BENNETT, TURNER & COLEMAN, LLP
1900 K Street, N.W.
Suite 750
Washington, DC 20006

Phone: (202) 833-4500
Fax: (202) 833-2859

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CITIZEN PETITION

The undersigned, Bennett, Turner & Coleman, LLP, submits this petition pursuant to Section 502 of the Federal Food, Drug, and Cosmetic Act, and 21 C.F.R. § 201.128, to request the Commissioner to clarify the Food and Drug Administration's (FDA's) policy with respect to the ability of pharmaceutical and biological product sponsors to define the "intended use" of regulated products and therefore to exert meaningful control over the content of product labeling.

A. Action Requested

Petitioner seeks a regulatory clarification from FDA that, absent a significant public health justification supported by substantial data, the uses of a product described in the labeling should be determined by the sponsor. Specifically, petitioner requests deletion of regulatory language in 21 C.F.R. § 201.128 indicating that a sponsor may be required to provide labeling for a use other than that intended by it simply because the sponsor has knowledge of these "unintended" uses by third parties.

B. Statement of Grounds

Factual Background

In the first instance, the sponsor of a new drug application (NDA) or biologics license application (BLA) determines the clinical indications and conditions of use for the product. The process is set in motion by the design of clinical trials that form the basis of the NDA or BLA. Thus, to the extent that a sponsor intends to market a product for a particular indication and under certain conditions of use, those elements are included in the studies that are submitted to FDA in support of the product application, and FDA generally has accepted the sponsor's views on those matters if they are consistent with the studies' results.

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FDA regulations provide that product labeling should include "adequate directions for use" consistent with the "intended use" of the product. 21 C.F.R. §§ 201.5, 601.25(d). In general, the sponsor's intention is determined by its "objective intent," as reflected in "labeling claims, advertising matter, or oral or written statements." 21 C.F.R. § 201.128. However, the regulations also provide a substantial exception to the general rule on intended use:

> "But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put." Id.

This exception, at least on paper, also extends to biological products, since FDA labeling regulations for biologics require compliance with Part 201.

As discussed in more detail below, this "exception" provision is inconsistent with the general regulatory scheme for review and approval of products based on claims made by the sponsor. Although included in the regulations for 25 years, we are aware of no situation in which it has been invoked to require labeling for an indication or use not sought by the sponsor. Thus, except for specific initiatives implemented through notice-and-comment rulemaking — notably regulations imposing certain requirements on tobacco products and on adult drugs that are foreseeably utilized by children — the "intended use" of regulated products is determined by the sponsors.

Recent developments, however, present a challenge to the sponsor's ability to influence in a meaningful way those important elements of product labeling. A number of citizen petitions have been submitted seeking to compel product labeling that is not consistent with the uses asserted by the sponsors. Although the agency has generally not responded favorably, it has also not rejected these petitions outright as it might have. Morever, in some circumstances, FDA itself has sought to impose on sponsors different uses than those that were originally intended.

Collectively, these actions pose a threat to the ability of sponsors to control their products and the manner in which they are used. If successful, these initiatives could have profound impact on many different aspects of drug and biological development, including incentives for research, exposure to product liability and ability to obtain third-party reimbursement.

Citizen Petitions

Among the privately initiated efforts to achieve involuntary labeling changes are the following:

- ☐ In November 1994, petitioners urged FDA to require manufacturers of certain oral contraceptive products to amend their labeling to include instructions for use of the products for postcoital emergency contraception. FDA declined to impose such a requirement, although the agency insisted that it had the legal authority to do so. Instead, FDA asked the Advisory Committee for Reproductive Health Drugs to review the available safety and effectiveness data for the new use and to outline specific prescribing information, which was then published in the Federal Register. Manufacturers were encouraged, but not required, to submit proposed labeling information as part of a new drug application (NDA). 62 Fed. Reg. 8610 (Feb. 25, 1997). Subsequently, in September 2000, the American Society for Emergency Contraception petitioned FDA to expand the published information about use of these products for the unlabeled purpose of emergency contraception.

- ☐ In July 1998, Blue Cross of California (now WellPoint Health Networks) submitted a citizen petition seeking an FDA-initiated "switch" of prescription antihistamine products to over-the-counter (OTC) status, regardless of whether any sponsor sought the switch. The petition specifically cited the newer generation antihistamines Claritin® (loratadine), Allegra® (fexofenadine), and Zyrtec® (cetirizine). This request was strongly opposed by industry. See statement of Russel A. Bantham, Pharmaceutical Research and Manufacturers of America, at OTC Drug Products Hearing, Docket No. 00N-1256 (June 28, 2000).

