOSE AND TYPES OF POSTED INFORMATION

Maine was proactive in establishing a statutory clinical trial reporting requirement prior to federal enactment of FDAAA, and now is wisely seeking to harmonize the state requirements with the federal reporting requirements under FDAAA. As discussed above, the proposed Maine regulation lists 26 categories of data, A through Z, many with sub-categories listed. While some of these categories are consistent with the FDAAA requirements, many are not. If compatibility with the FDAAA requirements is the goal, the categories of information in the proposed regulations that are not reflected in the FDAAA requirements should be eliminated. Requiring manufacturers to submit this enormous amount of information will not only place an extreme burden on manufacturers, it will unreasonably burden federal resources that are intended to be dedicated to implementing FDAAA – not to the implementation of additional state requirements. It is not clear that Maine has the authority to dictate this policy to NIH, putting NIH in the position of accepting additional work to satisfy requirements imposed by Maine. For example, the clinical trial reporting requirements implemented by NIH are triggered post-enactment of FDAAA (September 27, 2007), while the Maine requirements seek to include information that is post October, 2002.

BIO understands that the implementation of the clinical trials provisions of FDAAA has required a tremendous amount of effort by NIH. Any diversion of these federal resources would result in the undermining of the purpose and intentions of FDAAA, and obstruct the ability to maintain the information required to be posted on the publicly funded website, as required by federal law. In this case, it does not appear that the exertion of those resources would result in any benefit to patients or physicians in Maine, or elsewhere.

Specific categories of information that are inconsistent with FDAAA and present significant difficulties are:

- Phase 1 studies: FDAAA specifically excludes phase 1 studies from applicable drug clinical trials for purposes of registry and results reporting.[32] There is no specific language in the proposed regulation excluding phase 1 studies.

- Observational studies: FDAAA applies only to controlled clinical investigations.[33] While some observational studies are controlled, not all are. Additionally, as noted above, the inclusion by Maine of observational studies is problematic because it is vague and potentially very broad. The terms "observational" and "non-interventional" are used in several different ways. For example, sometimes the phrase "observational" is used to

[32] 42 U.S.C. § 282(j)(1)(A)(iii)(I).
[33] *Id.*

refer to studies in which there are no specific study-mandated interventions, and sometimes it is used to refer to studies in which there are no interventions at all. The term "interventional" is sometimes used to refer to clinical trials involving "interventions" such as treatments or tests administered to patients, and sometimes used to refer to clinical trials involving a methodology such as prospective randomization.

- Post-hoc analyses: FDAAA does not currently require the submission of post-hoc analyses. It does provide that a future regulation – to be promulgated by September 27, 2010 – shall address "the appropriate timing and requirements for updates of clinical trial information."[34] Accordingly, it is not yet known what update requirements will be established. BIO is concerned about the difficulties of complying with a requirement that appears to be extremely broad and unclear, and may exceed the technical capabilities provided by ClinicalTrials.gov for the entry of basic results.[35] Post-hoc analyses generally involve multiple studies and new research questions, and may not be relevant to the posted results of single studies with predefined endpoints. Further, to the extent that post-hoc analysis may include scientific conclusions, the inclusion of such information could raise promotional concerns.

These and other categories of information that are inconsistent with the FDAAA requirements are set forth in detail in the attached chart, with recommended changes to the proposed regulations.

B. TIMING AND RETROACTIVITY

The Maine statute authorizes the collection of clinical trial information for trials conducted or sponsored on or after October 15, 2002.[36] Manufacturers have included information regarding such trials as they posted information in efforts to meet the current regulations that became effective on March 1, 2007. To meet the provisions of the Maine Advisories issued in 2008 – which stated that www.clinicaltrials.gov was the one acceptable website for posting – manufacturers then proceeded to post information on that site (rather than other publicly accessible websites) to meet the terms stated in the advisories. Now, over two years after the initial rulemaking, Maine is proposing to require the posting of a significant amount of additional information regarding these same, previously disclosed and posted trials. Given that manufacturers have already dedicated significant effort to meet the current regulatory requirements, this change in policy appears arbitrary. Further, this is clearly not in the interest of compatibility with the capabilities of the publicly funded website, which is the stated purpose of the proposed regulations. While FDAAA requires the posting of clinical trials and results that were ongoing or initiated 90 days after enactment, *i.e.*, December 27, 2007,[37] the Maine law requires posting of trial information for the preceding five years, *i.e.*, trials conducted on or after

[34] 42 U.S.C. § 282(j)(3)(D)(v)(IV).
[35] For example, ClinicalTrials.gov limits the amount of text that can be entered into particular fields to 250 characters, which may be insufficient for the purpose of entering certain information responsive to Maine's proposed rule.
[36] 22 M.R.S.A. § 2700-A.3.
[37] 42 U.S.C. § 282(j)(2)(C) and (j)(3)(E).

