



# OFF-LABEL USES OF APPROVED DRUGS A New Compromise is Needed

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# OFF-LABEL USES OF APPROVED DRUGS A New Compromise is Needed

Robert H. Pritchard

Washington, D.C. is teeming with speculation regarding the likely effects of a new political scenery and the Republican Contract With America. As the new Congress is taking form and adjusting to a new reality, one voice stands out amid the uproar... House Speaker Newt Gingrich has an agenda, and his intentions, though not clearly spelled out, have certainly not been withheld from public discourse. One of Mr. Gingrich's strongly voiced concerns centers on structure of the FDA as it currently exists, and the effect that the entrenchment of bureaucracy has on the functioning of this agency. Mr. Gingrich frequently cites an example of a plunger-like cardiopulmonary resuscitation aid which, though invented in the United States and proven tremendously effective in Europe, is illegal and unavailable for use in this country.<sup>1</sup>

Mr. Gingrich's criticism of the FDA is not a new one. It is a common complaint that FDA regulation follows the path of a pendulum: sometimes it is too lax, and other times it is much too strict. The current FDA, with Commissioner David Kessler at its helm, is thought to be trapped in the latter position.

An issue that has been debated without resolution for many years centers on the topic of unapproved uses of drugs that have received FDA approval. Approval is required before a new drug can be marketed as such, and

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<sup>1</sup> [e - FDA • Is it Too Powerful?](#), Healthline. Dec. 12. 1994.

is granted only upon submission of proof that a drug is safe and effective for a specific use. Accordingly, any given drug is, technically, sanctioned only for the use and dosage on which its safety and efficacy studies focused. In essence, any change in use or dose from that studied in the clinical experimentation could be said to require FDA approval. Fortunately, it has been recognized that such a system would not only be unmanageable for the government, but would significantly undermine the effectiveness of medical practice. The primary drawback of such a broad approval requirement, as routinely voiced throughout the medical community, is that forcing physicians to use drugs only for their indications would... mean that people would die that didn't have to.<sup>2</sup> Simply stated, off-label drug uses are a medical necessity in a world where patients and strains of diseases often vary only slightly from one another, such that established treatments must be tailored to meet individual needs. Countering this need for flexibility, however, is the necessity of public protection from unsafe and ineffective drugs. For every piece of anecdotal evidence showing a death that could have been avoided if a particular drug or instrument had been available, there is a similarly compelling example of a situation in which a patient has died needlessly at the hands of an ineffective physician or method of treatment.

In attempting to balance these conflicting interests, the FDA has maintained a fairly consistent approach, endeavoring to ensure the availability of needed drugs without sacrificing high standards of safety. Unfortunately, the FDA's own difficulty in balancing these opposing concerns is reflected in regu-

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<sup>2</sup>Robert Goldberg. *AARP Hands Members a Poison Pill*. The Wall Street Journal. August 16, 1994. (Citing Lawrence Norton of Memorial Sloan-Kettering.).

latory inconsistency. While promotion of off-label uses is prohibited of manufacturers, physicians are generally free to engage in off-label prescribing. This seeming compromise hides a dangerous reality by permitting medical practice to proceed without the benefit of complete information.

This paper advocates elimination of this inconsistency from the regulation of off-label uses of approved drugs. Following an exploration of the statutory basis of FDA regulation of unapproved uses, it will be argued that the FDA should limit its intervention into the practice of medicine. FDA regulation in this area is unwise and infeasible; in addition, there are alternative mechanisms that are already in place which, working in combination, can promote the safety of medical treatment while preventing irrational delay in the marketing of drugs and treatments which could improve the lives of millions of Americans on a daily basis.

#### Statutory Authority to Control Off-Label Promotion and Prescription

Two pair of provisions within the Federal Food, Drug and Cosmetic Act<sup>3</sup> (the FDCA) are implicated in the analysis of the FDA's statutory jurisdiction over unapproved uses of approved drugs. The first, the New Drug Provisions, arise from Section 301(d) of FDCA which provides that it is unlawful to introduce into commerce an article that is in violation of FDCA Section 505. Section 505, entitled New Drugs, establishes a requirement that any new drug<sup>4</sup> receive FDA approval as to its safety and effectiveness before it is entered

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<sup>3</sup> 21 USC §301. et. seq. (1972).

<sup>4</sup> The term "new drug" is defined in FDCA §201(p) as "any... the composition of which is such that such drug is not generally recognized... as safe and effective for the use under the conditions prescribed, recommended, or suggested in the labeling thereof"

into interstate commerce.

The second set of relevant provisions, the Misbranding Provisions, involves Sections 301(k) and 502 of FDCA. Section 301(k) provides that it is unlawful to undertake the... doing of any..., act with respect to a food [on ~ug... if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being... misbranded. Section 502 provides the definition of misbranding in the context of drug labeling, and two particular provisions are relevant to this analysis: Section 502(a) provides that a drug is misbranded if its labeling is false or misleading in any particular; Section 502(b) stipulates that a drug is misbranded if it does not bear adequate directions for use

Under the 1906 Food and Drugs Act, the FDA had jurisdiction over misbranding and adulteration violations occurring at any stage of a drug's marketing and distribution process. It was presumed by the FDA that this authority was carried over into the 1938 FDCA<sup>5</sup>, which was more comprehensive and protectionist than its predecessor. Consequently, the FDA acted for many years on the presumption that it had the right to bring actions against foods and drugs which became adulterated or misbranded at any point prior to delivery to the ultimate consumer. In 1947, however, the FDA was dealt a blow by the Ninth Circuit Court of Appeals in United States v. Phelps Dodge Mercantile Co., 157

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<sup>5</sup> See. e.g. *Hearing on Seizure of Food and Drugs on HR. 3128*, 80th Congress. 1st. Sess. at 3 (1947). (*Reiterating that at the time of passage of the 1938 statute that "It was believed that the words "while in interstate commerce" were at least as inclusive as the language of the old law [and that it/here is nothing in the extensive legislative history of the new act that reveals anything but approval by the Congress and the regulated industries of the long-standing practice of condemning goods which after interstate shipment became adulterated.]*)

F.2d 453 (1946). In that case, a batch of pasta noodles became adulterated, while waiting to be distributed for sale, more than two years after it had been shipped in interstate commerce. When the FDA attempted to engage its powers of seizure over the items, its jurisdiction over the spoiled food was challenged. Relying on the FDCA as it appeared at the time, the court prevented the FDA from asserting jurisdiction, holding that if an item was not adulterated or misbranded before or during interstate shipment, FDA jurisdiction was improper.

The immediate response to this apparent deficiency in the FDCA was the introduction and passage of the Miller Amendment, 62 Stat. 582 (1948). The Amendment resulted in two changes in the FDCA: Section 301(k) was amended to include the phrase “(whether or not the first sale)”<sup>6</sup>, which, along with a similar addition to Section 304(a), had the effect of extending the misbranding and adulteration prohibitions for food and drugs to the time period after interstate shipment. As a result, it is now unlawful for an action to be taken which results in the misbranding or adulteration of a drug at any stage of the item’s marketing and distribution process, thereby reconciling the 1938 statute with statute that preceded it.

The Miller Amendment did not, however, provide the FDA with complete jurisdiction over post-shipment drug activity. Section 301(d), invoking the New Drug rules of FDCA Section 505, was not included in the Amendment. Consequently, the FDCA does not prohibit a drug from being rendered a knew

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<sup>6</sup>This provision now provides that adulteration or misbranding of a food or drug is actionable if such adulteration or misbranding occurs “while such article is held for sale (whether or not the first sale) after shipment in interstate commerce 21 USC §331(k) (1972) ((FDCA §301(k) )).

drug' after it has been shipped in interstate commerce, and then being sold without pre-marketing FDA approval as is generally required. Instead, the statute provides that if the Section 505 approval requirement has been met for a drug in the form in which it is transported in interstate commerce. a physician's subsequent prescribing activities should be held to neither reinvoke Section 505 nor be constrained by the provision.

Throughout the history of the FDCA, two theories have been posed in an attempt to create liability for a physician's off-label practices<sup>7</sup>. First, it has been claimed that a doctor who prescribes drugs for off-label uses creates a new drug that must obtain FDA approval before it can be marketed. A doctor's prescription of a drug for an unapproved use creates a new drug<sup>8</sup> which, if introduced into interstate commerce, would ordinarily be subject to the FDCA Section 505 approval requirement. Given current understanding of the Miller Amendment's limited reach, however, it is now commonly held that this approval requirement is not applicable where a doctor's prescribing activities occur after a drug has completed its interstate distribution. If an approved new drug is shipped in interstate commerce with the approved package insert, and neither the shipper nor the recipient intends that it be used for an unapproved purpose, the requirements of section 505 of the Act are satisfied.<sup>9</sup> Consequently, attempts

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<sup>7</sup>The existence and judicial acknowledgment of the following arguments shows that the exact scope and implication of the Miller Amendment and off-label prescription activities have been unclear at best for many years.