- ☐ The American College of Obstetricians and Gynecologists (ACOG) submitted a petition in November 2000 seeking new labeling for misoprostol. ACOG argued that current contraindications for use of the drug in pregnancy should be rescinded in order to facilitate its use in combination with mifepristone to achieve nonsurgical early pregnancy terminations. The petition also sought withdrawal of a warning letter forwarded to physicians from misoprostol concerning lack of labeling information about the use of the drug in connection with pregnancy termination or induction of labor. Consistent with current product labeling, the sponsor's letter stated that administration of misopristol to pregnant women is contraindicated because it can induce abortion. The sponsor indicated it had no intention of conducting studies to support label information about use of misoprostol for termination of pregnancy or induction of labor.

- Most recently, in February 2001, medical and public health organizations petitioned FDA to convert several FDA-approved emergency contraception drugs to OTC status on the ground that prescription dispensing is not necessary for the protection of the public health.

FDA Action

For the most part, FDA has not yet acted on the various requests for involuntary labeling changes set forth in the above-referenced citizen petitions. However, in several instances, FDA has acted on its own initiative to challenge fundamentally the longstanding ability of sponsors to determine the intended uses of their products as reflected in product labeling.

- The most prominent example of such FDA-initiated involuntary labeling changes is the regulation requiring manufacturers of certain products to conduct pediatric safety and effectiveness studies in order to support labeling for pediatric uses. 63 Fed. Reg. 66632 (Dec. 2, 1998). This regulatory requirement was the culmination of a multi-year process of review of perceived shortcomings in pediatric labeling and was explicitly based on a finding that the affected drugs were "commonly used" in children.

- Occasionally FDA has exerted influence on sponsors to include in product labeling information about uses that are not requested by the sponsors, that have not been studied by them, or that are not "customary or usual" as set forth in § 201(n) of the Federal Food, Drug, and Cosmetic Act ("the Act"). For example, manufacturers of certain biological products that are intended by sponsors to be administered by physicians and that have been studied in that context have been urged by FDA to include in the product labeling instructions for self-administration by patients.

Legal Issues

The legal authority of FDA to compel or coerce a pharmaceutical or biological sponsor to include in its product labeling information about a use that is not intended by that sponsor is highly questionable. The cornerstone of FDA regulation of pharmaceutical and biological products is the concept of "intended use," which is defined in agency regulations and practice. It is fundamentally inconsistent with longstanding FDA policy on "intended use" for the agency to

force sponsors to provide labeling for a use that is not only unintended but also unwanted, regardless of whether the agency is acting on its own initiative or at the behest of a citizen petition.

1. FDA lacks general authority to compel labeling for a use not intended by the sponsor.

The term "drug" is defined in the Act as including "articles intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(C). This could include a biological product, if it were to be intended to serve such structural or functional purposes. Congress and the courts have both regarded the limits of FDA's authority over drugs to be defined by the "intended use" of the product as stated by the product sponsor. Thus, the United States Court of Appeals for the District of Columbia Circuit, in ASH v. Harris, 655 F.2d 236, 238-39, noted that "the crux of FDA jurisdiction over drugs" is found in "manufacturers' representations as revelatory of their intent." In ASH v. Harris, FDA itself urged that position upon the Court in resisting efforts to assert jurisdiction over tobacco products.[1]

The concept of "intended use" is defined in FDA regulation at 21 C.F.R. § 201.128:

> " The words *intended uses* refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article."

For biological products, this definition is incorporated by reference through FDA's biologics regulations at 21 C.F.R. § 601.25(d), which requires compliance with Part 201.

Although the regulations squarely place the determination of "intended use" in the control of the sponsor, they also assert in the last sentence of § 201.128 that, in some circumstances, knowledge of other uses may require labeling:

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[1] Significantly, when FDA reversed its longstanding policy of resisting jurisdiction over tobacco products and sought to regulate them, it did so primarily on the basis of its discovery of numerous previously undisclosed documents objectively reflecting the intent of manufacturers to create drug-like effects. Despite this evidence of objective intent and despite FDA's assertion that the effects of tobacco "are so widely known and foreseeable that [they] may be deemed to have been intended by the manufacturers," 61 Fed. Reg. 44418, 44687 (1996), the Supreme Court rejected the agency's efforts to regulate tobacco products. FDA v. Brown & Williamson Tobacco Corp. 529 U.S. 120 (2000).

> "[I]f a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put."

21 C.F.R. § 201.128.

This provision is problematic for several reasons. First, it is inconsistent with the notion set forth in the same section of the regulations, that it is the stated intention of the sponsor, as reflected in advertising or labeling, that determines "intended use." If the sponsor's "intent" can be determined by the actions of others in pursuing alternative unlabeled uses of a product, then the concept of intention is rendered meaningless. Regardless of whether a sponsor has knowledge of a third party's "intended use," it is illogical to thereby impute intent to the sponsor when all its actions and statements are to the contrary.

2. <u>"Unintended" uses of a drug or biologic are not required to be included in labeling absent demonstrable safety concerns arising from such uses that are "customary or usual."</u>

The Act recognizes only one narrow and theoretical circumstance in which labeling might be required to reflect something other than the sponsor's intended result. In the determination of whether a drug may be "misbranded" and thus subject to regulatory action, the Act recognizes in § 201(n), 21 U.S.C. § 321(n), that such determination may be based on the adequacy of labeling with respect to "consequences which may result from the use of the article . . . under such conditions of use as are customary or usual."

