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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on Proposed Regulations Implementing Section 401 of FDAMA

Dear Commissioner Michael Friedman:

I am writing on behalf of Eli Lilly and Company ("Lilly") to offer comments on proposed regulations published by the Food and Drug Administration ("FDA") at 63 Fed. Reg. 31143 (June 8, 1998). When adopted, the proposed regulations will implement section 401 of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"). Section 401 permits the dissemination of information on unapproved uses for marketed drugs, biologics and devices in certain situations.

As an initial matter, Lilly understands and appreciates the significant time pressures that the FDA has been and continues to work under in order to comply with Congress' directive to implement section 401 by the one-year anniversary of the legislation. The FDA has worked quite diligently in crafting this proposal in the short time available. Moreover, FDA has done a good job of tracking the statute quite closely in several instances where the precise wording of the statute is important. For example, FDA has carefully followed the statute to explain that it is only "clinical research conducted by another manufacturer" that cannot be used under section 401, and not research conducted by independent third parties such as the National Institutes of Health. Proposed 21 C.F.R. 99.101(a)(5). That regulation also makes it clear that the scope of the statutory provision only extends to data from clinical trials on unapproved uses, and leaves in place the current rules for using reprints that report data on approved uses where resort to section 401 is not necessary.

Even so, as discussed below, we believe that the proposed regulations can and should be improved in several significant respects to faithfully implement both the letter and the spirit of section 401. We support the comments that PhRMA is filing on these proposed regulations, and seek to supplement those comments with our own. In addition to discussing the need to change particular sections of the proposal, where appropriate, we offer specific language for your consideration.

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OVERVIEW

Notwithstanding the clear intent of Congress and the language of section 401, in several instances FDA is proposing to erect some burdensome and extremely restrictive barriers that are seemingly intended to inhibit (not facilitate as Congress intended) the dissemination of important medical and scientific information on new treatment uses. The following is a summary of specific instances where we believe the agency has departed from Congressional intent:

I. FDA's Proposed Rules Limit The Types Of Information That Companies May Disseminate Far More Restrictively Than Congress Intended.

- **Eight Criteria.** Section 99.101 explains that to be disseminated, the article or reference text must present data derived from scientifically sound, prospectively planned clinical trials. In the preamble FDA spells out eight criteria that studies must meet to qualify as "scientifically sound." Depending on how they are interpreted, these eight criteria may go well beyond what peer-reviewed journals require for publication. The criterion that the study be prospectively planned is particularly limiting, and not what the statute requires.
- **Reference Texts.** The proposal virtually bans reference texts. Notwithstanding FDA's indications of flexibility in the preamble, the proposed rules require that reference texts report an individual clinical investigation in a reasonably comprehensive manner, which almost no reference text does to the degree that FDA contemplates.
- **Disclosure.** Proposed section 99.101(b)(1) requires a level of disclosure of study design not often present in published articles, and subjects the level of disclosure to second guessing by the agency despite the fact that the article already has been subject to peer review. The proposed requirement that reference texts and reprints contain a reasonably comprehensive presentation of the study design, conduct, data, analyses and conclusions seems to contemplate an impractical level of detail and would disqualify most of the important texts and many journal articles from dissemination. To make matters worse, the rules, as presently written, do not seem to permit manufacturers to supplement the articles with appendices that provide the needed detail. In light of the fact that the content of the reported study will have passed the scrutiny of peer review or be published in a mainstream reference text, permitting such supplemental disclosure seems appropriate.

II. FDA Creates Significant Impediments In The Process For Obtaining FDA Clearance To Distribute Reference Texts And Journal Reprints.

- **Time Limit for Completing Supplemental Studies.** While section 401 of the statute would permit the Secretary to grant extensions for filing supplements when the manufacturers first seek clearance of an article or reference text, proposed section 99.201 requires manufacturers to certify up-front that they will complete the necessary studies within 36 months, apparently without exception. That frustrates the Congressional goal of permitting timely dissemination of important data regarding diseases for which longer studies are usually necessary (*e.g.*, prevention trials, reduction in morbidity, cancer studies etc.). The statute specifically provides FDA with broad flexibility to accommodate various diseases by extending the time to whatever is appropriate; FDA's regulations should carry that flexibility through and should specify how the agency will select and evaluate studies for possible extensions when the issue does not involve a change in circumstances that delays a study. This process should take into account the fact that FDA can grant this type of extension at any time, including before the company has submitted an initial certification of its intent to file a supplement.
- **FDA Review Process.** In addition to the requirement that the articles reporting studies be rigorously reviewed by experts during the peer-review process, proposed section 99.101(a)(2) requires that the studies be "scientifically sound" as determined in an FDA review process. The point of relying on peer-reviewed articles was to make an up-front FDA review unnecessary, and to expedite the dissemination of important, new information. Creating a new scientific review process at FDA is duplicative and frustrates the goal of the provision.