<sup>8</sup>Anything which currently required a new drug application such as a new product *or new use for an existing product which is not generally recognized as safe* will in the future have to make the test of effectiveness [§505 FDCA] laid down in the bill as amended. (Emphasis added). S. Rep. No. 1744, 87th Cong., 2d. Sess. (1962). (Discussion in relation to 1962 Amendments to Food, Drug, and Cosmetics Act.)

<sup>9</sup>Legal Status of Approved Labeling for Prescription Drugs. 37 Fed. Reg. 16503 (1972).

to hold physicians liable for off-label activities through reliance on Section 505 of the FDCA are consistently rejected on the basis of the FDCA itself.<sup>10</sup>

Attempts have also been made to establish physician liability through reliance on the FDCA's misbranding prohibitions of Section 301(k). This provision is, as discussed above, applicable to any stage of a drug's distribution process, and is not limited by the restricted scope of the Miller Amendment. Section 502(f) requires that a drug bears... adequate directions for use.... Accordingly, it has been alleged, as in United States v. Evers, 643 F.2d 1043 (5th Cir. 1981), that a doctor's off-label prescribing resulted in a drug's being misbranded since the label did not contain adequate directions for the use promoted by the physician. In Evers, however, the court held that a doctor's off-label prescribing does not constitute misbranding when the physician is promoting the drug only to his own patients. The drug labeling provisions as set forth in the Regulations accompanying the FDCA<sup>11</sup> require that a drug's labeling provide instructions for use that would be sufficient and meaningful to a layman. For prescription drugs<sup>12</sup>, however, the layman requirement has been eliminated since prescription drugs are by definition presumed to contain elements unexplainable and incomprehensible to an individual lacking medical expertise. Accordingly,

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<sup>10</sup>One must note, however, that the language of the statute creates an exception to a doctor's freedom to prescribe. If a physician were to prescribe a drug for an off-label use to a patient who then purchased the drug in a new state or transported the drug to a new state, the physician would be reintroducing the drug into interstate commerce, and would theoretically be bound by the approval requirements of Section 505. In fact, however, I found no authority supporting such a broad interpretation of the FDCA.

<sup>11</sup>21 C.F.R. §201.5. et. seq. (1994).

<sup>12</sup>The status of prescription drug is assigned to a product which because of its toxicity or other potentiality for harmful effect, or the method of its use... is not safe for use except under the supervision of a practitioner licensed by law to administer such drug... [and is therefore] limited... to use under the professional supervision of a practitioner licensed by law to administer such drug 21 USCA §353(a) (1972).



prescription drugs are not subject to Section 502(f)(1), and instead are required to provide information sufficient for a physician to understand the conditions for proper use of the product.<sup>13</sup> Consequently, as held the court in Evers, a doctor providing drugs for off-label uses to his own patients owes a duty only to himself, and is not to be held liable for labeling violations.<sup>14</sup>

In contrast, drug manufacturers are not granted as much freedom with regard to unauthorized uses of the drugs that they produce. The law has developed, consistent with the language of the statute, such that a manufacturer is permitted to neither label nor promote a product for a use that has not received FDA approval. Manufacturer liability is established in practice under both the New Drug and the Mislabeling provisions.

Both provisions are called upon to prevent a manufacturer from including unapproved uses of drugs on the labels and package inserts which physically accompany drugs throughout interstate commerce. First, Section 505 provides that since a new drug is created upon inclusion of a new use on a drug's label, FDA approval must be obtained before interstate shipment (since the drug's 'newness' arises before interstate shipment, the limitation on the Miller Airindment has no effect here). Further, a manufacturer's label indicating

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<sup>13</sup>21 C.F.R. §201.100(d)(1) (1994). ~ David. A. Kessler. *Regulating the Prescribing of Human Drugs for Nonapproved Uses under the Feed, Drug, and Cosmetic Act*. 15 Harvard J. Legis. 693. 742. 747(1978): Ma~ee v. Wyeth Laboratories. 214 Cal.App. 2d 340. 350 (1963).

<sup>14</sup>Two unlikely exceptions to this §502 exemption are possible under the terms of the statute. First, if a physician were to promote an off-label use of an approved drug to other physicians. his actions would render the product misbranded since the label of the product would not convey sufficient information to explain the intended use to the recipient physician(s). In addition, a doctor's promotion of over-the-counter drugs for off-label uses would render the drugs misbranded, since the labeling would not sufficiently describe the intended use of the product to the end user (over-the-counter drugs. unlike prescription drugs. are subject to the layman requirements of §502(f).) I found, however, no cases which established liability for a physician in either of these two situations.

unapproved uses constitutes misbranding under FDCA Section 502(a)<sup>15</sup>. since inclusion of such uses on the label falsely indicates FDA approval of the use. As a result, a manufacturer is strictly prohibited from listing unapproved uses on a drug's label.

Similarly, a manufacturer is not permitted to promote off-label uses of a product beyond the confines of the label. The FDCA's misbranding prohibitions apply not only to a product's label, but to all elements of a product's labeling. Pursuant to FDCA Section 201(m), the labeling of a product includes all written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article. Much debate has arisen over the appropriate inclusiveness of this term. In general, courts concur that a product's labeling includes not only the indications affixed to the product and contained within the packaging in which the product is located, but also to all written and oral statements which supplement or explain the affixed literature.<sup>16</sup> Consequently, the FDA has the authority to take action against a manufacturer who describes off-label uses in any type of supplemental explanation provided in connection with a consumer's purchase of a drug. As will be discussed later, the FDA has greatly increased its powers in this area through an exceptionally generous interpretation of labeling.

In sum, this extremely inclusive regulatory structure prevents a manufacturer from promoting off-label uses of its drugs in any situation, and

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<sup>15</sup>A drug is misbranded if its labeling is false or misleading in any particular. 21 USC §351 (1972) ((FDCA §501(a) )).

<sup>16</sup>Kordel v. United States. 335 U.S. 345 (1948). See also United States v. Articles of Drug, 5906 Boxes, 745 F.2d 105. 114 (5th Cir. 1984).

at any time, during a drug's distribution process. A physician, on the other hand, is not prevented from prescribing approved drugs for off-label uses under certain conditions.

#### FDA Implementation of its Statutory Authority

The FDCA, its accompanying Regulations, and related case law provide the boundaries within which the FDA must operate in order to avoid being charged with exceeding its statutory authority, per the Administrative Procedure Act. Within these boundaries, however, the FDA is permitted to exercise discretion in deciding how to implement the statute, and it cannot be forced to take action merely to meet the letter of the statute.<sup>17</sup> The FDA's current policy regarding off-label uses of drugs provides that drug manufacturers cannot promote off-label uses either directly, through labels and package inserts, or indirectly through advertising and promotional activities. At the same time, the FDA maintains a position, somewhat skeptically, that off-label prescribing by doctors is permissible, since such activities are outside the jurisdiction of the FDA.

The FDA's position on off-label prescribing activities of physicians is embodied in a 1972 Proposed Rulemaking upon which formal action has never been taken<sup>18</sup>. This document briefly traces the statutory evaluation discussed

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<sup>17</sup>*Heckler v. Chaney*, 470 U.S. 821. 831 (1985) (*[A]n agency's decision not to ... enforce is a decision affirmatively committed to an agency's absolute discretion.*)

<sup>18</sup>Legal Status of Approved Labeling for Prescription Drugs: Prescribing for Uses Unapproved by the Food and Drug Administration. 37 Fed. Reg. 16503 (1972). The FDA recently considered revoking this proposal after it had remained pending for nineteen years. but in the end decided not to withdraw this proposed rule at this time. Instead, a task force has been created to study off-label uses of prescription drugs, and the FDA has deferred further action on the proposal until the task force has presented its findings on this widespread practice. Withdrawal of Certain Pre-1986 Proposed Rules. 56 Fed. Reg. 67440(1991).

in the prior section of this analysis, and concludes by providing that tince the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration. On somewhat shakier ground, the FDA concludes its proposal with an assertion that liwihen an unapproved use of a new drug may endanger patients or create a public health hazard, or provide a benefit to patients or to the public health, the Food and Drug Administration is obligated to take one or more of the following courses of action...<sup>19</sup>, which actions include requiring revision of the package insert and revocation of the drug's approval. J~1 at 16504.

Although the FDA's primary reason for existence is protection of the public from harms that may result from the marketing and prescribing of adulterated foods and drugs, the powers of the FDA to fulfill this role are not unlimited. Despite the fact that safety statutes such as the FDCA are meant to be interpreted liberally in order to further their safety goals, an agency cannot pursue a statutory interpretation through which it exercises powers which have not been delegated to it. Consequently, without statutory authority to do so. the FDA has no right to utilize its powers to curb off-label prescriptions by doctors merely because such uses become widespread or prove to be ineffective.