October 15, 2002.[38] While the Maine provision is already inconsistent with FDAAA, an expansion of the requirements via the proposed rulemaking will exacerbate the impact of this inconsistency by requiring a massive retrospective analysis. The proposal threatens not only to place a major burden on manufacturers – especially small manufacturers without resources to spare – it will undoubtedly impact the ability of NIH to carry out its mission of FDAAA implementation.

FDAAA provides that the Director of NIH shall ensure that clinical trial information submitted to meet disclosure requirements is posted within 30 days.[39] It appears that, given the volume of data to review and post, the agency may not be able to meet that statutory deadline. NIH recently reported that 678 results records have been submitted to ClinicalTrials.gov.[40] Yet, as of July 2, 2009, ClinicalTrials.gov shows that only approximately half of those – 339 results records – have been posted. Further, the rate of submission continues to increase; NIH is receiving 40 new records per week and anticipates this increasing to 160 per week.[41] There currently is a significant backlog of results that are either undergoing the NIH quality control review process or are in queue to do so.[42] Further, additional FDAAA requirements to be triggered in September 2009 will add to this workload.[43] By adding new requirements for manufacturers – information that must then be reviewed for quality control to ensure completeness and content of information, and that the information is not false or misleading and is not promotional[44] – Maine would be adding an exorbitant amount of work to be conducted by an already busy federal agency. This new information required by the Maine proposal is not required by federal law, yet it would divert agency resources that could be used to further the goals of FDAAA (and that reflect the goals of the Maine law). In short, Maine's proposal could frustrate the goals of posting the information that is required by federal law in a timely manner, and obstruct the ability to further implement pending provisions of FDAAA.

C. PREEMPTION

FDAAA instructs the Secretary of the Department of Health and Human Services (DHHS) to promulgate regulations to expand the federal registry and results data bank by September 27, 2010.[45] FDA and NIH have been seeking public comment on how best to implement these regulations, in which they intend to clarify current provisions of FDAAA as well as implement future requirements.[46]

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[38] 22 M.R.S.A. § 2700-A.3.
[39] 42 U.S.C. § 282(j)(2)(D)(i).
[40] Presentation by Deborah Zarin, Director of ClinicalTrials.gov, National Library of Medicine, NIH; Public Meeting on Expansion of ClinicalTrials.gov website (April 20, 2009).
[41] *Id.*
[42] *Id.*
[43] 42 U.S.C. § 282(j)(3) requires that regulations be enacted regarding posting of adverse events and regarding expansion of the FDAAA results databank, requirements that will involve considerable effort by NIH. The adverse events requirements in FDAAA go into effect on September 27, 2009; a rule addressing the remaining expanded provisions is to be finalized on September 27, 2010. 42 U.S.C. § 282(j)(3)(D) and (I).
[44] 42 U.S.C. §282(j)(3)(D)(v)(III).
[45] 42 U.S.C. § 282 (j)(3)(D).
[46] Pursuant to FDAAA requirements, NIH held a public meeting on April 20, 2009; public comments were accepted through June 22, 2009.

FDAAA further provides that upon expansion of the registry and results data bank, "no State or political subdivision of a State may establish *or continue in effect* any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database."[47] Therefore, after the federal implementing regulations are promulgated, any requirements established by the State of Maine for posting clinical trial information will be preempted. Maine's proposed regulations are exactly the type of state requirements that will be expressly preempted by the federal clinical trial disclosure requirements – requirements intended to establish a national, uniform system for the purpose of clinical trial transparency and to benefit public health.