III. FDA's Proposal Severely Limits The Mechanisms That Companies Can Use To Distribute Information To Those Who Need It.

- **Accompanying Promotional Materials.** In what may simply be a drafting mistake, the proposal does not allow promotional materials of any type (including those on approved uses) to accompany the reprints. We suspect this is simply an error because there is no policy or legal rationale for prohibiting companies from distributing information on approved uses with these reprints. Section 401 certainly does not include any such limitation. Indeed, the approved promotional materials can help clarify the extent of the approval.

IV. FDA Needs To Redefine The Scope Of The Rule.

- **Definition of New Use.** FDA's definition of new use is so broad that information directly related to approved uses could potentially fall within its scope. In the preamble, the proposal defines new use to include a new age group, another patient subgroup not explicitly identified in the current labeling, and comparative

claims to other agents for treatment of the same condition. In most cases, those types of information would be considered to fall within the approved uses of the drug, and should not be put through the elaborate process specified in section 401.

- **Definition of Supplemental Application.** FDA's definition of a supplemental application for drugs needs to be clarified to include any drug application that requests approval of a new use. Some drug review divisions request, for administrative reasons, that sponsors file "original" new drug applications for new uses, while other review divisions do not. Because of the inconsistency between divisions and because the focus of the statutory provision is on applications for new uses of already approved drugs, the regulation should clarify that the document does not need to be titled "supplemental" so long as the content of the application is a request for approval of a new use of an already marketed drug. FDA should deem these applications to be "supplemental" even though that word is not used in the title of the document.

BACKGROUND

As you know, section 401 of FDAMA created a process by which a manufacturer can submit to the FDA for clearance certain peer-reviewed journal articles and reference publications that discuss unapproved new uses of approved drugs, devices, and biologics. To disseminate these materials, the manufacturer must file or promise to file within a specified time a supplemental application with the FDA seeking approval for the new use. If the FDA does not object to the reprints or reference texts submitted, the company can disseminate those materials to certain health care practitioners, insurers, and others. In appropriate situations, certain additional materials also must be provided to ensure fair balance and appropriate disclosure of safety and other information.

The overall objective of section 401 is the "facilitation of greater access to timely and accurate information by health care providers." H.R. Rep. No. 105-310, at 60 (1997). Congress viewed access to such information as essential for those who have responsibility for making decisions about the treatment of patients. On the other hand, the House Commerce Committee Report emphasizes "FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice." *Id.*

At the same time it sought to provide greater access to information, Congress also granted the FDA limited authority to require manufacturers to disseminate certain additional information, where necessary, in order to achieve objectivity and balance. *Id.* Notwithstanding this grant of authority, however, Congress was clear that the FDA's role with respect to treatment decisions that are based on information derived from peer-reviewed articles and textbooks is quite limited. *Id.*

Unfortunately, the proposed regulations do not adopt this limited approach. Rather, the regulations clearly establish the FDA as an active reviewer and gatekeeper with respect to the dissemination of information to health care providers. The role the FDA has devised for itself through these proposed rules is at odds with the role intended by Congress.

SPECIFIC COMMENTS

Section-by-Section Analysis

I. Definitions (section 99.3).

A. The Definition Of Supplemental Application Is Too Narrow (section 99.3(j)).

The statute only permits a manufacturer to disseminate information on a new use if the manufacturer (i) has submitted a “supplemental application” to the FDA for such use, (ii) certifies that it will submit a “supplemental application,” or (iii) submits to the FDA an application for an exemption. See 21 U.S.C. § 360aaa-3(a).

The proposed regulations define a “supplemental application,” in relevant part, as “a supplement to support a new use to an approved new drug application.” Proposed 21 C.F.R. § 99.3(j)(1). In addition, the preamble states that “[a] supplement to an NDA could be a supplement to an application submitted under section 505(b)(1) . . . or section 505(b)(2) of the act.” 63 Fed. Reg. at 31145.

Although the language seems clear on its face, FDA’s administrative practices make the precise meaning of this language unclear. FDA has not declared a uniform rule for deciding when a supplemental NDA, in contrast to an original NDA, is appropriate. Instead, each review division within the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) appears to have a somewhat different standard for determining whether, for obtaining approval of a new use, an NDA should be supplemented or a new NDA must be filed. Congressional intent seems to be clear that the new rules must be broad enough to include any submission for a new use of an already approved product, whether such use is determined by FDA to require an NDA “supplement” or a new NDA for administrative convenience. The definition of the term “supplemental application” should be, for drugs, “an application to support a new use for an approved new drug,” and for biologics, “an application to support a new use for an approved biologic.” The variable criteria of the different review divisions should not determine whether section 401 applies.