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<sup>19</sup>Similarly. current FDA Commissioner David Kessler is quoted as saying that he intends to bring the full force of the law against anyone manufacturing, selling, shipping, or using drugs in an off-label fashion. Robin M. Henig. FDA Assails Off Label Uses of Cosmetic Drugs. The Washington Post, June 18. 1991 at z7.

Current FDCA Sections 301 and 505, as discussed above, limit the power of the FDA to take action against a physician's off-label activities, and make no distinction between off-label uses which are safe as contrasted with those that are not. The legislative history of the FDCA further indicates that the FDA was not meant to interfere in a physician's exercise of discretion in determining how an approved drug is to be utilized in treating a particular patient's ills, regardless of the success of the treatment. Remarking on the Act as introduced to the Senate in 1934, the bill's sponsor, Senator

Copeland, stated without condition that this bill makes certain that the medical practitioner shall not be interfered with in his practice.<sup>20</sup> Similarly, Senator Carroll, discussing the matter during Senatorial debate of the 1962 amendments to the FDCA, stated that I am not taking about regulating medicine between the physician and the patient.<sup>21</sup> In making such broad assertions, the legislators acknowledged not only the status of a physician as a trained professional with ethical responsibilities imposed by the medical profession, but also the presence of medical malpractice and other forms of civil liability which would suffice to provide remedy where a doctor's prescribing actions brought undue effects. Neither the statute nor its history indicates intent to condition the FDA's hands-off policy upon the eventual success or failure of the innovative treatment.

Indeed, in presenting the FDA's intention to take such bold regulatory action, the text of the proposal offers no justification or source of power

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<sup>20</sup>78 Congressional Record 2728 (February 19, 1934).

<sup>21</sup>108 Cong. Record 17398 (August 23, 1962).

under which the FDA might act. Further, there seems to be no clear statutory authority for the FDA to take action pursuant to a physician's actions per se. Action may be warranted, though, if the effects of a physician's activities as evaluated according to the New Drug provisions of FDCA Section 505 were to be imputed to the *man ufacturer*.

A defining feature of a drug is intent.<sup>22</sup> Following significant debate, the current consensus provides that the 'intent' underlying an item's status as a drug is that of the manufacturer of a drug, and not that of the consumer or prescribing physician.<sup>23</sup> Similarly, a new drug is to be defined as a drug 'intended by the manufacturer to be used as a drug' which has not been generally recognized as safe, as defined in FDCA Section 505. At one level, then, it appears that significant off-label use of a prescription drug is

- to - irrelevant in ascertaining whether an item is a drug, or a new drug, as such use does not indicate manufacturer intent. Consequently, a manufacturer is generally not to be held liable for marketing a new drug without FDA approval merely because an approved drug is used by consumers in an off-label manner.

There is, however, an exception to the 'manufacturer intent' requirement, whereby consumer use may in fact be imputed to a manufacturer and deemed manufacturer intent. In such a situation, it is theorized, a manufac-

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<sup>22</sup>A drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease 21 USC 321(g)(1)(B) (1972) ((FDCA §201(g)(1)(B) )).

<sup>23</sup> See *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (CA D.C. 1980) (*Statements by petitioners and citations in the petition that cigarettes are used by smokers ... are not evidence of such intent by the manufacturers or vendors of cigarettes, as required under FDCA §201(g)(1)(B)*) .. See *National Nutrition Foods Association v. Mathews*, 557 F.2d 325, 333 (2d Cir. 1977) (*The vendors intent in selling the product to the public is the key element in this statutory definition.*)

turer's failure to act to prevent an unapproved use in the face of widespread off-label use implies that the manufacturer intended for the use to continue without limitation. The basis for the exception is articulated in Hanson v. United States, 417 F.Supp. 30, 35 (D.Minn. 1976), wherein the court stated that the 'intended use' of a product... is determined from its label, accompanying labeling, promotional claims, and any other relevant source. It has been held that consumer use of a product can serve as a 'relevant source' in certain situations. The court in National Nutritional Foods Association v. Mathews, *supra* n. 23. implied that consumer use could substitute for objective manufacturer intent where the item was used almost exclusively for therapeutic purposes. Mathews at 336. Similarly, the court in Millet. Pit and Seed Company v. United States, 436 F.Supp. 84, 89 (E.D. Tenn. 1977) stated that the seller's knowledge of the consumers' uses for his product is a factor to be considered [in evaluating all factors to ascertain manufacturer intent],..., but we do not agree with the apparent theory of the government that if *any* consumers use a product as a drug, such use, if known by the seller, is determinative on this issue. These cases indicate that although widespread consumer use can be imputed to a manufacturer as intent, implied intent under this theory is to be found only in rare situations where consumers... use the product predominantly and in fact nearly exclusively with the appropriate intent.... Action on Smoking and Health, *supra* n. 23 at 240. Therefore, although FDA jurisdiction may be justified in certain situations, it is ó116 clearly not so merely because an unapproved use of an approved new drug becomes widespread....

A related justification for manufacturer liability due to physician or consumer usage arises by analogy to the tort concept of 'attractive nuisance'. According to this theory, a party is deemed to have an affirmative obligation to protect the inexperienced and those who lack maturity in judgment... from injuries which were, under the circumstances, foreseeable.<sup>24</sup> In its pure form, the doctrine is applicable only to situations in which children are injured while trespassing. Given the physical and psychological effects of severe illness, however, it could be asserted that like children, individuals facing a choice of death or an unapproved use of a drug are incapable of making a mature decision with respect to untested uses of approved drugs, thereby establishing a duty for the manufacturer to take steps to prevent off-label uses. If this proposition were accepted, the FDA would be able to curb off-label uses merely by showing that an off-label use was foreseeable, whereby a manufacturer's failure to take action to prevent off-label drug use would be equated with intent to promote the off-label use. Unlike the burden to be met in creating manufacturer liability given widespread off-label use alone, a lower threshold of foreseeability under attractive nuisance theory would permit the existence of significant unlabelled drug use alone to carry significant weight in imputing manufacturer intent through consumer action.

The current scheme, whereby manufacturer intent is inferred from consumer action in only a very narrow range of situations, may be thought to severely limit the FDA's power to take action, but is crucial to a free market

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<sup>24</sup>J.D. Lee & Barry Lindahl. 3 Modern Tort Law. 59 (1994).



economy. Any time that a product is created, there is a significant chance that some people will use it in a manner not intended by the manufacturer. Similarly, many products entail a measurable degree of risk in general use, so that the number of likely injuries is statistically calculable. Just as a manufacturer is not liable for its ability to calculate such statistics, it

- 12 - is imperative that a manufacturer not be held liable for 'creative' product applications except in the most extreme of circumstances. If the status of an item as a drug or new drug were dependent on the actions of consumers rather than the intent of the manufacturer, the intrusiveness of the FDCA would become unbearable, and manufacturers would quickly find themselves unable to keep abreast of the burdens imposed by the statute. The likely result would be eventual termination of the marketing of many products that are valuable and essential in daily life. If consumer practices controlled an item's status as a drug, manufacturers would be held accountable for the whims and imaginations of a nation of consumers. By instead tying FDCA obligations to objective evidence of a manufacturer's intent, the statute provides a manufacturer with a reasonable degree of control over its own fate.<sup>25</sup>

Consequently, although the FDA's stated intent, to take action whenever an off-label drug use becomes widespread, could possibly be justified under the FDA's existing powers, this is a policy that should not be pursued. Instead, the FDA should work to further its broadly stated policy of ~~ interfering with a doctor's prescribing activities.

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<sup>25</sup>A manufacturer must still be aware, however, that such control is not complete. especially given the FDA's current interpretation of labeling which serves as evidence of a manufacturer's intent.

The FDA's current policy on manufacturer-induced off-label drug use is also capsulized in the 1972 Proposed Rulemaking. In the text of the proposed rule, the FDA cited the now-familiar statement that [i]f an approved new drug is shipped in interstate commerce with the approved package insert, and neither the shipper nor the recipient intends that it be used for an unapproved purpose, the requirements of Section 505 of the Act are satisfied.<sup>26</sup> In general, the FDA has chosen to execute its powers regarding manufacturers and off-label drug use with only minimal variation from the powers granted by the FDCA.

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The FDA has, however, adopted two questionable interpretations of the statute in order to increase its power over manufacturers. First, the FDA utilizes FDCA Section 505 in a way that allows it to avoid the Miller Amendment limitation, whereby it imposes manufacturer liability for actions undertaken after interstate shipment has concluded. It is the FDA's position that a manufacturer's initial compliance with Section 505 includes a binding commitment through which the manufacturer has an ongoing obligation to abide by the terms (and hence the listed uses) of the approved New Drug Application. Deviation from the exclusive terms of the NDA, it is argued, constitutes a breach of this obligation and a violation of Section 505. This is clearly a situation where the FDA has expanded its powers beyond those provided through the statute itself, as the FDCA clearly contemplates termination of FDA jurisdiction with termination of interstate transport.

