

WASHINGTON LEGAL FOUNDATION

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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parklawn Drive  
Room 1-23  
Rockville, MD 20857

Re: Dissemination of Information on Unapproved/New Uses  
for Marketed Drugs, Biologics, and Devices  
(63 Fed. Reg. 31143, June 8, 1998; Docket No. 98N-0222)

Dear Sir/Madam:

The Washington Legal Foundation (WLF) submits these comments in response to the Food and Drug Administration's (FDA) proposed regulations designed to implement provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA) with respect to permissible manufacturer dissemination of off-label information regarding approved drugs and medical devices. As FDA may be aware, WLF believes that FDAMA is not sufficient by itself to safeguard the First Amendment rights of those seeking to convey and those seeking to obtain off-label information. WLF believes that FDA's proposed regulations to some extent carry out congressional intent as expressed in FDAMA. WLF believes, however, that the proposed regulations should be amended in several respects in order to carry out that intent more fully.

WLF has three principal concerns regarding the proposed regulations. First, the proposed regulations state that manufacturers will never be permitted to disseminate off-label information for approved § 510(k) medical devices where the off-label use would require submission of a PMA. There is no indication that Congress intended to impose that limitation, and FDA's limitation is not supported by any statutory language. Second, the proposed regulations appear to construe far too narrowly the circumstances under which a manufacturer may seek an exemption (from the supplemental application requirement) under § 554(d) of the Food, Drug, and Cosmetic Act (the "Act"), 21 U.S.C. § 360aaa-3(d). In particular, the proposed regulations suggest that exemptions may be denied even in circumstances in which the manufacturer could not reasonably expect to profit from submission of a supplemental application. Third, the proposed regulations appear to allow FDA too much leeway to undermine the intent of § 554(d)(3) of the Act, 21 U.S.C. § 360aaa-3(d)(3), regarding "deemed" approval of exemption applications not denied within 60 days of submission. In particular, the proposed regulations permit FDA to inappropriately delay the date on which an application is deemed submitted; also, while WLF concurs with FDA's assertion that it ought to be permitted to revoke "deemed" approvals

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under certain circumstances, WLF believes that FDA has placed insufficient limitations on the exercise of that authority.

***Interests of WLF.*** WLF is a nonprofit public interest law and policy center with supporters in all 50 states. While WLF engages in litigation and administrative proceedings in a variety of areas, WLF devotes a substantial portion of its resources to promoting the interests of a free-market economy and to defending the rights of individuals and businesses to go about their affairs without undue influence from government regulators. In particular, WLF petitioned FDA in 1993 to lift its overly-severe restrictions on the dissemination of information regarding off-label uses of FDA-approved products (a petition that currently is the subject of litigation in the United States District Court for the District of Columbia) and in 1995 petitioned FDA to ease its restrictions on direct-to-consumer prescription drug advertisements. Among WLF members are individuals who seek to disseminate information regarding off-label uses of FDA-approved products, and other individuals who seek to receive such information.

***I. Limitations on § 510(k) Medical Devices.*** FDAMA permits drug and device manufacturers to disseminate information about an off-label use of an FDA-approved product if they, *inter alia*, have “submitted to the Secretary a supplemental application for such use.” 21 U.S.C. § 360aaa-3(a)(1)(A). FDAMA does not define precisely what is meant by the term “supplemental application,” but it is reasonably clear from the statute that Congress intended that term to apply to *any* application to FDA for permission to market a previously-approved product in a manner not included within the previous approval.

FDA, however, has proposed giving a more restrictive definition to “supplemental application”:

*Supplemental application* means:

- (1) For drugs, a supplement to support a new use to an approved new drug application;
- (2) For biologics, a supplement to an approved license application;
- (3) For devices that are the subject of a cleared 510(k) submission, a new 510(k) submission to support a new use or, for devices that are the subject of an approved premarket approval application, a supplement to support a new use to an approved premarket approval application.

Proposed (“Prop.”) § 99.3(j).

Thus, the proposed regulations single out precisely one type of FDA-approved product that is not eligible for FDAMA's liberalized information-dissemination rules: devices that are being marketed pursuant to a cleared § 510(k) submission where approval of the generally-accepted off-label use would require submission of a premarket approval application (PMA). FDA provides absolutely no policy-based rationale for its restrictive definition of "supplemental application." In its description of the proposed regulation, FDA states: "There are instances when a new use for a 510(k) device would require the submission of a PMA, but this would not be the equivalent of a 'supplement' and thus, has not been included in the definition." 63 Fed. Reg. at 31145.

WLF is not sure what FDA means when it says, "[T]his would not be the equivalent of a 'supplement.'" WLF is unaware of any statutory definition of the term "supplement" or of any use of that term in connection with § 510(k) devices. More importantly, the word "supplement" appears nowhere in FDAMA, so meanings that FDA may on its own have attached to that term are irrelevant for present purposes. Rather, Congress used the term "supplemental application" in FDAMA. A straightforward reading of that term as used in 21 U.S.C. § 360aaa-3(a)(1)(A) indicates that Congress intended to encompass any application to market in a new manner a product whose current marketing is approved by FDA. Under that reading, an application for a new use for a § 510(k) device would in all instances constitute a "supplemental application," regardless whether the application takes the form of a § 510(k) submission or a PMA.