B. The Definition of New Use Is Overly Broad (section 99.3(g)).

In the preamble to the proposed regulations, FDA sets forth a partial list of “new uses” that would require approval of a supplemental application, including “comparative claims

to other agents for treatment of the same condition.” 63 Fed. Reg. at 31145. Lilly assumes that the reference to comparative claims is not an attempt to redefine all comparative claims (including comparative claims for on-label uses) as “new uses,” but rather merely imprecise drafting intended to convey that the FDA wants comparative data for unapproved uses to go through the process outlined in section 401. We suggest that the final regulations clarify this ambiguity. In its comments, PhRMA explains the need for clarification here in greater detail.

II. Information That Can Be Disseminated (section 99.101).

Under section 401, a manufacturer may disseminate certain articles and reference publications containing information on an unapproved new use as long as the information meets specified requirements. With respect to a reprint, Congress placed the following limitations: the article (i) must be unabridged, (ii) must have been peer-reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved, (iii) must have been published in a scientific or medical journal, (iv) must be about a clinical investigation with respect to the drug or device, and (v) would be considered to be scientifically sound by the experts who conducted the peer review. In addition, the information must not (a) pose a significant risk to the public health, (b) be false or misleading or (c) be derived from clinical research conducted by another manufacturer without permission. 21 U.S.C. § 360aaa-1(a)(1)-(5).

With respect to reference publications, Congress imposes somewhat different conditions. Specifically, the reference publication must (i) be unabridged, (ii) include information about a clinical investigation with respect to the drug or device, and (iii) contain information that would be considered scientifically sound by qualified experts. 21 U.S.C. § 360aaa-1(a)(1)(B). As with articles, information contained in a reference publication also must not pose a significant risk to the public health, be false or misleading or be derived from clinical research conducted by another manufacturer without permission.

A. The Eight Criteria For Determining Scientific Soundness Unreasonably Restrict Dissemination of Important Information.

The proposed regulations define a “clinical investigation” as “an investigation in humans that is prospectively planned to test a specific clinical hypothesis.” Proposed 21 C.F.R. § 99.3(b). The proposed regulations further require that the clinical investigation be “scientifically sound.” Proposed 21 C.F.R. § 99.101(a). The preamble explains that this requirement contains eight separate criteria for deciding whether a study reported in an article or text is scientifically sound. 63 Fed. Reg. at 31146-47; see proposed 21 C.F.R. § 99.101(b).

If interpreted narrowly the eight criteria specified in section 99.101 approach the quality of evidence required to gain approval of a new use. Congress clearly contemplated that the dissemination of this scientific information could occur years before the sponsor has

collected enough data to obtain approval of a new use. Depending on how FDA interprets the criteria, the result may be that very few articles published before a drug is approved for a new use will ever qualify for the expedited dissemination that Congress intended to effect. In the preamble to its final rule, to help clarify the proper interpretation of these criteria and to put them in context, FDA should articulate the principal ways in which the quantity and quality of the data reported in the articles and texts may differ from the quantity and quality of the data required to obtain approval of a new use.

These criteria also appear inconsistent with the rest of FDAMA which is written flexibly, rather than prescriptively. Section 115 of FDAMA amended 21 U.S.C. § 355(d) by adding the following provision: "If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence." Indeed, FDA itself has taken a very flexible approach to the evidence it requires in supplements as explained in its Guidance to Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998). Because Congress expressly desired the dissemination to occur well before the sponsor is ready to seek approval of the new use, and because a single reprint is unlikely to contain the quantity of data or number of studies normally required for FDA approval, FDA should adopt a more flexible approach to the evidence needed to qualify for dissemination under section 401.

While the eight criteria collectively are too restrictive, the first one is particularly limiting and lacks any basis in the statute or in sound science. This requirement that the reported study be prospectively planned would eliminate a whole subset of scientifically sound studies, including retrospective studies, modeling studies, reference articles, and meta analysis. FDA offers no scientific, policy or legal support for its categorical exclusion of those study methodologies. Such an exclusion would only be sensible if no study of those types could produce valuable information. The demand of the scientific community for such articles is evidence of their value. The requirement that the study should be prospectively planned should simply be deleted in favor of a requirement that the study be appropriately designed.