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<sup>26</sup>37 Fed. Reg. at 16503.

A second, and much more controversial, deviation from the FDCA involves the FDA's current interpretation of labeling. As previously mentioned, it is unlawful for a drug's 'labeling' to include information about unapproved uses. By adopting an extremely liberal definition of this concept, the FDA has significantly increased its control over off-label drug usage. The FDA's interpretation is statutorily justifiable due to the vagueness of both FDCA Section 201(m)'s definition of labeling and the case law arising under that provision. For the past several years, the FDA has regulated as labeling nearly any statement by a manufacturer relating to an off-label use of a drug, regardless of the credibility or truthfulness of the statement, and without consideration of the promotional or descriptive nature of the announcement. The FDA has deemed it illegal to include any information about off label uses even when such uses dominate medical practice for the drug involved, are endorsed by respected authorities, and are recommended by FDA staff themselves.<sup>27</sup> Accordingly, the FDA prohibits a manufacturer not only from notifying interested parties of promising off-label drug uses,

- 14 - but also from distributing independent journal articles which analyze particular off-label uses. In addition, the FDA's current definition of 'labeling' includes a manufacturer's provision of financial support to a medical symposium at which doctors discuss off-label uses of the manufacturer's products – even if the manufacturer had no indication in advance that its products were to be discussed.<sup>28</sup>

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<sup>27</sup>Stephen Chapman. FDA Censorship is a Real Danger to your Health. Chicago Tribune. April 15, 1993. at P25. (*Quoting* Professor John Calfre).

<sup>28</sup>Richard A. Samp. What the FDA Doesn't Want You to Know Could Kill You. Legal

In one of its most hotly contested recent actions, the FDA seized a medical textbook as misbranding of a drug product when the independent text contained information about off-label uses of a manufacturer's drug.<sup>29</sup> A significant problem with this form of FDA intrusion is its effect on the medical industry and the science of medicine. Kim Pearson, publisher of the Food and Drug Insider Report, has stated that [several companies have abandoned plans to include the most up-to-date use information disclosed by medical journals for fear that the FDA will restrict distribution of their texts in retaliation.<sup>30</sup> The FDA's zealousness in attempting to prevent the distribution of off-label uses of drugs has, unfortunately, resulted in a situation where independent educational materials withhold valuable information from even medical students. This is especially dangerous, as medical education can hope to be effective only if there is freedom of discussion and exploration of ideas, both traditional and novel, which is possible only if there is full access to all available information. The FDA must be made to realize that its current intentions, while justified in the short-term, have significant long-term consequences that should not be ignored.

This latest action has resulted in the filing of a lawsuit by the Washington Legal Foundation.<sup>31</sup> The lawsuit, naming Commissioner Kessler

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Backgrounder. V.9 No.34. Oct. 7. 1994.

<sup>29</sup>James Bovard. Medical Follies at the FDA, Washington Times. Dec. 20. 1994. at A17. (The text was The Chemotherapy Source Book, which the manufacturer was distributing to doctors and practitioners without approval).)

<sup>30</sup>Id.

<sup>31</sup>Washington Legal Foundation v. David A. Kessler. C.A. No. 1:94 CVO 1306 (District Court. District of Columbia 1994). At the current time. WLF has submitted its brief. and rather than responding as required. Kessler and the FDA have issued a Request for Comments. 59 Fed. Reg. 59820 (1994).

individually, alleges

- 15 - that the FDA's policy on educational and scientific activities<sup>32</sup> interferes with First Amendment freedom of speech (both that of the manufacturer in distributing this information and that of patients and practitioners in receiving the information), and that it unjustifiably interferes with the efforts of health care professionals to provide effective medical care. In defending itself and its actions, the FDA has set forth examples of its flexibility in permitting certain types of educational and scientific information to be disbursed by the FDA, reflecting its desire to promote scientific ingenuity in situations lacking elements of manufacturer promotion. Analysis of the FDA's policy, however, in combination with a comparison of this policy and examples of its implementation, show that such a degree of discretion is afforded the FDA that justification, accountability, and consistency, all of which are crucial to a workable program, are not required of the FDA.

Although it is beyond the scope of this paper to discuss the legal background of the WLF case, it is evident that the current FDA policy on manufacturer involvement in off-label uses is thought to be a compromise by the FDA, balancing the needs of medical science for information and innovation with the FDA's own statutory obligation to promote public safety and prevent harm from unsafe or ineffective drugs. Unfortunately, the compromise as currently struck by the FDA, while nearly constituting an outright ban on off-label drug use, is actually more dangerous than a complete ban would be, as it permits

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<sup>32</sup>FDA Policy Statement. 57 Fed. Reg. 56412 (1992).

off-label drug use to continue without the benefit of full information.

Taking an aspirin every day, scientific studies have established, may reduce your risk of heart attack and even cancer. I'm allowed to tell you that. The American Heart Association is allowed to tell you that. Kermit the Frog is allowed to tell you that. *But one group is forbidden to tell you that.' aspirin makers.*<sup>33</sup> The irony in the current system is clear; a system that values a free flow of information would insist that the manufacturer be the one party that could distribute this information. Of all parties

- 16 - with an interest in the advocacy and utilization of off-label uses of approved drugs, it is the drug manufacturers who have the most at stake. Manufacturers whose products find legitimate and effective alternate uses have tremendous potential for additional gain, in the form of direct profits and positive name connotation, both of which can be used to develop and market additional products. Consequently, a manufacturer unfettered with regulatory burdens would have tremendous incentive to support, develop, and analyze scientific research relating to alternate uses of existing products. In addition, drug manufacturers are most likely the only parties possessing the resources needed to invest the time and money required to support industry inventiveness on a regular basis. Once a manufacturer is forced to face FDA regulation unless it ceases to provide funding for independent drug use research, support for the development of such data falls solely to the efforts of various private and nonprofit scientific foundations. Though new uses can arise out of such organizations, a

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<sup>33</sup> Chapman. *supra* n. 27 (emphasis added).

lack of funding and financial stability greatly reduces the efficacy of such new use development. Further, the manufacturer is the party in the best position to gather and disseminate independently gathered information about off-label uses of drugs; a single manufacturer can accumulate and distribute information much more quickly and efficiently than a number of distinct entities. Under the current regime, however, the conditions under which a manufacturer can undertake these activities are unclear at best. Faced with growing insecurity and significant likelihood of FDA intervention, manufacturers have quickly retreated from information production, collection, and dissemination activities, and much available information no longer reaches practitioners and patients who could most use and benefit from the information.

Consequently, the FDA's current policy on off-label drug use is not merely inconsistent, but is also quite dangerous.<sup>34</sup> A corollary to the need for doctors to employ off-label uses of therapeutic products is that they must be able to learn which such uses are medically recognized. Under the current regime, physicians are

- 17 - permitted to utilize drugs for unauthorized purposes, but they do so under a significant handicap: much of the information that could be used to enhance the effectiveness of treatments, and perhaps even to motivate a decision to not to use a particular off-label use in a specific situation, is being censored and even seized by the agency that has a responsibility to assure that drugs are not used in a manner outside of the best interests of the consuming

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<sup>34</sup>The Gray Sheet. 20(25): 17-18. June 20. 1994.

public.

The Benefits of Off-Label Prescribing Support an Exception to Pre-Market Approval

As evidenced by the FDA's inconsistency in regulating off-label uses of approved drugs, experience has proven that off-label uses are often not only necessary, but in many cases are extremely beneficial.<sup>35</sup> Even the FDA, while executing a mission to curb such uses of FDA approved drugs, has admitted that [u]nlabelled uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature.... Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations.<sup>36</sup> At the same time, however, it cannot be denied that serious harm can occur when physicians and manufacturers abuse their bounded powers with regard to off-label drug therapies.<sup>37</sup> Given the substantial interests promoted by permitted off-label drug uses, however, as well as the alternative safety incentives that are already built into current legal and medical systems, the potential harms of off-label use should not be called upon to justify the FDA's current policies.

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It is important to note that the practice of off-label drug use need

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<sup>35</sup>See, *c.g.* Thomas Laetz & George Silberman. Reimbursement Policies Constrain the Practice of Oncology. 266 JAMA 2996 (1991). (*Citing 1990 GAO survey showing that more than 33% of cancer drugs are used for off-label purposes, with many such uses arising in situations where no alternate treatment would be available*).

<sup>36</sup>12 FDA Drug Bulletin 4 (1982).

<sup>37</sup>See, *e.g.*, Henig. *Supra* n. 19. (*Discussing the recent debacle involving the use of Retin-A and other prescription drugs for cosmetic purposes*).



not be equated with back-alley tactics of unqualified and unethical physicians. Nor should discussion of this topic evoke images of physicians' using ill patients as human guinea pigs. In many situations, particular uses of drugs remain unlabelled not because a use is unsafe or ineffective. Instead, incentives flowing from the FDA and from the marketplace in general often encourage a manufacturer to forego the process of receiving FDA approval for alternative uses of approved drugs.

