
NATIONAL WOMEN'S HEALTH NETWORK

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12420 Parklawn Drive, rm. 1-23

Rockville, MD 20857

Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices; Docket No. 98N-0222

To Whom It May Concern:

The National Women's Health Network is writing to urge the Food and Drug Administration to enact strong regulations governing the dissemination of information related to unapproved and new uses of marketed drugs, biologics and devices. It is imperative that the FDA take every step possible to ensure that all information meets the highest scientific standards and is presented in a context that clearly informs recipients that the products have not been proven safe and effective for the indication being promoted.

In passing Sec. 401 of the Food and Drug Administration Modernization Act (FDAMA), Congress created an exception to one of the most fundamental tenets in the nation's regulatory system -- that new products be proven safe and effective prior to their marketing by the manufacturer -- and moved the FDA into uncharted territory. The Network strongly believes that the dangers of this new system are clear and present a threat to women's health. Many drugs and devices have been and continue to be prescribed off-label to women to treat a wide spectrum of diseases, often with little or no proof of safety and effectiveness. As recently as last year, women bore the brunt of unlabeled therapies as thousands of women were injured as a result of taking Phen-Fen, a diet pill combination which had not undergone clinical testing.

The Network is also aware that some providers are now prescribing the osteoporosis drug Evista to prevent breast cancer and as an alternative to hormone replacement therapy. Though, doctors have always had the ability to prescribe off-label, the fact that companies can now market drugs and devices for unapproved uses leads us to believe that even fewer products will be proven safe and effective through well-controlled clinical trials, leaving women with even less information about therapies.

New uses often apply to a much larger and different patient population and often for a significantly different use. Congress is now allowing manufacturers to actively disseminate information about such new uses in order to build market share without first conducting research to prove that the uses are safe and effective. As a result, millions of Americans will be using products whose safety and effectiveness have not been established,

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In creating this exception, Congress **did not intend** to abdicate all safeguards to prevent harm to patients **as** a result of using a product for an unproven use, The Network believes that there is the very **real** potential that patients will be prescribed drugs advertised off-label which **will later** be found to be ineffective and consumers and patients may well suffer side effects and complications from these products. Indeed, safeguards are more important when safety and effectiveness **have** not been established. Public involvement at **every** stage **of** the process will **help** to ensure that such safeguards **are** used **to the full extent** possible. The **resource-strapped** FDA **must** incorporate appropriate public participation **in** order to **sufficiently** monitor the actions of the manufacturers and to help prevent manufacturers from abusing the privileges granted to them **under** this section.

Public Information

Manufacturer's Submissions to the FDA

Sec. 401 of the statute, and the ensuing regulations, require manufacturers to **submit** a **number** of important documents to the FDA prior **to dissemination of** information **and after** dissemination commences, **Prior** to dissemination, the manufacturer must submit, in addition to the information **to be** disseminated: all other clinical information **that** it has relating to **the safety** or effectiveness of the new use, **any** reports **of clinical** experience pertinent to the **safety** of the new use and a summary of such information, and **the** search strategy used for developing the required bibliography.

In relation to the required submission **of** a supplemental application **for** the new **use**, the manufacturer must provide:

- a supplemental application for the new use;
- a certification **that** an application **will** be submitted **within** six **months** of dissemination;
- a proposed protocol and schedule for conducting the trials necessary for a supplemental and certification that such **trials** will be completed in 36 months; or
- a request for an exemption from the supplemental application requirements.

Specifically, when requesting **an** exemption, **the manufacturer** is required to explain why an exemption is sought, along with materials demonstrating that it would be economically prohibitive or unethical to conduct the studies needed for submission **of** a supplemental application.

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Once dissemination has begun, the manufacturer **must** submit any new information that becomes available **about** the **new** use. Every six **months** the manufacturer is required to submit lists of the titles of the articles and publications that have **been** circulated in the previous six-month period and the individuals or categories that have received the materials. Manufacturers that have committed to conducting studies **necessary** for a supplemental application must also submit status reports on **those** studies. They may also **submit** a request for an extension **of** the 36 month period **for up to** 24 additional months and, **if** granted, must **submit** a **new** time frame for the completion of studies.

The Public's Right to Know

Clearly, much of this information is of vital importance to the health of the public. Both the individuals and their physicians who use **a** product for the new use and those who can provide appropriate balancing information and monitor **the** progression of clinical **investigations** need **access** to the information submitted by **the** manufacturer. Women and their health care providers have **a** right to know **all** additional safety and effectiveness data available so that they can be fully informed **prior to using** a drug for **a** promoted off-label use. The **public** has a **right** to know what studies are being conducted to **prove** safety and effectiveness and the status of those trials. Thus, it is critical **that all** the information submitted **in** Sec. 551, 552, 553, and 554 **of the** Food, Drug, and Cosmetic **Act**, as outlined above, be available **to** the public.