B. FDA Review Of Scientific Soundness Is Not Appropriate.

One of the key criteria with respect to both articles and reference publications governed by section 401 is that they would be considered "scientifically sound" by the qualified experts who conduct peer reviews. Based on the description of the review process FDA contemplates as communicated at the July 8, 1998 public meeting, FDA's plans seem to ignore the plain wording of the statute and turn that provision in section 401 into a requirement for FDA to determine before dissemination whether a clinical investigation is indeed considered to be "scientifically sound." The proposed regulations state that such determination "will rest on whether the design, conduct, data, and analysis of the investigation described or discussed in a reprint or copy . . . reasonably support the conclusions reached by the authors." Proposed 21

C.F.R. § 99.101(b)(1). Those issues are examined in a “substantive review” by the agency. Proposed 21 C.F.R. 99.201(d).

Proposed sections 99.101(b)(1) and 99.201(d) exceed the statutory requirements of section 401 by imposing a duplicative and unnecessary layer of review on top of the peer review process that already apply to articles. In that regard, articles must undergo a vigorous peer review process by experts who are qualified by scientific training or experience to evaluate the substance of the materials. This, in itself, should suffice as an adequate pre-dissemination check of an article's scientific validity. The justification for imposing elaborate requirements that limit the articles to those from qualified peer-reviewed journals is to avoid the need for substantive scientific review by FDA.

There is no basis in the statute or elsewhere for requiring such duplication of effort to implement section 401. Indeed, quite the opposite—Congress is quite explicit that a review of the scientific soundness of the article by FDA is not to take place before dissemination. Congress very clearly stated that articles and reference text must be of a type that “would be considered to be scientifically sound by [qualified] experts.” (Emphasis added.) Congress certainly knows how to require that a study pass a scientific standard judged by FDA during an application process. It has done just that in section 505 of the Federal Food, Drug and Cosmetic Act (“FFDC Act”). But Congress quite deliberately did not do so here. It set up a test which FDA could apply in a post-dissemination enforcement context to protect the public health, but it did not create a mechanism for pre-dissemination, substantive, FDA review and approval. It set up a simple notification provision designed to give FDA some control and ability to monitor, but not to substantively review. Section 551(b)(4) as added by section 401 of FDAMA makes it clear that Congress did not envision a substantive review by the agency, but rather a reliance on the other safeguards in the act (e.g. peer review process, journal of national reputation, etc.)

Congress' reason for not imposing a substantive review seems clear: the FDA already is struggling to keep up with the regulatory work that it has. There is no need to add further to its already growing responsibilities, and risk delaying the release of important information by requiring substantive FDA review of articles. Pharmaceutical companies already must pay millions of dollars to support the review of marketing applications, and there is no reason to duplicate the work of peer-review organizations by setting up a second review process at FDA. Indeed, the FFDC Act does not authorize the use of user fees to support any review activities in connection with section 401.

For the reasons set forth above, proposed section 99.201(d) should be revised by deleting the last sentence of that subsection, and replacing it with the following: “For purposes of this part, a submission shall be complete when FDA determines that the manufacturer has submitted each of the required items.”

C. The Disclosure Requirement Is Unrealistic (section 99.101(b)(1)).

The proposed regulations mandate that in order to be deemed scientifically sound by the FDA, the article or reference publication must “include a description of the study design and conduct, data presentation and analysis, summary of results, and conclusions pertaining to the new use.” Proposed 21 C.F.R. § 99.101. In addition, the proposed regulations mandate that the article to be disseminated describe the study design. Proposed 21 C.F.R. § 99.101(b)(1). A clinical investigation that does not include such a description will not qualify for dissemination because it will not be deemed “reasonably comprehensive.” Id.

These provisions exceed the statutory language, and effectively exclude many useful articles. Specifically, the statute only requires that articles be “about a clinical investigation.” There is nothing in the statute that suggests such disclosure of the design is required. A reasonable disclosure is likely to occur under the peer review process but it may not include all of the data that FDA has specified. FDA’s proposed approach frustrates the overall purpose of section 401, which is to facilitate health care provider access to relevant clinical information.

In addition to lacking a legal basis, there is a policy issue with FDA’s approach. Because the process for preparing manuscripts for publication is outside the manufacturer’s control, the study authors may not have all eight criteria in mind when they write their manuscripts. That does not mean that the reported study contains any less important information. Indeed the articles must be written in a manner that will pass muster under a peer review process designed to ensure the integrity and objectivity of the report. If the manufacturer identifies a deficiency in an article that it would like to disseminate, the final regulations should allow the manufacturer to make the article comply with the statute by attaching any omitted information.