Since a new use of an approved drug creates a new drug within FDCA Section 505, a manufacturer's instinctive desire to obtain approval for all valid uses (and therefore be permitted to include such uses in labelling and advertising) is offset by the reality of the FDA's New Drug Application (NDA) process. Accordingly, studies and control testing must be undertaken so that a manufacturer can provide the FDA with information sufficient to justify an expert opinion that the drug is safe and effective for each new use. Although the FDA has, in recent years, acknowledged that the length and expense of its approval process can serve as a disincentive to drug development, the agency's steps to streamline and modernize the approval process have not proven overwhelmingly significant in reducing the burden that a manufacturer faces in seeking FDA approval. As a result, it is not uncommon for a manufacturer to face a nine-year process costing roughly \$230 million to obtain approval of a new use of an approved drug.<sup>38</sup> The high cost of this approval process is somewhat surprising since the drug itself has already been proven generally safe for human

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<sup>38</sup>Bovard. *Supra* n. 29.

consumption. One would imagine that the approval process for an alternate use would involve an abbreviated process in which the sole issue would be that of effectiveness of the drug for the additional use. More specifically, it would seem that approval cost and time would be significantly reduced since the initial phases of testing (Preclinical and Clinical, Phase I) would be identical to those phases of testing of the drug itself. In fact, however, the

- 19 - impact of these savings is more than offset by the treatment afforded an NDA for a new use. The FDA, faced with a backlog of applications, gives significantly higher priority to applications seeking approval of new drugs than those seeking authorization of new uses of existing drugs. Consequently, the time and money involved in seeking approval of a new use are significant, and provide great disincentive for submission of alternate uses for FDA approval.

In addition to the mere financial burden of FDA approval, manufacturers often face another source of disincentive: insufficient market demand. In many instances, the alternative uses of a drug, discovered through a doctor's attempts to find treatment for a specific patient's disease, are extremely useful in only a small number of cases. In such situations, the manufacturer cannot economically justify pursuing the steps required for FDA approval. If the market for a drug's use is not large enough to provide the manufacturer with a reasonable return on the expenditure required to obtain approval, the use, though potentially invaluable and unmatched in effectiveness, will not be brought forward for FDA approval.

One example of this disincentive is pediatric drugs, and more specif-

ically cancer drugs for children. When a drug receives FDA approval, it is generally approved only for use in adults. For the drug to be labeled for use in children, an NDA would have to be submitted with data establishing safety and effectiveness resulting from clinical studies using children as participants<sup>39</sup>. The burden of such studies is not insignificant (up to \$30,000 per child)<sup>40</sup>, and manufacturers are aware that there is insufficient market demand for these drug uses to justify the expenditure that would be required for FDA

- 20 - consent. Consequently, many pediatric treatments depend completely on off-label uses of adult-approved drugs.<sup>41</sup>

In addition, manufacturers often face a free rider problem when deciding whether to obtain FDA approval for additional uses of approved drugs, and this as well provides disincentive to a manufacturer considering submission of a new use NDA. For common over-the-counter drugs and drugs whose use patents have expired, a manufacturer has virtually no incentive to get a new drug use approved, regardless of the size of the potential new market. The nature of FDA proprietary rights is such that in these situations, a manufacturer who pursues new use authorization will have no legal authority to prevent competitors from capitalizing on the approved new use. Consequently, a manu-

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<sup>39</sup>The FDA is, fortunately, currently considering taking action to relieve this burden by waiving the requirement for separate testing of children in situations where the manufacturer is able to use other methods to prove that the drugs are safe and effective for use in children (e.g. chemical analysis accompanied with proof that the effect in children would not be different from the already-approved effect of the drug on adults). Charles G. Moertel. Off-Label Drug Use for Cancer Therapy and National Health Care Priorities, 266 JAMA 3031(1991). citing 57 Fed. Reg. 47427 (1992).

<sup>40</sup>Bovard. *Supra* n. 29.

<sup>41</sup>If I didn't prescribe off-label, my ability to treat children effectively would be severely limited. (*Statement of Dr. Mark Riddle, Director of child and adolescent psychiatry at Johns Hopkins University*). Malcolm Ritter. Questions Urged on Desinramine, Los Angeles Times. February 20, 1994. at A1.

facturer would likely find his reward for the tremendous expenditure for securing FDA approval being a new market with competitors who are able to charge less for the same product. Although the single manufacturer would presumably obtain a use patent for the new use, any promotion of this product would benefit existing substitute products known to be equivalent, while the manufacturers of the substitutes would have invested no time or money seeking FDA approval. This, not ineffectiveness or lack of safety, is a significant reason that aspirin, widely supported as an anti-blood coagulant, has not been proposed for FDA approval as such.<sup>42</sup>

Even in situations where FDA approval has not been sought because of insufficient testing and knowledge to support an NDA, off-label drug use must still be permitted in appropriate circumstances. Some have sarcastically asserted that the arguments supporting permitted off-label drug use could be extended, ad absurdum, to the proposition that the FDA should refrain from interfering in a doctor's practice of

-21 - medicine altogether, and that doctors should therefore be permitted to execute medical therapies utilizing drugs which have received no FDA approval whatsoever. This is not a legitimate extension, however, and the distinction between these situations provides support for bounded approval of off-label drug usage. In order for off-label use of a drug to even be considered, the

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<sup>42</sup>The drug companies that manufacture aspirin aren't going to spend the money to substantiate [the anti-blood coagulant] claims because if, for instance, Bayer substantiates a claim, St. Joseph's can put it on their label and share the benefit without having shared the cost of research. Debra Carr-Elsing, Aspirin A Day Might Keo Illness at Bay, The Capital Times, June 8, 1993 at ID. (*Quoting Robert Persk's author, "wi Wonder Dru ~ What the Label on Your Aspirin Bottle Doesn't Tell You."*)

drug itself must have already been subjected to the rigors and analysis accompanying a new drug NDA. Through this process, it will have been determined that the drug itself is tolerable to the human anatomy. Further, successful marketing of the drug ensures, as studies alone cannot, that the drug is in fact safe for human consumption. Consequently, aside from the ever-present risk that a specific patient's condition will cause an adverse reaction, the primary risk involved in off-label drug use is that the drug will not be effective for treating the condition to which it is being applied. This is very different from a situation in which an unapproved drug is introduced to the general populous, as in such a case, basic safety cannot even be assessed. As will be discussed, a compromise between a complete off-label ban and free off-label use can be structured in order to significantly reduce the risk of drug ineffectiveness in the case of unapproved uses of approved drugs while maintaining the highest possible level of safety assurance.

It is commonly recognized that no drug is safe. Part of the intrigue of drug safety and effectiveness stems from the fact that it is often the dosage of a drug that determines its overall usefulness. When a physician decides whether to prescribe a particular drug for a specific condition, much of the ultimate decision rests on the outcome of a cost-benefit analysis. Similarly, the FDA's new drug application process reflects the FDA's need for information so that it can properly perform a cost-benefit analysis in determining whether or not to approve a drug for general marketing.<sup>43</sup> In a situation where a manufacturer is

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<sup>43</sup>*Drug Safety: Hearings Before a Subcommittee of the House Committee on Government Operations*. 88th Cong., 2d Sess. (1964).

seeking approval of a new drug, it is appropriate that

- 22 - the FDA perform the cost-benefit analysis. The FDA, utilizing the information required of the manufacturer, is sufficiently equipped to carry out this analysis. Although the FDA's decisions are often inefficiently conservative, it is appropriate that the FDA, the party with ultimate responsibility for public safety, serve as the final barrier to widespread consumer marketing of a new product.

Conversely, in a situation where a doctor is considering employing the use of an FDA-approved drug for an unapproved purpose, it is more appropriate for the physician to perform this analysis. In contrast to a situation involving pending release of a drug for wide-scale public consumption, off-label drug use typically originates under a single working doctor/patient relationship. Such a relationship assures that the drug is being prescribed for a particular reason and that there will likely be close individual monitoring of the affected patient during the period of drug ingestion.