Accordingly, upon expansion of the federal registry, the Maine regulations would be preempted, and despite the enormous burden required to comply with the proposed regulations, they would only be effective for an extremely short period of time. The proposed expansion would burden research-intensive biotechnology companies and impose on federal resources. No benefit of this additional information has been expressed or identified. After the short window during which the Maine regulations would be effective, in order to comply with FDAAA, Maine would presumably be required to withdraw the proposed regulations. Given the significant burden involved in complying with the proposed regulations and the extremely short time frame during which the rules would be effective, BIO respectfully suggests that the implementation of these rules would be wasteful of state and industry resources, and of no benefit to the public.

If the proposed expansion is adopted, it will create confusion and raise significant questions. For example, it is unclear what will happen to the information required to be posted once federal preemption is triggered. Once Maine is no longer permitted to continue these requirements, it will need to be determined whether the posted information would then need to be eliminated from the federally-funded website; what system would be employed to assure that information posted for the purpose of the short-term Maine requirements is updated and accurate; and whether federal and private resources would then need to be used to update posted information. Additionally, it will require addressing what quality assurance methods, if any, will be used for reviewing the information required by Maine that is outside the scope of the FDAAA requirements. FDAAA requires that regulations be adopted to address procedures for quality control to assure that required content is complete, not false or misleading, and non-promotional.[48] These additional procedures will not be adopted until after the time that the Maine law is preempted, so it is not clear how will there be any assurance or uniformity of quality of the information submitted to satisfy Maine's proposed requirements. These are significant questions that warrant review to assure that any new requirements are consistent with protection of the public health.

IV. THE PROPOSED REGULATION IS EXTREMELY BURDENSOME, AND MAY BE IMPOSSIBLE TO COMPLY WITH IN THE TIMEFRAME PROVIDED

[47] U.S. Public Law 110-85, Title VIII, § 801(d)(1) (emphasis added).
[48] 42 U.S.C. § 282(j)(3)(D)(v)(iii); to be adopted by September 27, 2010.

As discussed throughout these comments, and set forth in detail in the attached chart, the proposed regulations would constitute an extraordinary burden on those involved. We respectfully disagree with the statement in the "Concise Summary" of the proposed regulations that "[t]he rule change is not anticipated to have any adverse impact on small business."[49] The attached chart provides a section-by-section analysis of the proposed regulations, BIO's issues/concerns, and proposed changes. While, as discussed above, BIO believes that the proposed regulations raise significant legal and policy concerns, we also want to suggest mechanisms that might improve feasibility.

Conservatively, we estimate that it would take 40 hours per clinical trial to seek to comply with the proposed regulations. We believe that the number of hours could be considerably greater for older trials. Furthermore, many companies have numerous trials that would need to be posted or updated. One BIO member (a large biotechnology company) estimated the types and amount of work that would be involved, as follows:

- Clarify which studies are within the proposed regulations (60 days)
- Locate the study report and dataset (1-2 weeks per study)
- Re- analyze data from the International Conference on Harmonisation's (ICH's) E3 summary format[50] into the tabular ClinicalTrial.gov format, and review the data for quality control (30 days per study)
- Populate and approve ClinicalTrials.gov tables (30 days per study)
- Obtain NIH high level comments (30 days per study)
- Respond to NIH high level comments & re-enter (30 days per study)
- Obtain NIH detailed comments (30 days per study)
- Respond to NIH detailed comments & re-enter (30 days per study)

BIO has engaged a consulting firm to quantify and assess the amount of resources necessary to: (1) replace the study synopses that currently exist on ClinicalStudyResults.org (http://www.clinicalstudyresults.org/);[51] (2) quantify and assess the resources necessary to update information already posted on or submitted to clinical trials.gov with the additional categories of information proposed by Maine; and (3) estimate the additional burden on NIH.[52] The initial results of this assessment are as follows:

- Estimate for Reposting Study Results on ClinicalTrials.gov for Industry

  The number of studies on ClinicalStudyResults.org was used as the base to construct a model for the effort to post results on ClinicalTrials.gov of phase 2-4 covered clinical trials to comply with the proposed Maine regulation. The model

[49] Proposed Rule; "concise summary" (June 9, 2009).
[50] ICH E3 is currently available at http://www.ich.org/LOB/media/MEDIA479.pdf.
[51] ClinicalStudyResults.org is a database developed by the Pharmaceutical Research & Manufacturers of America (PhRMA) to compile clinical trial results voluntarily submitted by pharmaceutical and biotechnology manufacturers, since 2002. The information is in a different format from the information on ClinicalTrials.gov, so it would have to be reformatted with new categories of information that would be required by Maine and would have to be identified, analyzed, and entered.
[52] Report produced by Pat Teden, Teden Consulting LLC, South Orange, NJ. (July 10, 2009).

subtracts from the total any studies on ClinicalStudyResults.org that would not fall under the Maine law, such as trials started prior to October 15, 2002, and trials for products not yet approved in the U.S. Phase 1 trials were not included in the analysis. The model also accommodates the addition of relevant trials sponsored by pharmaceutical and biotechnology companies that chose to post their study results on sites other than the PhRMA website (usually a corporate website).