Apart from the statutory and policy issues, FDA has not established in the administrative record the need for this type of information. In addition to needing to have some statutory basis for a requirement of this type, FDA needs to have a factual basis. We believe that including too much information is counter-product because it will cause a health care practitioner pressed for time to miss the most important information. FDA should do market research like the Federal Trade Commission does to determine the optimal level of disclosure. The optimal level of disclosure is not self evident, nor should FDA simply guess at such an important issue. FDA is not entitled under law to arbitrarily set disclosure rules that may be counterproductive, and should establish the facts necessary to underpin its rule, particularly where the statute is silent.

FDA is on particularly weak ground in requiring this level of disclosure for reference texts. Congress understood that most reference publications do not discuss particular clinical trials in detail, and specifically limited permissible reference publications to those that do not focus on one particular drug. 21 U.S.C. § 552(b)(4). Congress did so to make sure that the reference publications are mainstream texts, rather than materials influenced by a company. Because Congress wanted section 401 to apply to these mainstream texts, it frustrates that intent

for FDA to now require that the disseminated texts be written differently than those mainstream texts.

Perhaps more to the point, requiring significant disclosure in texts is flatly inconsistent with the requirement that the reference texts not focus on a particular drug. An author could not both (1) include all of the information that FDA wants and (2) avoid focusing on a particular drug as section 401 requires. FDA suggests that it realizes this outcome, and proposes to draft a guidance to address reference materials, apparently based on some other statutory provision. But its own conclusion suggests the error of its logic. FDA says, "because reference publications rarely include detailed discussions of clinical investigations, FDA recognizes that the majority of such publications would probably not meet the requirements of section 401 of FDAMA and this proposed implementing regulation." 63 Fed. Reg. at 31146. Congress, however, did not write 24 pages of legislation to accomplish nothing. Congress clearly did not intend for FDA to require a level of disclosure that would render the statutory provision meaningless.

The solution, which makes all of the provisions work in harmony, is to permit the use of articles and reference texts that contain the typical level of disclosure for such materials. The last sentence in section 99.101(b)(1) should be revised to read: "A clinical investigation must be presented in a format that provides the customary disclosure of study design, conduct, data, analyses and conclusions for that medium. For any article or text that does not contain that customary level of disclosure, the manufacturer may collect the missing information and present it in an attachment to the article."

D. Focus of Reference Texts.

Like the overly demanding disclosure requirement, by its own characterization, FDA interprets the reference text provision in a second way that virtually eliminates the impact of the provision. This second error is the requirement that reference materials "be about" a clinical trial. FDA states, "Because the statute requires the information being disseminated to be about a clinical investigation, it seems unlikely that many reference publications will meet the requirements for dissemination under this provision." 63 Fed. Reg. at 31146. Just as with the disclosure issue, this very conclusion represents perhaps the clearest evidence that FDA is wrong in its interpretation. In fact, FDA misreads the definition of reference publication, and completely misapprehends the role such materials are supposed to play.

In drafting its proposed section 99.101(a)(1), FDA simply misreads the deliberately different language Congress used to define reference publications with regard to their focus on a clinical investigation, and ignores the requirement that reference materials not focus on a particular drug. In contrast with journal articles, the statute requires that the reference text simply "include information" about a clinical investigation, not "be about" such investigations. The difference is more than semantics; it expresses a very different focus for the reference materials that is in harmony with the language that reference texts not focus on a particular drug. In the statute, Congress contemplated that reference materials would discuss a

topic generally, without a narrow focus on a particular drug and without providing more than the typical amount of disclosure for a text.

Congress used this different standard because it recognized that reference publications do not typically discuss in detail the design and other aspects of clinical studies. FDA needs to understand that the journal article and reference text provisions stand on different footings. Congress deemed journal articles to be acceptable, with certain specified safeguards, because of the rigorous peer review process that ensures the scientific merit of the materials. Congress deemed reference texts, on the other hand, to be acceptable, even though they are not peer-reviewed, because mainstream textbooks convey general information and are not written to focus on a particular drug. Congress wanted both to be used, and tailored its requirements to reflect the differences between those types of materials.

Because the proposed regulations do not comport with the statutory language, FDA should delete section 99.101(a)(1). It can simply be deleted because sections (2)(i) and (2)(ii) have the proper wording with regard to being about a clinical trial or merely containing information about a clinical trial, as the case may be. Section (a)(1) was redundant in addition to being wrong.