In addition, the analysis underlying an off-label drug use, unlike that for initial approval of a new drug, typically occurs once market evidence is available as to the safety and efficacy of the drug. The FDA's requirement of control studies is presumably based on the need for comprehensive, reliable information in a situation where evidence from actual application of a product is not available. It seems that this requirement has, however, taken on a life of its own, whereby the notion of control study is given much more significance in the regulatory scheme than it merits. A doctor who is weighing treatment

alternatives in the face of established scientific and anecdotal evidence compiled during public use of a product should be encouraged, not constrained, as it is this type of information, rather than solely clinical evidence compiled under contrived circumstances, that indicates the true safety and effectiveness of a drug.<sup>44</sup>

In a situation involving an individual treatment decision rather than general approval of a new drug item, a more accurate cost-benefit conclusion will be

- 23 - reached if the doctor rather than the FDA performs the evaluation. The conservativeness of the FDA, problematic in a new drug decision, becomes unbearable in a situation involving off-label drug use in a particular instance. As an agency of the federal government charged with promoting public safety, the FDA has incentive to be extremely conservative, denying every application for which denial would not be patently unjust. The FDA is aware that if it approves a drug which turns out to be unsafe, it will face procedural hurdles under FDCA Section 505(e) in order to withdraw its approval of the item.<sup>45</sup> Faced with the possibility of such an expensive and time consuming process, it is not surprising that the FDA is extremely cautious in granting approvals in the first place. The problem of revocation of approval is exacerbated by the fact that a physician is not required to notify the FDA of adverse reactions

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<sup>44</sup>In fact, the early period following general marketing of a new drug must be regarded as a final step in the testing of the product. There is no way to duplicate fully in clinical trials the great variety of use conditions under which a new drug will be employed when it is finally approved.... *Id.*

<sup>45</sup>Section 505(e) requires notice and hearing before a drug's approval may be withdrawn. An exception is created whereby in cases of 'imminent hazard to public health an item may be de-classified immediately. but even this requires that the FDA pursue post-revocation process in order to uphold the constitutional rights of the manufacturer.

arising from the use of prescribed drugs.<sup>46</sup> Accordingly, the FDA has a legitimate concern that it will not learn of such problems quickly enough to respond in an efficient manner, whereby the FDA's initial failure to prevent an unsafe drug from being marketed would be magnified while the FDA was unaware of existing problems. In addition, as a political creature, the FDA is properly concerned about the political fallout that it will face if it approves a drug which turns out to be unsafe or ineffective. Finally, much of the FDA's effectiveness depends on voluntary cooperation of the parties within its jurisdiction.<sup>47</sup> Consequently, the FDA is hesitant to risk loss of public approval by permitting the marketing of a drug which ultimately harms the consumers whom the FDA is obligated to protect. At the other extreme, however, an FDA denial of approval will, at most, prevent a helpful drug from entering the market. FDA accountability for such action is likely minimal, since the tremendous power of the FDA discourages manufacturers from challenging the decisions

- 24 - of the agency. Further, if its decision is challenged, the FDA is able to maintain public favor by calling upon the strict requirements of the FDCA and arguing that they were not met. As a result, one estimate describes the outcome of FDA decisionmaking as such that approximately four thousand NDA's are rejected for every one that is approved.<sup>48</sup> Although it is likely that not all of these applications identified adequately supported drugs, it is similarly

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<sup>46</sup>37 Fed. Reg. 16503. *Supra* n. 18.

<sup>47</sup>Although the FDA is provided with enforcement mechanisms, the realities of FDA funding and staffing are such that if the FDA were required to bring formal action in every instance of regulation, the backlog and expense would be unmanageable.

<sup>48</sup>Abel Torres. The Use of FDA-Approved Medications for Off Label Uses. Archives of Dermatology. p. 32(1994).



implausible that all were invalid.

A doctor making a decision of whether or not to undertake a particular off-label use in the course of treatment of an individual patient is not exposed to these same external pressures. Pursuant to the Hippocratic Oath, a physician has an obligation to provide medical therapy solely for the good of [the physician's] patients according to [the physician's] ability and [the physician's] judgment.<sup>49</sup> Similarly, the World Medical Association's Declaration of Helsinki Code of Ethics provides that a physician is obligated to consider only the interests of the patient, and is to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering.<sup>50</sup> A physician, therefore, has strong incentive to not discount the potential benefits of a treatment when carrying out a cost-benefit analysis.

In contrast to the FDA's decision to approve a new use for a drug, a physician's off-label prescribing does not invoke instantaneous, widespread acceptance of such use. Consequently, the threat faced by the FDA of immediate human carnage is not a necessary element of a physician's decision process. Further, a physician has an obligation to monitor the progress of his patient, and therefore has the power to prevent the breakdown in communication that is possible following FDA approval of a drug. Finally, a physician who becomes aware of an adverse reaction has the power to immediately terminate the patient's ingestion of the harmful product, so delay costs need

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<sup>49</sup>Dorland's Medical Dictionary. 27th Edition, Harcourt Brace Jovanovich. Inc.. p. 768 (1988).

<sup>50</sup>T.L. Beauchamp and J.E. Childress. Principles of Biomedical Ethics 60 (1983).

- 25 - not be considered by the doctor. In the end, it is likely that a physician's particular prescribing practices constitute an area of drug approval in which it is wholly appropriate, and indeed the superior alternative, for the physician to conduct the cost-benefit analysis.

#### Benefits of Availability of Off-Label Uses

The practice of off-label prescribing itself has notable benefits. In some situations, an off-label prescription is the only treatment available to a patient, either because a more targeted drug does not exist, or because other methods of treatment are ineffective or unavailable due to patient intolerance. In these situations, off-label uses of drugs provide the only chance of restored health.

Off-label prescription activities also have benefits which extend beyond merely bringing relief to an individual patient in a single situation. History is replete with examples of significant medical advances that have arisen from happenstance, or because of a well-conceived theory that was pursued by an enthusiastic physician or scientist. If such ingenuity is to continue, off-label uses must be permitted. Drug manufacturers will always have incentive to investigate, and physicians will have incentive to demand, radical new drugs involving cutting-edge technology and intensive research. Manufacturers know that such drugs, which permit them to create and service entirely new markets, provide immeasurable benefits to corporate well being. At the same time, however, it is important to recognize that one need not, and often cannot, reinvent the wheel in order to treat each individual patient. This is the role that must be

filled by off-label drug uses.

If manufacturers know that they will be unable to promote new uses for drugs without FDA approval, and that FDA approval is infeasible given the nature of the drug or the size of the market, they will have no incentive to pursue alternative uses for existing drugs. Similarly, if a physician knows that altering a prescription from the

- 26 - package insert of a drug will bring interference from the FDA, there will be little incentive to utilize knowledge and accumulated expertise in order to provide tailored treatments to individual patients. Under such a regime, a physician would fill the role of an over-qualified pharmacist by merely matching symptoms with drugs, and then prescribing medicines according to the written instructions provided by the manufacturer. The cost of this system in terms of human lives would be incredible. In cancer treatment alone, fifty-six percent of affected patients receive at least one off-label drug,<sup>51</sup> while for stomach cancer in particular, more than sixty percent of current treatment is off-label<sup>52</sup>. In many situations, these inventive uses and combinations of drugs are the only hope for current treatment and future development of even more effective medical remedies.

#### FDA Intervention is Impractical

FDA regulation of off-label drug use would not only be improper; it would also be impractical. The FDA currently suffers from a problem that

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<sup>51</sup>Lou Fintor. Reimbursement Influence Choice of Cancer Therapy, 83 *Journal of the National Cancer Institute* 1606 (1991).

<sup>52</sup>Thomas Laetz & George Silberman. Reimbursement Policies Constrain the Practice of Oncology. 266 *JAMA* 2997 (1991).

is common among governmental entities: there is much too much work for the number of people and current budget of the agency. Resources are already strained, undermining the effectiveness of the FDA. Narrowed jurisdiction and/or an increase in the agency's budget would permit the agency to sufficiently focus on important individual issues rather than having to provide minimal coverage to a wide range of activities. Consequently, it is somewhat perplexing to observe the FDA's determination to increase its jurisdiction over physicians and their off-label practices. If the FDA were to finalize the rule that would permit intrusion whenever an off-label use became 'widespread', the regulatory jurisdiction of the agency would immediately increase by more than 650,000 individuals.<sup>53</sup> It is

- 27 - unlikely that this additional burden could be carried in any meaningful way by the current

FDA.

#### FDA Interference is Unnecessary

FDA jurisdiction over off-label drug uses would needlessly interfere with an existing incentive system which has tremendous potential to prevent abuses of such drug uses. Medical malpractice and medical industry self-policing can, in combination, prevent many potential abuses present when physicians are permitted to exercise discretion in selecting patient treatments. Addition of FDA regulation is not only unnecessary, but constitutes a waste of resources, since the enforcement powers of the FDA are inferior to those already existing

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<sup>53</sup>As of 1992. there were approximately 653,100 physicians practicing in the United States. Statistical Abstract of the United States. United States Department of Commerce. 121 (1994).

under these alternative regulatory schemes.

The FDA possesses four primary tools for enforcing the FDCA: injunction proceedings (FDCA Section 302), criminal penalties (FDCA Section 303), seizures (FDCA Section 304), and revocation of FDA approval of drugs (FDCA Section 505(e)). Although these remedies provide the FDA with adequate power to control abuses in many situations, they are not sufficient to permit effective regulation of off-label drug use.