Moreover, FDA is being inconsistent in the application of its prior administrative definitions of the term "supplement." As FDA tacitly acknowledges (63 Fed. Reg. at 31145), it has never deemed a new § 510(k) submission to be a "supplement" when the device in question is the subject of a cleared § 510(k) submission, yet FDA proposes to include such submissions within its definition of a "supplemental application." Prop. § 99.103(j)(3). FDA's inconsistent treatment of § 510(k) devices thus renders FDA's proposed definition of "supplemental application" indefensible.

In sum, Congress clearly intended in FDAMA, through use of the term "supplemental application," to cover applications for *any* new use of a product currently being used with FDA permission. FDA's proposed definition of "supplemental application" should be amended to reflect that intent.

**II. Exemption from Supplemental Application Requirement.** FDAMA provides an exemption whereby manufacturers may disseminate truthful information about off-label uses of approved products even without submitting (or promising to submit) a supplemental application for FDA approval of the off-label uses. Such exemptions are to be granted when "it would be economically prohibitive with respect to such drug or device for the manufac-

turer to incur the costs necessary for the submission of a supplemental application, ” *or* when “it would be unethical to conduct the studies necessary for the supplemental application. ” WLF is very concerned that FDA’s proposed regulations take far too restrictive a view of when it would be “economically prohibitive” for a manufacturer to incur the costs necessary for the submission of a supplemental application.

WLF is particularly alarmed by FDA’s repeated statements in its notice of proposed rule that such exemptions will “rarely” be granted. See, e.g., 63 Fed. Reg. at 31148 (exemptions are appropriate only in “rare circumstances”); *id.* at 31149 (“exemptions . . . are to be rare”); *id.* at 31150 (“Congressional intent was clear in expecting exemptions to be rare.”). The word “rare” appears nowhere in § 360aaa-3, nor can any such congressional intent be discerned from the statutory language. While FDA may be aware of some secret congressional intent to which WLF is not privy, WLF respectfully suggests that FDA -- in discerning congressional intent -- ought to be guided by what Congress wrote in its statute. Moreover, it is implausible that Congress would have gone to the trouble of creating an exemption from the “supplemental application” requirement if it did not believe that the need for an exemption would arise in a fair number of circumstances.

WLF also believes that FDA has departed from congressional intent in its definition of what constitutes “economically prohibitive” circumstances. The proposed regulations state that a manufacturer seeking an exemption must “at a minimum” provide evidence “[demonstrating that the estimated cost of the studies needed for the approval of the new use would exceed the estimated total revenue from the drug or device less the cost of goods sold, and marketing, and administrative expenses attributable to the product. ” Prop. § 99.205(b)(1).<sup>1</sup> Under that definition, manufacturers would almost never be able to demonstrate “economically prohibitive” circumstances. If the “estimated total revenue from the drug or device” -- including revenue already being derived from on-label uses -- is to be taken into account, then the costs of needed studies are highly unlikely to exceed a manufacturers’ expected profit. Yet no economically rational manufacturer will go to the expense of undertaking the studies necessary to support a supplemental application unless it is likely to recoup those costs through increased sales *directly attributable to the new use*. A course of action is “economically prohibitive” whenever it inevitable will result in a net loss, not simply in those circumstances in which the action will drive a company into bankruptcy.

FDA’s interpretation of “economically prohibitive” is unfaithful not only to the

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<sup>1</sup> FDA’s “at a minimum” language is unwarranted; if a manufacturer provides the evidence required under the statute and regulations, nothing further can be required, and issuance of the exemption is mandated.

statutory language but also to the purposes underlying FDAMA. Congress was concerned that truthful information regarding off-label uses was not reaching doctors because manufacturers were prohibited from disseminating that information yet lacked the economic incentive to seek the supplemental approval necessary to permit such dissemination. Congress adopted § 360aaa-3(d) to deal with that precise situation. Yet, FDA's crabbed definition of "economically prohibitive" would mean that doctors would continue to be denied access to valuable information about off-label uses of approved products -- because no manufacturer will incur the expenses associated with a supplemental application unless it has reason to believe that it will generate a net profit thereby.

Moreover, FDA's definition of "economically prohibitive" is inconsistent with statements made by FDA in its "Reg-Flex" analysis of the proposed regulations. In that analysis, FDA states:

Firms choosing to disseminate the new use information will do so only if the expected increased sales revenues exceed the associated regulatory costs. Because no firm will experience a reduced net income, the proposed rule will not have a significant adverse effect on a substantial number of small entities and no further analysis is required under the Regulatory Flexibility Act.

63 Fed. Reg. at 31153. Yet, FDA's definition of "economically prohibitive" is predicated on its conclusion that *some* manufacturers will submit supplemental applications for existing off-label uses even though such a submission would reduce net income.<sup>2</sup> Accordingly, FDA's definition of "economically prohibitive" *does* require FDA to undertake further analysis under the Regulatory Flexibility Act.