The Role of the Public in Providing Balancing Information

Given the FDA's extremely limited resources and the substantial new burden that **these** regulations place on the FDA, the public also has a pivotal role to play in monitoring the dissemination **of information** about unapproved uses.

Many women and their health care **providers** have **an** in-depth knowledge of **the** published studies related to a specific disease or condition, which the FDA itself may **not** have. Given the value **of** this resource **and** the important role that it can play **in** facilitating distribution **of** the most balanced information possible, the FDA, upon receiving a submission from the manufacturer [99.20 1], should publish immediately in **the** Federal Register **the** citation for the article and the **bibliography** to be disseminated and solicit additional published information that might be appropriate for **distribution** or inclusion in the bibliography. Just as the public has the opportunity to comment prior to **the** marketing approval of new products or supplemental applications, so too should the public be given **the opportunity** to comment prior to **the** granting of approval for dissemination **of** information on an off-label use.

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The Role of the Public in Monitoring Trials

Congress **placed** great weight **on** the diligent conduct and timely completion of the trials necessary for a supplemental application **in** allowing the dissemination of information **on** unlabeled **uses**. Again, given the FDA's limited resources and expanding responsibilities, **the** public has **an** -important role **to** play **in** monitoring the conduct and completion of these trials. Although FDA **has** responsibility for monitoring **these** trials, **given the** resources currently available to the agency, the public also needs to monitor **these** studies. **Public** monitoring is all the more necessary **given the** significant portion of required post marketing studies that have not been completed in the past and the FDA's poor track record **of** monitoring their status. Thus, all information submitted under Sec. **554 of the** FDCA must be public so that **the** public can **fulfill** its important role in monitoring the progress **of** these studies to facilitate **their** timely completion.

The Public's Right to New Information

If patients **are** more **likely** to take a **drug** for an unproven use, which is the manufacturer's goal in disseminating that information, then they and their health care providers have a **right to all known** information about the safety and **effectiveness of that** use. By definition, the safety and effectiveness **of** the use have **not** been established and, **thus**, patients are **using** the product in an uncontrolled **setting**. This is especially troubling for women, since women have traditionally been under-represented **in** clinical trials to determine **safety** and effectiveness of drugs and devices,

Therefore, patients and their practitioners must have **access to all** data, including trial designs, possible adverse **events** contemplated by the protocol, adverse events as **they** arise over **time**, and any other **safety** or effectiveness information that would facilitate **the most** appropriate care. **For** these reasons, when the FDA approves the manufacturer's request to disseminate the information, the public should then have access to any existing or future safety **and** effectiveness **data**. To keep such information **from the public**, while **allowing that use to be** actively promoted by the manufacturer, would be unethical and counter to the best interests of the public's health.

The Public's Right to Participate in the Exemption Process

The process **of** deciding whether or not to **grant** an exemption from **filing** a supplemental application on economic **or** ethical grounds **must** be conducted on **the record** and include **meaningful** public input. The magnitude of the FDA's decision in these circumstances is tremendous. By granting such an exemption, the FDA will be giving the manufacturer **the right to** promote a use **of** a product indefinitely without ever establishing its safety and

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effectiveness. Under such circumstances, there **is** the **potential** for harm to **the** public. Therefore, prior **to** granting any **exemption**, the FDA should **hold** a meeting of the appropriate advisory committee(s), so that the public has the opportunity to **review** and comment upon the

request. Granting exemptions under any **circumstances** is, given the great potential for harm to the public, **itself** an ethical decision (**e.g.**, deciding that the economic constraints outweigh **the** possible risks of never establishing a product's safety and effectiveness is **an** ethical decision). It would **be** totally inappropriate for ethical decisions with such **a** tremendous impact on the public **health** to be **made** behind closed **doors** and without the involvement of **the** public.

As **the** FDA stated correctly in the proposed regulations, Congress intended for the granting of any exemption to be rare, so the inclusion of **an** advisory committee meeting in the process should **not create** an undue burden on **the** FDA.

Claims of Confidentiality of Information are Baseless

Some may argue that information submitted to the **agency** under Sec. 551, 552, 553, 554 should be accorded the level **of** confidentiality given to information in new drug applications. Such arguments are baseless, inappropriate and contradictory. Arguments that supporting materials should be **kept confidential** are not applicable given the fact that **the** manufacturer is **proactively** circulating information in **an** attempt to **get** more doctors **to** prescribe their product **for a** given use. To prohibit the public **release** of all supporting data prevents practitioners and their patients from acting with the full range of available information, which would be especially **ironic** given that **Sec. 401 of FDAMA** was supposedly **enacted** so that doctors and patients would have better access to information.