FDA revocation of a drug's approval is the ultimate power that the FDA possesses, and carries perhaps the best deterrence available. It is, however, simply not a suitable remedy for dealing with off-label uses of drugs. As previously mentioned, the procedural hurdles that the FDA faces in pursuing this remedy render it significantly burdensome. In addition, revocation of a drug's approval would prevent the drug from being available for not only off-label uses, but also for the uses for which the drug has been proven safe and effective. Such action would likely result in significant public uproar and would inflict tremendous injury on the public, and hence is not ordinarily a viable remedy.

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Similarly, criminal penalties against manufacturers and individuals (both physicians and corporate executives) serve as a tremendous deterrent to aberrant behavior, as they implicate two fundamental interests: financial well-being and personal freedom. Indeed, many cynics assert that the possibility of a jail sentence is the only truly effective weapon that the FDA possesses.

Although criminal fines may effectively further the interests of the FDA, the option of imprisonment is rendered infeasible by the current magnitude of off-label prescribing. It has been estimated that roughly 400 million of the annual 1.6 billion prescriptions issued by doctors in the United States are for off-label uses).<sup>54</sup> It is neither possible nor reasonable to imprison all of the individual doctors who are engaging in this practice given the extent of existing and feasible jail facilities in the country.

Injunctions and seizures are similarly impractical as mechanisms for FDA control over off-label uses of drugs. The degree of FDA intrusion that would be required to issue and enforce an injunction against individual physicians' off-label prescribing practices would be intolerable. Further, the necessarily constant and continual monitoring of physicians' activities would undoubtedly stretch the resources of the FDA beyond a feasible level. Even more devastating consequences would attach to FDA attempts to control off-label drug uses through seizures. Under such a plan, the FDA would not only be required to monitor individual physicians, but also to pursue discovered violations by contacting individual patients and confiscating the actual bottles of drugs. Such action would clearly be overwhelming for the FDA and would prevent it from pursuing its legitimate objectives.

Medical malpractice as it already exists is a major source of deterrence against abusive off-label drug prescription. This remedy is available to patients harmed by a physician's improper activities, parties with tremen-

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<sup>54</sup>MAlt Freudenheim. Creative Drug Use Gets FDA Scrutiny, Miami Herald. June 30, 1991. at 6A.

dous incentive to monitor the appropriateness of their physicians' prescribing practices. Unlike criminal fines provided

- 29 - for under the FDCA, a malpractice judgment is determined solely through analysis of the situation in which the activity took place and through which the injury arose, and not through a pre-determined formula. This lack of predictability, combined with the sheer magnitude of judgment likely in a malpractice award, provides much more incentive against physician impropriety than could criminal penalties. Though a malpractice award serves only as an ex-post remedy in any individual case, the threat of such suits (where settlements commonly occur at amounts in excess of \$1 million) provides tremendous incentive for a physician to avoid the possibility of such a suit by carefully analyzing a treatment situation and assuring himself that a selected treatment is appropriate and justified.

The current standard for medical malpractice due to a physician's deviation from a drug's labeling provides that although such activity is not per se negligence, evidence of the departure from the recommended use can be admitted as evidence of impropriety.<sup>55</sup> Though the exact use to which such evidence can be put differs among jurisdictions<sup>56</sup>, a physician is assured that under the current system, he will be given the opportunity to present a jury with the information that was used in assessing the treatment alternatives for the patient. The physician will therefore have the opportunity to justify himself

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<sup>55</sup>Peter B. Hutt and Richard A. Merrill. Food & Drug Law 630(1991).

<sup>56</sup>See. e.g. Salvo v. Leland Stanford Jr. Bd. of Trustees. 317 P.2d 170 (CA 1957) (labeling constitutes evidence of appropriate standard of care. but not conclusively.) *Contra* Mulder v. Parke Davis, 181 N.W.2d 882 (MN 1970) (physician package insert constitutes prima facie evidence of standard of care.)

and his decision to depart from the indications for use approved by the FDA and listed by the drug's manufacturer.

It is noteworthy that despite the likelihood of facing a medical malpractice lawsuit, physicians prefer the current system of regulation, with the opportunity to determine patient treatment methods and then justify such a decision to a jury. Even though juries are likely to favor a plaintiff and are inclined to award a huge sum of money to a stricken patient, one practitioner, undoubtedly aware of the potential liability posed by the current regulatory scheme, indicates that he would prefer to take his chances and

- 30 - have the opportunity to utilize off-label treatments and then justify his actions, saying I would rather have the FDA withdraw a drug from the market for adverse effects than have the FDA limit how the drug can be prescribed....Otherwise the FDA would be involved in actually regulating the in-office practice of medicine by the individual physician. And frankly, I don't trust the government to do that.<sup>57</sup>

Another element undermining the argument that FDA involvement in regulating off-label drug usage is required is the strong communication system that exists among practicing physicians. As evidenced by the prevalence of off-label practices promoted by unsponsored intra-professional communication, the medical community is tightly bound by communication networks, made up in part by numerous journals, periodicals, and associations. Running through this structure seems to be a strong policing power instituted by the industry itself,

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<sup>57</sup>Henig. *Supra* n. 19. (Quoting George Lundberg, editor *cf.*).



evidencing efforts by individual practitioners to join forces in order to promote the interests of the medical industry through accurate and efficient dissemination of information. At the same time that doctors are notifying others of discoveries and breakthroughs that have been found, t'medical literature reflects a parallel concern to provide notice of problems that have arisen as experience is gained with new drugs and new treatments.

It is widely recognized that members of an industry benefit individually when the industry as a whole is viewed favorably by the clientele that it serves. In many situations, however, economic and market incentives provide motivation for selfish actions which promote individual rather than collective interests. Although the nature of the medical industry does not fully promote collectivist goals, the reality of current conditions assures that physicians have incentive to work together in order to maintain the integrity of, and encourage confidence in, the medical industry. Public sentiment is, like never before, putting the medical industry as it has been known for many years into serious jeopardy. This has been equated of late into several significant political

-31- recommendations which aim to radically and irreversibly alter the practice of medicine in the United States. Consequently, physicians know that every action that they take is likely to be strictly scrutinized, so that there is tremendous incentive to disburse information, including that of adverse reactions to popular off-label uses.

There is evidence that such self policing of physician activities took place even before the medical industry came under fire. The case of the drug

'desipramine' serves as a good example of effective industry self-regulation. Desipramine is a drug which was approved for use in adults for the treatment of depression and similar psychiatric conditions. In the 1970's, the drug gained widespread acceptance for off-label treatment of adolescent hyperactivity and depression. After this use had gained acceptance, it was discovered that the long-term effects of the drug on children were unfavorable, even fatal. Within a relatively short period of time, the same communication network that had promoted the acceptance of desipramine use in children had been utilized to warn doctors not to use the drug in children, and the incidence of this practice has been greatly reduced.<sup>58</sup>

#### Freedom of Choice

One element that separates humans from animals is that humans have been granted the ability to think and reason, and are able to gather information and analyze it in order to form rational decisions. Wars have been fought over the importance of freedoms such as the liberty to choose one's destiny. In reality, however, no freedom is more important or fundamental than the ability to choose between life and death. FDA intervention in off-label drug use takes this choice away from many individuals, and as such should not be tolerated.

The purpose of the FDA, it is repeatedly said, is to protect the ignorant, the unthinking, the credulous. In most situations, this is a crucial role that must be filled,

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<sup>58</sup>Ritter. *Supra* n. 41.

- 32 - protecting the lives and health of countless American citizens.

In certain circumstances, however, it is crucial that the FDA back away from its strict watchdog position, and permit ill patients to work with their doctors in order to implement medical treatments that have not, for any of the several reasons cited above, received the FDA's stamp of approval.

It is beyond doubt that there is patent cruelty in a doctor's providing false hope to a dying patient in the form of an ineffective new drug or treatment. Conversely, however, it seems equally, if not more, reprehensible for the government (through the FDA) to deny a dying patient the right to even a *chance* of life merely because it has set up a system in which drug manufacturers have no incentive to seek approval for new uses of approved drugs. Further, a doctor has an ethical duty to work solely to extend the life of his patient, and realistically has no incentive to maliciously taunt a patient with hollow possibilities of restored health. Medical malpractice, as discussed above, deters a physician from engaging in such behavior by punishing not only the act itself, but also the marginal trauma resulting from delays in seeking other, possibly effective, legitimate treatments.<sup>59</sup>

#### Compromise is Available

It is imprecise to evaluate the situation of off-label drug activities as having solely two extreme poles: offensive FDA intervention at one end, and chaotic quackery with runaway physician discretion at the other. Instead, there

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<sup>59</sup>e.g. George v Kaiser Foundation Healthgroup, Case No. L79507 (11-1-88) (*Patient awarded \$775,000 to compensate for reduction in chances of survival due to doctor's delay in diagnosing*).

is a compromise that can (and should) be struck between these two positions. Among the various sources of communication that bind the medical industry are various medical compendia. These are medical texts created by associations within the medical industry, providing detailed information for physicians on the approved drugs that are on the market at any given

- 33 - time. Unlike the Physician's Desk Reference<sup>60</sup>, these compendia list not only the approved uses of these approved drugs, but they also refer to off-label drug uses that have support in the medical industry. The rationale for listing such uses is set forth in the Preface to the American Medical Association's Drug Evaluations, one such compendium:

Because indications approved for labeling by the FDA may lag behind both the world literature and medical practice or because the manufacturer has not submitted an application for a new use, this book comments on uses of drugs regardless of their status in official labeling.