A conservative estimate of total studies that would need study results reformatted and entered into ClinicalTrials.gov was 2,795 studies (35% of the approximately 8,000 studies on ClinicalStudyResults.org). 40 hours of work by sponsors per study was used as an effort estimate (again, this is an estimate that we believe to be a conservative one). With those two assumptions, approximately 112,000 hours of sponsor effort will be required. Assuming labor costs of $100/hour, costs for this work would exceed $11 million. One hundred thirty (130) dedicated full-time equivalent staff will be needed to perform the work within 180 days.

- Estimates for Industry Updating of Study Registration Records on ClinicalTrials.gov

  Using the same assumptions as above, the estimates for updating study registration records for Maine covered clinical trials are that approximately 3,900 study registration records would require updating at a total cost of $1.9 million.

- Estimate for Reposting Study Results on ClinicalTrials.gov for NIH's National Library of Medicine (NLM)

  There is justifiable concern about NLM's ability to absorb an *additional* 2,800 studies in the short term due to the proposed Maine regulation. In the ten months that ClinicalTrials.gov study results capabilities have been available, approximately 1,000 study results have been submitted and 366 study results have been published as of July 8, 2009. The estimate shows the NLM throughput capacity to review and publish studies is about 14 studies a week, and the current submission rate is 40 studies/week. NLM would need to address that gap in the short-term, plus build capability to handle 150 studies/week, which is the NLM estimate of steady state.[53] That represents a 10-fold increase in throughput, which is a significant challenge without the additional proposed new requirements from Maine.

Given the tremendous burden involved and extremely limited benefit accrued in implementing the Maine requirements, BIO again emphasizes that the proposed requirements should be reconsidered in terms of the facts and circumstances. BIO's members are extremely concerned about their ability to meet such requirements, especially in the time frame provided. The proposed Maine regulations state that the manufacturer or labeler shall have 120 days after

[53] Presentation given by Rebecca J. Williams, Pharm.D., MPH, ClinicalTrials.gov, on June 22, 2009 during a Clinical and Translational Science Awards (CTSA) workshop.

adoption of revisions to these rules to post or re-post information necessary to comply with the revisions, or 180 days to re-post information posted prior to December 8, 2008 on a publicly available website other than ClinicalTrials.gov.[54] For retrospective trials this would be a huge hardship in terms of resources required, and impossible to achieve within this time frame. For example, older trials that were posted on ClinicalTrials.gov and ClinicalStudyResults.org were formatted in compliance with ICH E3 guidelines, which require summaries of efficacy results and safety evaluation. Given that these summaries are not compatible with the data fields on ClinicalTrials.gov, it would involve considerable time and effort to reanalyze and rewrite the information. The ClinicalTrials.gov format and the proposed Maine regulations both differ from the standard industry practice. Accordingly, the proposed rule would require reanalysis of every study; a huge, difficult, and time-consuming undertaking, especially for older studies where it is difficult to find experts with both knowledge of the study and the skills to reanalyze the data. Manufacturers are already encumbered by seeking to comply with the existing Maine and FDAAA requirements; these additional proposed requirements may adversely impact those efforts as well.

In light of this extreme burden that would be presented by the proposed regulations, BIO respectfully requests that Maine reconsider the adoption of this proposal with these facts in mind. Alternatively, BIO believes that Maine's goals could potentially be achieved through more targeted requirements.

First, if the additional requirements in the proposed regulations were to apply only prospectively, the burden on manufacturers and NIH — the hundreds of thousands of hours and millions of dollars, as set forth in the previous section — would be significantly reduced.