E. Accompanying Materials.

The proposed regulations prohibit the dissemination of promotional materials that accompany the reprint. See proposed 21 C.F.R. § 99.101(b)(2). Specifically, the proposed regulations state that “[s]uch reprint, copy of an article, or reference publication shall not be disseminated with any information that is promotional in nature.” *Id.* The preamble uses the term “accompany” in describing the scope of this prohibition. FDA uses the term “accompany” broadly to mean more than just physical accompaniment. See Kordel v. U.S., 335 U.S. 345 (1948).

One reading of this language would prohibit a sales representative from distributing materials that discuss “on-label” uses of a drug while, on the same visit, disseminating journal reprints containing information on unapproved uses. We do not believe that is what FDA or Congress intended because we can see no legal basis or policy justification for such a requirement.

To address that ambiguity, we recommend that section 99.101(b)(2) be clarified to permit the dissemination of reprints under section 401 and the dissemination of “on-label” materials to occur simultaneously. For example, that section could be revised as follows: “Such reprint, copy of an article, or reference publication shall not be disseminated with any information that promotes an unapproved use.” If we are wrong about assuming this to be simply a loosely worded provision, and FDA actually intends to prohibit the concurrent dissemination of “on-label” promotional materials with reprints under section 401, FDA has grossly overstepped its statutory authority and we request an opportunity to address that issue.

To do so, however, we would need some explanation by FDA of the legal and factual basis for such a requirement.

F. The Need for Examples.

Perhaps our greatest concern regarding the proposal is the significant amount of subjectivity left to FDA. After reading the proposed regulations, we are really not sure which articles will qualify and which will not. Given the ambiguity of the proposed regulations and the concerns that FDA may interpret them restrictively, we request that the agency reference in the preamble to the final rule about a dozen specific example articles and texts which it believes do pass this test, and which span the various therapeutic areas. Such a list would serve as useful guidance on how FDA plans to interpret these provisions, and may be the best way to limit the subjectivity of the current proposal.

III. Manufacturer's Submission to the Agency (section 99.201).

A. The Regulations Should Be More Flexible Regarding the Use of Manuscripts.

Proposed section 99.201(a)(1) requires that the manufacturer submit an "identical copy" of the information to be disseminated. However, due to the significant amount of time involved in the printing process, we believe the FDA should build some additional flexibility into the regulations by allowing manuscripts to be submitted as a press-ready proof. These proofs are the copies that the publisher sends to the printer for the mechanical task of mass producing. The press-ready proof thus represents the point of no return for the publisher, where it is clear that the article will be published in its then-current form.

If the FDA insists on waiting for an actual copy and then takes up to sixty days to review the materials, the information will not be very timely by the time the physicians receive it. As a consequence, FDA should accept press-ready proofs, and the 60 day clock should start upon receipt of that copy. Section 99.201(a)(1) should read, "The text of the information to be disseminated, including"

B. The Proposed Regulations Should Clarify the Confidential Nature of Communications Between the FDA and a Manufacturer.

Under proposed section 99.201, it is not clear whether, and to what extent, correspondence and interaction between the FDA and a manufacturer will be kept confidential by the FDA. Lilly assumes that all such communications and other interaction (both the interaction surrounding the filing and review of the supplement, including the time of filing, and the interaction around the information to be disseminated) will be treated by FDA as confidential commercial information and/or trade secrets, and thus not disclosed publicly. This includes the fact of the submission, and not just its content.

Even though the articles and texts are by their very nature public (or will be public in the case of the materials that will accompany the reprints), the fact that a company plans to use these materials and file a supplemental NDA in the future has competitive implications. This information in most cases will remain confidential until the company actually begins to disseminate the materials. In this way, these materials are very different from the promotional materials that DDMAC receives at time of first use.

Thus, Lilly believes this issue should be clarified before publishing final regulations to state that the content of these submissions and the fact of the submissions represent confidential commercial information and/or trade secrets (if that status is claimed) as long as the company maintains the information as confidential.

IV. Request To Extend The Time For Completing Planned Studies (sections 99.203 and 99.303).

In drafting the portions of its proposed rule that relate to extensions of time for completing the required studies to support a supplement, FDA unfortunately does not follow the specific requirements of the statute. New section 554(c)(3) of the statute provides:

The period of 36 months authorized in paragraph (1)(A)(ii) for the completion of studies may be extended by the Secretary if—

- (A) the Secretary determines that the studies needed to submit such an application cannot be completed and submitted within 36 months; or
- (B) the manufacturer involved submits to the Secretary a written request for an extension and the Secretary determines that the manufacturer has acted with due diligence to conduct the studies in a timely manner, except that an extension under this subparagraph may not be provided for more than 24 additional months.
(Emphasis added.)