However, it is by no means clear how the agency is to determine what uses are "customary or usual." At the very least, it would seem that there must be substantial evidence of "customary or usual" usage before the agency could compel a sponsor to provide labeling consistent with such usage. In addition, because the Act focuses on "consequences" of such usage, it seems that compelled labeling would of necessity be based on safety concerns in a setting where the product is being widely used for unlabeled purposes.

Thus, when FDA initiated the so-called pediatric rule, it did so only after a multi-year rulemaking process in which it sought to justify and define carefully the limits of its ability to require labeling beyond that proposed by the sponsor. The rule was based on documented findings that many drugs labeled only for adult usage were in fact widely prescribed for children and that the absence of pediatric safety, efficacy and dosing information posed a significant health hazard that could only be remedied through mandatory pediatric labeling.

The pediatric rule has been challenged as inconsistent with the Act and is currently under review by the United States District Court for the District of Columbia. Petitioner takes no position with respect to the validity of the pediatric rule or the appropriate outcome of the litigation seeking to nullify it. However, the pediatric rule certainly represents the outer boundaries of FDA authority to compel labeling that is not proposed or supported by the product sponsor. And it is significant that the agency believed it could exercise that purported authority only through an extensive rulemaking process.[2]

Policy Considerations

Aside from the doubtful legality of efforts by FDA to impose unwanted labeling on product sponsors (whether or not data exist to support such labeling), there are very strong policy reasons why the agency should not seek through such involuntary labeling to stimulate uses of a product that are different from those actually intended by the sponsor. Among these are the following:

Liability Concerns – Pharmaceutical and biological products are prominent liability targets. In such an environment, a manufacturer should have the ability to limit product labeling to uses that are considered not just medically appropriate but also defensible from a product liability perspective. FDA should not assert unilaterally that the product may be used in ways different from the sponsor's intentions because this advice from the agency could encourage uses that subject the sponsor to unwarranted liability exposure.

Reimbursement Concerns – Some third-party payers, notably the Medicare program, place limitations on the circumstances under which they will cover the cost of prescription drugs. Medicare rules, for example, have traditionally refused payment for self-administered drugs while covering physician-administered drugs. In that setting, labeling that provides for self-administration of drugs that have been customarily and usually administered by physicians could have profound implications for patients dependent on Medicare reimbursement.

Proprietary/Exclusivity Concerns – Under a variety of statutes, ranging from the Hatch-Waxman legislation to the Orphan Drug Act, the vulnerability of product sponsors to generic competition may be influenced by the scope of the labeling of their products. For example, the labeled uses of a product could be protected by patents, while FDA might compel the addition of another unpatented or less protected use. In that case, generic versions might gain marketing approval based on the compelled addition. Absent a substantial public health interest and specific statutory or regulatory authority, FDA should not insinuate its regulatory authority into a process that has significant implications for protection of the sponsor's proprietary interests.

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[2] When FDA sought to rely on "foreseeable" uses to support agency jurisdiction in the tobacco regulation, it also apparently felt it necessary to do so through legislative rulemaking.

Sponsor and Labeling Autonomy – Actions by FDA that seek, absent extraordinary circumstances, to control the content of product labeling by expanding the "intended" labeled uses are fundamentally inconsistent with the regulatory scheme established by the Act. It is the product sponsor that typically decides which uses of the product will be pursued, designs and conducts (in consultation with FDA) clinical studies to support such uses, and proposes product labeling that captures both what is known about the safety and efficacy of the product and what uses are intended. A different approach, in which FDA determines which uses are "intended" by the sponsor, essentially restructures the regulatory scheme envisioned by Congress and enforced by FDA for decades. Abrogating sponsor control over "intended uses" would represent a major departure from longstanding agency policy and practice.

CONCLUSION

FDA efforts to enforce involuntary labeling changes may be justified, if at all, only in certain limited circumstances, such as those reflected in the pediatric rule, where they are supported by a protracted rulemaking process and evidence of "customary and usual" pediatric usage of adult products. Absent extraordinary circumstances involving demonstrable health hazards associated with customary and usual usage, the determination of "intended uses" of products should be in the absolute control of the product sponsor. Petitioner urges FDA to initiate a rulemaking in which the last sentence of 21 C.F.R. § 201.128 is deleted to make the regulation consistent with the concept of "intended use" embodied in the Act, the implementing regulations and decisions of the courts.

C. Environmental Impact

The action requested is subject to a categorical exclusion from environmental assessment under 21 U.S.C. § 25.30(h).

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), Bennett, Turner & Coleman, LLP will provide data concerning the economic impact of the action requested should such information be requested by FDA.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Terry S. Coleman
Bennett, Turner & Coleman, LLP
1900 K Street, NW, Suite 750
Washington, DC 20006
(202) 833-4500