The reliance on such anecdotal and marketplace scientific information that is reflected in these widely used medical texts indicates the value placed by physicians on this type of experience data. The fact that physicians use these sources on a daily basis in constructing patient treatments satisfying their professional and ethical obligations suggests that FDA approval is not, in the end, the sole indicator of a drug's safety and effectiveness. There is, moreover, additional evidence that this information is extremely valuable and reliable. In January of 1994, Medicare began paying for certain treatments

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<sup>60</sup>Fran Kritz. FDA Seeks to Add Drugs' New Uses to Labels, Washington Post. March 29, 1994 at zI 1.

of cancer utilizing off-label treatments involving oral cancer drugs.<sup>61</sup> In order to qualify for coverage, however, the treatment must be one which appears in any one of the three authoritative medical compendia... the American Hospital Formulary Service, the United States Pharmacopoeia Drug Information, or the American Medical Association Drug Evaluations.<sup>62</sup> It is clear from this policy that the United States Congress concurs in the judgment that these medical sources m'nerit significant reliance.

The most encouraging evidence suggesting that reliance on this type of information is legitimate is that the FDA itself, in discussing insurance coverage of off-label treatments with private insurance companies, has encouraged the companies to look beyond the labeling of a drug. Indeed, Dr. Stuart Nightingale, Associate Commissioner

- 34 - for FDA Health Affairs, encouraged private insurers to rely on market data and compilations of experiential data from sources such as medical compendia, urging that [a]n FDA label is not meant to be the arbiter of appropriate treatment.<sup>63</sup> As a result, the current model legislation for state laws relating to insurance coverage of off-label drug uses provides that insurance policies that pay for medication must pay for off-label treatments if the drug in question is recognized for that indication in one of the three standard references<sup>64</sup>

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<sup>61</sup>F. Rep. No. 403. 103rd. Cong.. 2d Sess. (1994).

<sup>62</sup>*Id.*

<sup>63</sup>Tim Friend, Best Cancer Drugs Often Not Covered, USA Today. June 29. 1989 at 1A. *Contra* Fran Kritz, *Supra* n. 60. (*Citing Commissioner Kessler, The labels really are the best scienqfic knowledge of how a drug can be safely used.*)

<sup>64</sup>Kate Nagy, States Aim Laws at Off-Label Reimbursement, 85 Journal of National Cancer Institute 701 (1993). (*Citing policy set forth by Association of Community Cancer Centers*).

Given the significance of this information among members of the FDA, Congress, and practitioners within both the medical and insurance industries, it seems incomprehensible that the FDA has consistently refused to fully acknowledge the validity of these alternative sources of medical authority. The FDA recognizes the validity of this information when passing judgment on it indirectly, but refuses to apply the same reasoning when its own policies and objectives are under consideration. If the FDA were to fully embrace these sources of data, it could use this information (which is cost-free to the agency) in order to bring consistency to its regulation of off-label practices by permitting promotion of appropriate off-label activities while at the same time not forsaking its obligations to promote public safety and health.

In analyzing the current status of FDA regulation of this issue, the medical and pharmaceutical industries have recognized that there are two conflicting interests at stake in the regulation of off-label drug use: the desire to attain the benefits that would be available in a system permitting the free flow of information pertaining to legitimate off-label uses of FDA-approved drugs, and FDA's obligation to fulfill its role as monitor and provider of public safety. In accommodating these interests in a workable format, it has been suggested that the FDA might permit a labeling practice in which a drug

- 35 - manufacturer would be permitted to disclose off-label uses of a drug, provided that the uses were listed in one of the authoritative medical compendia and were supported by substantial high-quality evidence.<sup>65</sup> If it

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<sup>65</sup>e.g. Off-Label Drug Use. *The Pink Sheet*, 54(22). October 29, 1990. (Citing Peter Bewley, *Associate General Counsel, Johnson and Johnson Company*).

were to permit this type of labeling, the FDA would be assured that the only information disseminated would be that pertaining to valid, legitimate, and scientifically supported uses of drugs. In addition, the inclusion of this information on the labeling of the product would give the FDA complete control over the content and format of the information, under the FDCA's prohibitions against misbranding of drugs found in FDCA Section 502. Permitting labeling of this type allows high-quality information about valuable medical treatment to be received by those who are most likely to benefit from the knowledge. At the same time, manufacturers and physicians will once again have incentive to engage creativity and ingenuity in order to derive valuable new uses of available drugs. Once the distribution of substantiated information is permitted, incentive to establish such information is restored, as manufacturers and doctors no longer face the unjust consequences of being prevented from benefiting from valuable discoveries.

It is argued that a problem with this scheme is that it removes incentive for a manufacturer to seek FDA approval for any new drug use. Although such a result may not be unreasonable, the prediction itself is not necessarily correct. First, it is important to recognize that the approved package insert would necessarily include bold disclaimers as to unproven safety and efficacy of a drug use, as well as a balance of available information pertaining to any such half-listed drug use. This would require that the manufacturer disclose any negative information relative to the drug. If the use were approved, however, the extent of required disclosure would be greatly reduced, permitting the

manufacturer to withhold some of the minor irregularities arising in individual studies. In addition, approval of the use would permit the manufacturer to actively promote the use of the drug. As a half-approved use, the required disclosure

- 36 - would be so extensive that advertising of the use would be effectively banned due to the costs and structural barriers posed by advertising. Consequently, a manufacturer would have incentive to seek approval of those drugs whose off-label uses prove to be sufficiently accepted and acceptable. Indeed, manufacturers would benefit from this half-label allowance. Under such a scheme, manufacturer decisions as to which uses are to receive approval would be preceded by substantial marketing and the anecdotal and clinical information that arise from such marketing, allowing for more efficient decisionmaking.

If the predicted incentives are not sufficient, and manufacturers are not, in fact, encouraged to seek approval for accepted new uses of existing drugs, the consequences need not be devastating, and in many ways may be positive if not preferable to the current approval scheme. The FDA, in approving a drug, recognizes that it is making an important decision in the face of uncertainty. A positive decision is made only if there is sufficient evidence of safety and efficacy as established through clinical control tests, since actual response data is not available. When a drug has significant market experience and investigation, the FDA clinical evidence requirement is not necessarily appropriate.

The FDCA could actually be interpreted as supporting a distinction in drug approval between those with market experience and those that had



not yet been released for public use. The definition of new drug in FDCA Section 201(p) provides for a drug status corresponding to the drug's recognition as being safe and effective. The FDA currently maintains a policy that the GRAS drug exception is not actually an exception at all, and that equivalent clinical evidence is required for approval without regard to a drug's being generally recognized safe. Statutes are rarely interpreted in ways that render specific words or phrases superfluous, as the FDCA has been in this instance. Consequently, it would be entirely appropriate for the FDA to establish a policy under which a drug could gain approval through submission of sufficient market study, exactly

- 37 - the type of data that would support the half label theory proposed above. Commissioner Kessler has indicated interest in considering the approval of new drug uses in which the medical literature on the unlabelled use [would] contain all of the data [needed] for an approval.<sup>66</sup> Action has not, however, been taken on such a radical change in FDA policy, because the statute as it is currently written and interpreted does not support such an approval process.

It is too early to predict the outcome of Mr. Gingrich's crusade against the excesses of the FDA. It is clear, however, that rigorous scrutiny and public debate are likely to arise, and at least some change is likely to result. The latest signals from the FDA show increased tension between proponents of the opposing goals of drug safety and drug availability, signaling that the FDA is soon likely to once again squarely face this issue and attempt to strike

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<sup>66</sup>FDA Encouraging Supplemental NDA filings for Off-Label Uses. The Pink Sheet. 54(5):8-9. February 3, 1992.

a satisfactory balance. Hopefully the FDA will finally acknowledge that the strong hand of government need not be utilized where private incentives and marketplace regulation can work together to achieve an acceptable solution. If not, the combined forces of the medical and pharmaceutical industries will continue in their campaign to work with the government in deriving a solution that prevents the stifling of innovation and senseless suffering that results from excessive regulatory zeal, while promoting the public safety by making available only those drugs that are sufficiently safe and effective. Whichever of these is to be the outcome, only time will tell...