Because subparagraphs (A) and (B) are connected by an “or,” this provision sets up two different means by which the deadline may be extended.

The first is when the Secretary determines that an application cannot be completed and submitted within 36 months. That provision, which we will call Procedure A, does not dictate when the determination is to be made, so it can be made at any time, including the outset when the manufacturer is submitting articles and a certification of its intent to file a supplement. Indeed, the statute specifically states that the certification will promise that the application will be submitted no later than 36 months after the date of the initial dissemination of information under section 551 “(or, as applicable, not later than such date as the Secretary may specify

pursuant to an extension under paragraph (3).” (Emphasis added.) FDA explains in its preamble that “Section 554 of the act (21 U.S.C. 360aaa-3) anticipates that there will be times when the 36-month period for filing a supplemental application for a new use based on new studies will not be enough time. It provides, therefore, that FDA may, on its own initiative at the time of initial dissemination, give the manufacturer more than 36 months....” 63 Fed. Reg. at 31148. The extension may be for any amount of time.

The second means for providing an extension, which we will call Procedure B, is when the manufacturer tries to complete the studies within 36 months, and determines that it cannot despite due diligence. Presumably, this type of request is initiated after the manufacturer certifies its intent to complete the studies within 36 months, because past due diligence is an element of the request. In these cases, in contrast to Procedure A, the extension may only be for up to 24 months.

Both types of extensions are important. Obviously, Procedure B is needed to address those situations where the unforeseen happens, and the study cannot be completed despite the manufacturer’s best efforts. On the other hand, while many phase III studies can be completed in about three years, Procedure A is necessary when a given disease state or a particular use simply requires longer than three years to study. For example, most disease prevention or mortality studies can take perhaps 5-10 years to complete because of the endpoints that need to be measured. In particular, the Tamoxifene breast cancer prevention study and the Gusto mortality study comparing TPA to Streptokinase for treatment post myocardial infarction both took well over five years to complete. Procedure A gives FDA the flexibility to allow the dissemination of important information in a timely manner even though everyone agrees up-front that the necessary studies to obtain approval of a supplement for the use will take more than three years to complete. There is no 24 month restriction on this type of extension.

Lilly does not believe that the proposed regulations adequately address (1) how the FDA will treat extensions of time under Procedure A or Procedure B, (indeed the regulations tend to blur those two procedures) or (2) the process to be followed for the manufacturer to identify a need for an extension under Procedure A. We think the regulations should set out these two procedures separately. In the current draft, while it is certainly not self evident, based on a close reading of the statute, FDA’s regulations seem to correspond to the statutory procedures as follows:

<u>Regulation</u>	<u>Statutory Procedure</u>
99.203	Procedure B
99.303(a)	Procedure A
99.303(b) and (c)	Procedure B
99.303(d)	Both Procedure A and B (this is not clear because this section requires filing a “new” certification stating the extended time which would not necessarily happen under

Procedure A because the extension can be granted before any certification is filed.)

In reorganizing these sections to clarify the differences between these two procedures, FDA should specify how under Procedure A the agency will select and evaluate studies for possible extensions. This process should take into account the fact that FDA can grant this type of extension at any time, including before the company has submitted an initial certification of its intent to file a supplement. Thus FDA needs some mechanism for learning about appropriate circumstances for granting an extension even before such certifications are submitted.

In addition to those clarifications, we ask that FDA clarify the required initial certification. The proposed regulations currently require a manufacturer to certify that it will complete the clinical studies for a supplemental application within 36 months of the initial dissemination of information. Proposed 21 C.F.R. § 99.201(a)(4)(ii)(B). That statement is simply too broad given the flexibility available in Procedure A for obtaining an extension prior to certifying a time period. The regulations should track the statute, including the parenthetical in new section 554(c)(1)(A)(ii). Under Procedure A the company initially may certify a longer time if the Secretary has determined that a supplemental application will take more than three years to submit because, for example, the study endpoints require a longer period.

The period of extension also needs to be clarified. As already noted, the proposed regulations state that any extension of time requested by a manufacturer may not exceed an additional 24 months. Proposed 21 C.F.R. § 99.303(b). The regulations need to clarify that the 24 month limitation only applies to studies initially thought to be capable of completion within 36 months (*i.e.*, Procedure B). The regulations need to specifically acknowledge that the statute does not place that limit on extensions granted under Procedure A.

The regulations also do not address whether more than one 24 month extension can be granted under Procedure B. We think that can happen, because the difficulties encountered could continue through no fault of the manufacturer. It makes sense, however, to only grant extensions for purposes of Procedure B in 24 month increments. The final regulations should clearly state that the FDA has the discretion to grant more than one such extension.