Second, the proposed regulations refer to manufacturers reporting to the Department in regard to clinical trial results posted on other publicly available websites, "so that the Department may create linkages to such websites."[55] BIO requests that the Department clarify how this provision interacts with other proposed provisions that state that information should be re-posted.[56] Further, we propose that Maine accept information regarding the existence of information on other websites, for the purpose of linking, as meeting the proposed requirements.

Finally, even assuming Maine's proposed expanded requirements could be sustained as lawful under the authorizing legislation, an additional amount of time will be necessary for compliance. Based upon the previous discussion of the time and resource burden that implementation of the proposed regulations would impose, BIO recommends that manufacturers should have 12 months at a minimum after the adoption of revisions to these rules to post or re-post information necessary to comply with the proposed regulations.

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[54] Proposed Rule at §1.04-2 (B).
[55] *Id.* at § 1.05-2.
[56] *Id.* at § 1.04-2(A)(iii).

V. CONCLUSION

BIO appreciates this opportunity to comment on the proposed rule "Reporting Requirements for Pharmaceutical Manufacturers and Labelers." We would be pleased to provide further input or clarification of our comments, as needed. We respectfully request the opportunity to meet with you to discuss these issues, alternative solutions, or ways to make this effort feasible, and we will contact you shortly in this regard.

Sincerely,

/S/

Sandra J.P. Dennis
Deputy General Counsel for Healthcare
Biotechnology Industry Organization

/S/

Katherine McCarthy
Director, Science & Regulatory Affairs
Biotechnology Industry Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. DEFINITIONS		
1.02-2	The term observational is vague and broad. We suggest clarifying the definition of observational studies. Furthermore, we recommend deleting the following wording because it is too vague and impossible to ensure effectively: "… and any investigation relied upon by a manufacturer or labeler for claims made in marketing, promotional or educational efforts or materials to prescribers or consumers …" For example, results of studies in Asia might be provided to prescribers in the US (or a US territory) upon request from physicians for Asian data. In a large company, it is virtually impossible to know which studies might be cited, or when.	If Maine's intent is to report on the follow up of patients from interventional trials after they stop (or take open-label) study medication, BIO suggests the language be revised as follows (new language indicated by underline and deleted language indicated by strikethrough): "(2) any post-marketing clinical investigation by the manufacturer or labeler on the safety or efficacy of an FDA-approved prescription drug or biological product, including investigations of off-label uses, observational safety and/or effectiveness studies involving subsequent follow-up of patients from interventional trials after they stop the study medication or take open-label medication ~~(non)interventional) studies and any investigation relied upon by a manufacturer or labeler for claims made in marketing, promotional or educational efforts or materials to prescribers or consumers~~; and (3) any study testing the bioequivalency of a drug against the innovator drug or biological product, or against another drug or biological product.
1.02-2	Section 12.3(b) of Title 21 should be 312.3(b).	
II. TRIAL REGISTRY DATA		
1.03-1-B	"Acronym or initials" are not required by US Public Law 110-85, Section 801, or by	We suggest deleting the language indicated by strikethrough; "The protocol title intended for the lay public~~, and any acronym~~

SECTION	ISSUE	PROPOSED CHANGE
	clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html). To require them places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health.	~~or intials used to identify the study;~~"
1.03-1-B	*Initials* is misspelled in the proposed language.	
1.03-1-H	This field is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html). This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health beyond that provided by the short description of the protocol	We suggest deleting the words indicated by strikethrough, "~~An extended description of the protocol~~;"
1.03-1-J	This field is not consistent with the Maine law. This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health. Further, the field for information regarding status may be too limited in size to permit adequate brief explanation of the reasons for suspension, termination, or withdrawal.	We suggest deleting the words indicated by strikethrough, "~~The overall recruitment status, and if the investigation was suspended, terminated or withdrawn, a brief explanation of the reason(s)~~;"
1.03-1-K	This information is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html). This places new regulatory burden on manufacturers without providing additional	We suggest deleting the language indicated by strikethrough; "The date of the start of enrollment to the protocol; the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome; ~~and the final date on which data was collected, or expected to be collected;~~"