It is implausible to suggest that commercial considerations require such data be **kept from** the public. By circulating the article, the manufacturer has declared publicly that they have or will conduct clinical investigations **on** this specific use with **the aim** of getting **that use** added to the approved labeling. Competitors **will** undoubtedly know about a drug that is already approved, in use, studied sufficiently **to** produce journal articles and reference works on **new** uses, and **the subject of** materials distributed to practitioners and others to highlight other uses.

There are no convincing arguments for **confidentiality** when compared to the compelling public need for such information. Unlike other situations in which patients take a drug whose **safety** and effectiveness have not been established (**i.e.**, clinical trials of new drugs), these patients are taking such drugs in an **uncontrolled** environment under the supervision of

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providers who **will** often not be expert in **the drug** or its potential effects. Such providers **and** such patients should have **all** possible information to **help** assure **the** safe and effective use of these drugs that have not gone through the usual demonstration of **safety** and effectiveness.

Criteria for Information to be Disseminated

The statute states that reprints and reference publications be “about a clinical investigation,, which would be considered **to** be scientifically sound by [qualified] experts, ” The FDA’s **draft** regulations outlining the criteria for acceptable reprints and reference publications are necessary **to comply** with the clear **meaning** of the statute. Requirements that the reprint or reference publication contain comprehensive trial report information including the **study’s** design, conduct, data, analyses, and conclusions [99, 101 (b)(1)] are all necessary for determining the scientific soundness of the clinical investigation that **is** the subject of the article *or* publication. The Network believes that this portion **of** the proposed rule is a **clear** and reasonable definition of “scientifically sound” that gives clear guidance to manufacturers as **to** the type of studies that **will** be acceptable.

Disclosure Statements

The statute requires **that the** manufacturer include with **the** information that is to be disseminated a “prominently displayed” **statement** disclosing a list of important information [99, 103]. The FDA’s proposed regulations outline what criteria **it** will use **in** determining whether the statement is “prominently displayed” in **an** effort **to** make **the** implementation of **the** statutory requirement consistent and simply reiterates the list of information that must be included in **the** disclaimer as required **by** the statute. Such guidance is **necessary** to clarify what is meant by “**prominentl**y displayed” so **there** is no confusion **about** what is required of manufacturers. The “prominently displayed” disclaimer in no way interferes with the manufacturer’s ability to disseminate information,

Definition of New Use

The proposed regulations logically state that **any** use that **is** not **included** in the approved labeling **of** an approved **drug** or in the statement of intended use for a **cleared** device is **con sidered** a new use. This **regul** story definition of “new use” is consistent with **the** statute, which applies to uses “not described in **the** approved **labeling** of a drug or device. ” The FDA has correctly interpreted this to mean any use that would require a supplemental application in order to be included **in** the label, This **regulatory** definition of “nc w use” is appropriate and must be **preserved** in **the** fired regulations.

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Record Keeping

One important safeguard in the legislation requires a **manufacturer** to maintain records of the recipients of the disseminated materials so that the manufacturers can notify the recipients if it is later determined that the **new** use is ineffective **or** poses a significant risk to public health. The proposed regulations permit **the** manufacturer' to decide whether **to** keep records that identify **the** individual recipients of the **information** or the category of recipients. In **order** to ensure **that all the** people who have seen and relied on the disseminated information **will learn** of the risks associated with the promoted use, the FDA should **use** the discretion **given it by** Congress to require **the** manufacturer **to** maintain specific records **of the** individual recipients of the **information** in **all** cases. A categorical **list** of recipients is not **sufficient** to comply with **the** safeguard outlined **in** the statute. Complete and thorough corrective actions **appropriate** for the protection of public health will **occur only** if the manufacturer keeps **specific** records identifying **the** individual recipients of the disseminated information **and then** notifies those individuals directly.

In addition, requiring manufacturers to maintain **lists** of individual recipients will help **meet** another safeguard **of** the legislation -- that the information **be disseminated** on] y to individuals **in** select categories. By requiring companies to maintain **lists** of recipients, **the** FDA will **help to assure** that companies distribute materials **only to** the appropriate individuals by using tightly controlled mechanisms, such as direct mailings, that will facilitate maintaining an accurate list **of** recipients.

Conclusion

As the FDA moves forward with **the** implementation of **the final** regulation, **it is** crucial that every possible safeguard be **put** in place **in order to** protect the health of **the** American public. The FDA must take every step possible to fulfill its mission **to** protecting **the** public health in the face of regulations that **will** put into **place** a mechanism allowing the promotion **of new** uses **that** have not **been** proven safe and effective,

Sincerely,



Cynthia A. Pearson
Executive Director