A major purpose of FDAMA was to ensure wider dissemination of truthful information about existing off-label uses of FDA-approved products. Because it lacks authority to regulate the practice of medicine, FDA has no authority to regulate such uses. Off-label uses that are widely accepted within the medical community will continue, with or without FDA's blessing. Given that reality, it makes sense to permit dissemination of *truthful* information about accepted off-label uses from the party likely to know the most about such uses: the product's manufacturer. While in a perfect world, FDA might prefer manufacturers to seek FDA approval for accepted off-label uses, history indicates that they will not do so unless they can derive a net profit thereby. In recognition of that fact,

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<sup>2</sup>Unless FDA has reached such a conclusion, then its definition of "economically prohibitive" would be nothing more than a cynical attempt to write § 360aaa-3(d)'s exemption provision out of FDAMA.

Congress adopted § 360aaa-3(d). FDA's definition of "economically prohibitive" renders § 360aaa-3(d)'s exemption provision a dead letter, and ensures that doctors will continue to prescribe products for off-label use without the benefit of truthful information that Congress intended to permit manufacturers to convey under these circumstances.

**III. "Deemed" Approval of Exemption Applications.** Once a manufacturer has filed an application pursuant to § 360aaa-3(d) for an exemption from the supplemental application requirement, FDA has 60 days to approve or deny the application. If the exemption application is not denied within 60 days of its receipt, FDAMA deems the application to be approved. 21 U. S .C. § 360aaa-3(d)(3)(A). Congress's obvious intent in adopting the "deeming" provision was to ensure that FDA acts quickly on such application and that valuable information should not be suppressed due simply to FDA's tardiness.

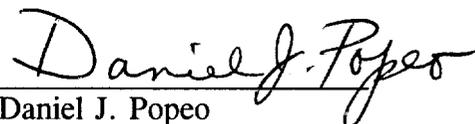
WLF is concerned that several provisions of the proposed regulations tend to undermine Congress's intent in adopting the deeming provision. First, the proposed regulations state that the 60-day period does not begin to run until FDA has received a "complete" submission, which FDA's proposes to define as existing only "if FDA determines that it is sufficiently complete to permit a substantive review." Prop. § 99.201(d). That definition is contrary to the statute, which says nothing about a "complete" exemption application, and states unequivocally that the application is "deemed to be approved" if not denied within 60 days of receipt of "the application." FDA is free, of course, to deny an exemption application (within 60 days of receipt) on the ground that it is not "complete," but it has no authority to seek to rescind a deemed approval on the ground that the 60-day clock never started running because the application it received was not "complete."

The proposed regulations also state that after an exemption application has been submitted, FDA may "[r]equest additional information or documents to assist the agency in determining whether the information to be disseminated complies with the requirements under this part. This may include, but is not limited to, copies of articles listed by the manufacturer in its bibliography." Prop. § 99-301(a)(2). WLF agrees with FDA that it possesses the statutory authority to seek such information. But WLF is concerned that FDA reviewers may seek to use this provision as a back-door method of extending the 60-day review period. FDA should be as explicit as possible regarding the types of information necessary to sustain an exemption application, so that manufacturers can include such information in the initial submission. The regulations should make clear that it is not an acceptable practice for FDA reviewers to deny exemption applications on the 59th day based on lack of completeness, where the manufacturer was not on notice when it submitted the application that the information alleged to be "missing" was a required part of the application.

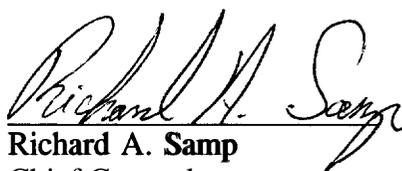
Finally, the proposed regulations provide that “[i]f an application for an exemption is deemed to be approved, FDA may, at any time, terminate such approval if it determines that the requirements for granting an exemption have not been met.” Prop. § 99.305(a)(2); *see also* Prop. § 99.403(a). That proposed regulation is directly contrary to the terms of the statute. FDAMA provides that FDA may terminate a deemed approval only “[i]f pursuant to a deemed approval . . . a manufacturer disseminates written information under § 551 [21 U.S.C. § 360aaa] on a new use.” 21 U.S.C. § 360aaa-3(d)(3)(B). Section 99.305(a) should be modified to conform to the limitations imposed by FDAMA on FDA’s revocation authority. In the absence of such limiting language, § 360aaa-3(d)(3)(A) would be rendered virtually meaningless.<sup>3</sup>

**Conclusion.** WLF believes that the proposed regulations more-or-less carry out congressional intent with regard to their treatment of submissions for which a supplemental application has been filed or is expected to be filed. WLF believes, however, that FDA’s proposed regulations regarding applications for exemption from the supplemental application requirement do not accurately reflect congressional intent and would render the exemption process a virtual dead letter.

Respectfully submitted,



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Chairman and General Counsel



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<sup>3</sup> At a minimum, Prop. § 99.403(a)(3) should be amended to eliminate an obvious typographical error. The eighth word of that provision should be changed from “or” to “and.”