SECTION	ISSUE	PROPOSED CHANGE
	assurance of patient safety or public health.	
1.03-1-M-6	This field is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html). This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health.	We suggest deleting the words indicated by strikethrough, "~~The classification of the investigation, i.e., the type of primary outcome or endpoint for evaluation; and.~~"
103-1-N-2	This field is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html). This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health.	We suggest deleting the words indicated by strikethrough, "~~The biospecimen retention policy, including information on all types of biospecimens retained.~~"
1.03-1-O	This field is not required by US Public Law 110-85, Section 801 for retrospective studies. This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health.	We suggest deleting the words indicated by strikethrough, "~~The primary outcome measure, including the specific measure used to determine effect, the time frame by which the measure is assessed, and whether the measure is a safety issue.~~"
1.03-1-P	This field is not required by US Public Law 110-85, Section 801 for retrospective studies. In addition, clinicaltrials.gov only requires key secondary outcomes. The requirement to include "all secondary outcome measures" places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health. Please note that there	We suggest deleting the words indicated by strikethrough, "~~All secondary outcome measures, including the specific measure used to determine effect, the time frame by which the measure is assessed, and whether the measure is a safety issue.~~"

SECTION	ISSUE	PROPOSED CHANGE
	can be on the order of 20 secondary outcome measures, many of which are of an exploratory nature and which thus provide limited -- if any -- information relevant to use of the product being studied in a clinical trial.	
1.03-1-Q	This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health. Further, it is inconsistent with the Maine law.	We suggest deleting this section: "~~Arms, groups and interventions, including: 1. For interventional studies, for each arm: (a) The short name used to identify the arm; (b) The arm type; (c) A brief description of the arm; 2. For observational studies: (a) All predefined participant groups; (b) The short name to identify each participant group; (c) An explanation of the nature of the study or participant group.~~"
1.03-1-R	This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health. Further, it is inconsistent with the purpose of the Maine law.	We suggest deleting this section: "~~The type of intervention, a brief descriptive name of the type of intervention, a description giving key details of the intervention, identification of which arms or groups designated for the intervention, and any other names used to identify the intervention~~;"
1.03-1-S	This information is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html). This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health.	We suggest deleting: the words indicated by strikethrough, "The primary disease or condition being studied, or the focus of the investigation, ~~and key words or phrases that best describe the protocol;~~"
1.03-1-W	This field is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see	We suggest deleting the words indicated by strikethrough, "~~Contact information for the facility, by either phone or email, and for a central contact person and second contact person.~~"

SECTION	ISSUE	PROPOSED CHANGE
	http://prsinfo.clinicaltrials.gov/definitions.html). This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health.	
1.03-1-X	This field is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html). This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health. Note also that for older trials, "the principal investigator and other persons responsible for overall scientific leadership of the protocol" may have changed their place of employment and therefore may no longer be appropriate points of contact for information regarding a trial.	We suggest deleting the words indicated by strikethrough, "~~The names, degrees, roles and affiliations of the principal investigator and other persons responsible for overall scientific leadership of the protocol;~~"
1.03-1-Y	This field is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html). This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health.	We suggest deleting the words indicated by strikethrough, "~~Citations to publications related to the protocol, by the PubMed Identifier or full bibliographic citation, indicating also whether the reference provided reports on results from the investigation at hand;~~"
1.03-1-Z	This field is not required by US Public Law 110-85, Section 801, or by clinicaltrials.gov (please see http://prsinfo.clinicaltrials.gov/definitions.html).	We suggest deleting the words indicated by strikethrough, "~~Z. The following links: 1. Any link directly relevant to the protocol; and 2. Once available, a link or links to a publicly accessible website containing FDA-approved labeling information, and information~~

SECTION	ISSUE	PROPOSED CHANGE
	This places a new regulatory burden on manufacturers with no clear benefit to patient safety or public health.	~~of a Class 1 or Class II recall, of a market alert by the FDA; and 3. Once available, a link or links to any applicable medical product safety alert by the FDA.~~"
III. TRIAL RESULTS DATA		
1.03-2	"Optional" data elements should continue to be optional.	We suggest the revised language, "The manufacturer or labeler shall complete all of the following reporting categories: Results Point of Contact, Certain Agreements, Participant Flow, Baseline Characteristics, Outcome Measures, and Adverse Events. All mandatory data elements ~~and all other relevant ("optional") data elements~~ must be completed (provided the data are available) ~~for the optional data element)~~."
1.03-2	The Secretary of the U.S. Department of Health and Human Services is charged with making a decision about reporting of adverse event (AE) data by Sept 2009. We recommend clarification that Maine's requirements for posting adverse event data will not take effect prior to the federal requirements taking effect. Furthermore, a threshold of 5% is not standard, and this criterion would create an enormous burden for companies. It is extremely difficult and time-consuming to go back and locate data from studies completed years ago to reanalyze them simply to satisfy an arbitrary threshold. Please note also that sometimes the databases exist in older systems and it is difficult to find staff who are familiar with them.	We recommend deleting the words indicated by strikethrough: "… ~~For purposes of completing the Adverse Events reporting module, if no threshold is specifically required on the publicly funded website for the reporting of "other" adverse events, a threshold of five (5) percent is required.~~" We recommend replacing the words deleted above with the following (new language indicated by underline): <u>Adverse event reporting requirements will not take effect prior to the time at which requirements under 42 USC 282 (j)(3)(I) "Adverse Events" take effect</u>.