V. Application For Exemption From The Requirement To File A Supplemental Application (section 99.205).

The FDA has greatly expanded the type of information it would require before granting, for either economic or ethical reasons, any exemptions from the need to file a corresponding supplement. Much of this additional information is irrelevant, time consuming to review and misdirected. For example, the preamble to proposed 21 C.F.R. § 99.205(b)(1) states that when analyzing a request for an exemption due to a study being “economically prohibitive,” FDA “is not focusing only on sales from the new uses because the agency does not believe that it would be ‘prohibitive’ if the sales from the new use did not cover the cost of the studies. In such

a situation, it might not be economically wise to conduct the studies, but it would not rise to the level of being prohibitive.” 63 Fed. Reg. at 31149.

Well-accepted economic theory explains that publicly-traded companies with shareholders to whom they must report try to behave in an economically rational manner. And it is not economically rational (nor is it “economically wise”) to spend more money on conducting studies than the uses being studied could potentially bring in through increased revenue (even ignoring the risk issue inherent in deciding whether to pursue clinical studies). We do not understand FDA’s position that companies can act “economically unwisely,” so the agency will expect them to do so in order to provide information to those doctors treating patients with rare diseases.

The studies will not be done unless doing so is economically rational, so the agency’s proposal seems quite clearly to reject the Congressional determination that doctors treating patients with rare diseases also need access to information. “Economically prohibitive” must mean that point at which an economically rational company will not pursue the research. That point is the point at which the expected revenue that the studies would produce (discounted by the risk that the studies will fail to produce revenue) falls below the expected cost of the studies and associated research plus the expected cost of producing and selling the additional product, all taking into account the time value of money. Interpreting “prohibitive” to mean anything other than rational behavior simply rejects the Congressional mandate and ignores the needs of the patients with rare diseases.

VI. Applicability Of Labeling, Adulteration, And Misbranding Authority (section 99.405).

Proposed section 99.405 purports to give the FDA the authority to take enforcement against a manufacturer that does not comply with the detailed part 99 requirements on the grounds that it has distributed false or misleading “labeling.” Labeling that is false or misleading renders the associated drug misbranded under section 502 of the FFDC Act. The consequence of a drug being misbranded is that each introduction of the drug into interstate commerce constitutes a separate prohibited act under section 301 of the FFDC Act. And for each prohibited act, FDA under the FFDC Act can levy its full enforcement authority including seizures, injunctions and criminal penalties calculated on a per violation (*i.e.*, per product) basis.

For a violation of part 99, FDA would have as enforcement options the specific corrective actions provided in section 555 (*e.g.*, dear doctor letters, cessation of dissemination). Moreover, section 557(b) adds to section 301 a subparagraph that renders “the dissemination of information in violation” of part 99 a “prohibited act” under section 301. While prohibited acts under section 301 are subject to the full set of enforcement options—*i.e.*, the full panoply of civil and criminal enforcement options FDA has at its disposal—a violation of the procedures in part 99 would constitute one violation rather than a violation for each product sold.

Thus, section 99.405 is too broad and goes beyond the statute when it says that the failure to comply with part 99 results in misbranded drugs. It is true that distribution of off-label materials without pursuing the procedures outlined in part 99 should produce that outcome. But for a firm that tries to follow the requirements of part 99, FDAMA has prescribed specific enforcement consequences for a failure to comply that FDA should turn to first. And those consequences include the corrective actions in section 99.401 and a single violation of the prohibited acts in section 301 of the FFDC Act. FDA does not have the authority to allege multiple violations based on multiple misbranded drugs, and seek multiple penalties for every drug unit sold, for a failure, for example, to submit to FDA the report required in 21 U.S.C. § 553(a)(1).

CONCLUSION

Lilly appreciates the opportunity to comment on these important regulations. We are concerned that given the very short time frame allowed for preparation of these comments there are other potential issues presented by the regulations which will not be properly addressed. These regulations have the potential to improve many lives by ensuring that useful information is provided to health care practitioners in a more timely manner, and at the same time ensuring that research continues. Unfortunately, if FDA broadly interprets the restrictions outlined above, we believe that very few articles and reference texts would ever find their way into the hands of the health care practitioners who need them.

We support the purposes of the statute, and are ready to help with the implementation in any way that we can. This includes jointly conducting market research with the agency to determine the optimal presentation of the information health care practitioners desire. Please let us know how we may help.

Sincerely,

Handwritten signature of Timothy R. Franson, M.D. in black ink.

Timothy R. Franson, M.D.

Vice President—Clinical Research and Regulatory
Affairs—U.S.

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