SECTION	ISSUE	PROPOSED CHANGE
1.03-2	The language regarding clarity and precision is vague and impossible to ensure.	We suggest deleting the words indicated by strikethrough; "Data submissions for posting to the publicly funded Internet website must be valid, internally consistent, logical and meaningful. ~~The resulting tables must be clear and precise, so that the full range of readers reasonably can be expected to understand the information.~~"
IV. SUBMISSION SCHEDULE		
1.04-1-A (2)	The proposed language requiring posting 21 days after patient enrollment has begun only appears to apply to completed or discontinued trials. Therefore, Subsection (2) is impossible to achieve for completed or discontinued trials.	We suggest that this requirement be removed.
1.04-1-B	The 120 day timeframe for posting or reporting of information would be a huge hardship in terms of resources required, and impossible to achieve. BIO member companies estimate that it would take approximately 8 1/2 months (at a minimum) to post the retrospective trial data on ClinicalTrials.gov. In addition, to meet the demands of the retrospective analysis, BIO members would need to reallocate existing resources from current planned submissions and projects to the retrospective analysis or hire several additional medical writers, statisticians, and data entry administrators, at a minimum. Please note also that is difficult to find and recruit knowledgeable people to perform these activities. One BIO member company reports that it has up to 300 clinical trials with results already posted at the PhRMA site and it would be virtually impossible to recruit the necessary staff and perform the activities below simultaneously for all of these studies in order to meet Maine's timelines. If observational studies are included the number might be much higher, depending on the definition of observational. Therefore, BIO recommends a 12 month timeframe at a minimum. Even that may not be achievable if manufacturers have to go back to 2002, and/or if observational studies are included.	

SECTION	ISSUE	PROPOSED CHANGE

Step	Resources	Time Estimate
1. Clarify which studies are within the proposed regulations	Compliance, legal, regulatory affairs	60 days
2. Locate the study report and datasets	medical writer (study report), statisticians and programming (datasets)	1-2 weeks per study (older studies/datasets might need to be retrieved from off-site archives)
3. Re-analyze data from ICH E3 format into the tabular ClinicalTrial.gov format and review the data for quality control	statisticians and programming	30 days per study (would need to produce ClinicalTrials.gov's non-serious adverse event tables, as well as redo some efficacy analysis due to ClinicalTrials.gov restrictions; will need time for the team to (re-)familiarize themselves with study conduct, data collection, statistical analysis plan, etc.
4. Populate and approve ClinicalTrials.gov tables	Medical writer, statisticians, regulatory affairs, clinical research, pharmacovigilance, and compliance	30 days per study
5. NIH high level comments	NIH	30 days per study
6. Respond to NIH high level comments & re-enter	Medical writer, statisticians, regulatory affairs, clinical research, pharmacovigilance, and compliance	30 days per study
7. Obtain NIH detailed comments	NIH	30 days per study
8. Respond to NIH detailed comments & re-enter	Medical writer, statisticians, regulatory affairs, clinical research, pharmacovigilance; and compliance	30 days per study
9. Study results released publicly		

SECTION	ISSUE	PROPOSED CHANGE
1.04-2-A iii	Making the posting of results retroactive places a significant burden on manufacturers with no clear benefit to patient safety or public health.	We suggest that this requirement be removed.
1.04-D	When an extension of time for good cause is granted by NIH, this information does not appear in ClinicalTrials.gov.	Please clarify whether Maine must be notified of an extension for good cause, and how.
1.04-2-E & F	Requiring post hoc analysis reaches beyond the statutory authority of Maine Law.	We suggest this requirement be removed.