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## Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions

*Gregory Gentry*



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# Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions

GREGORY GENTRY\*

## INTRODUCTION

Your company has spent months designing a compliance program and training your sales representatives. They know never to mention the off-label uses of your product. If they are asked about the off-label uses by the physician they are detailing, they know to forward those inquiries to the scientific liaisons at headquarters. But, could your company still be in legal jeopardy simply because it knows that the product is being used for an off-label purpose? This article attempts to track the Food and Drug Administration's (FDA's) shifting interpretation of its "intended use" regulations, from focusing entirely on the statements of the manufacturers to focusing on the knowledge of the industry, indeed, of the consumers of products, in determining the true intended use of a product. It will look at several recent attempts by FDA to use that new interpretation of the regulations to expand its power: to regulate tobacco and to require pediatric indications for any new drug. Finally, it will look at several recent examples of how this new interpretation has manifested in actions by FDA and the Department of Justice (DOJ)

## I. OFF-LABEL USE VERSUS OFF-LABEL PROMOTION

Prescription drugs and medical devices are required to be approved (or cleared) for an "intended use" before a manufacturer can market them. Once it is on the market for an approved use, however, physicians are allowed to use that product for any medically appropriate use.<sup>1</sup> As every edition of the *Physicians' Desk Reference* states, "Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling."<sup>2</sup> Use for an indication not in the labeling of the drug is called "off-label use." Off-label use is widespread. In 2001, one study tracked 160 medications (the top 100 medications and 60 randomly chosen medications) and found that 21 percent of the prescriptions were off-label.<sup>3</sup> For some patient populations and diseases, the majority of medications prescribed are off-label. It has been reported that 80 percent of all medications prescribed for children had FDA-required

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\* Gregory Gentry is an associate at the law firm of Morrison Mahoney, LLP in Boston, Massachusetts. The views expressed in this article are those of the author and do not necessarily reflect the views of Morrison Mahoney or any of its clients.

<sup>1</sup> 21 U.S.C. § 396 (1994) ("Nothing in this Act shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship.")

<sup>2</sup> PHYSICIAN'S DESK REFERENCE (2008), Foreword (62nd ed. (2007)). *see also*, Richardson v. Miller, 44 S.W.3d 1, 14, n.11 (Tenn. Ct. App. (2000)), ("Because the pace of medical discovery often runs ahead of the FDA's regulatory machinery, the off-label use of some drugs is considered to be 'state-of-the-art' treatment.") and Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001) (Off-label prescribing "is an accepted and necessary corollary of the FDA's mission to regulate.")

<sup>3</sup> D.C. Radley, S.N. Finkelstein & R.S. Stafford (2006) Off-label Prescribing Among Office-based Physicians, ARCH. INTERN. MED. 166: 1021-1026.

disclaimers about the use in children because of the paucity of pediatric research.<sup>4</sup> Some patient populations may never have on-label drugs available to them. As one pharmaceutical executive asked, "Who in his right mind would work on a product that would be used by pregnant women?"<sup>5</sup> Also, rare diseases may never have an on-label drug use. Most diseases afflicting fewer than 200,000 Americans are "totally without" FDA-labeled treatment. Some "90 percent of [patients] must rely on 'off-label' uses" to have any treatment at all, said Abbey S. Meyers, President of the National Organization for Rare Diseases.<sup>6</sup> It is a crime, however, to ship a regulated product that is adulterated or misbranded.<sup>7</sup> Products can become misbranded in a number of ways, one of which is the failure to include adequate directions on the label for all intended uses.<sup>8</sup> The crime of shipping a misbranded or adulterated product is a strict liability crime, requiring no proof that the manufacturer knew its product were misbranded or adulterated.<sup>9</sup> It is through these statutes that FDA regulates off-label promotion, on the theory that promoting a product for uses that are not approved creates a new intended use, making the products misbranded. That active promotion of off-label uses creates a new intended use is uncontroversial. What is troubling, however, is when the unpublished desires of a company create a new intended use.

## II. THE TROUBLING DEFINITION OF INTENDED USE

Intended use is defined similarly for both drugs and medical devices.<sup>10</sup> The following definition is for medical devices:<sup>11</sup>

The words intended uses or words of similar import in 801.5, 801.119, and 801.122 refer to the *objective intent* of the persons legally responsible for the labeling of the devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. *It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.* The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor or seller intends an article for different uses than those intended by the person from whom he received the devices, such packer, distributor or seller is required to supply adequate labeling in accordance with the new intended uses. *But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones*

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<sup>4</sup> Robert Levine, *Ethics and Regulation of Clinical Research* 241 (2d ed. (1986)).

<sup>5</sup> Peter W. Huber, *Liability: The Legal Revolution and its Consequences*, 155 (1988).

<sup>6</sup> Abbey S. Meyers, Pres., National Org. for Rare Diseases, Inc., Prepared Testimony before Subcomm. On Human Resources and Intergovernmental Relations of the House Comm. On Gov't Reform and Oversight (Sept. 12, 1996).

<sup>7</sup> 21 U.S.C. § 331(a).

<sup>8</sup> 21 U.S.C. § 352(f)(1).

<sup>9</sup> 21 U.S.C. § 331, *see* *Untied States v. Dotterwiech*, 320 U.S. 277, 280-281 (1943).

<sup>10</sup> Drugs: 21 CFR § 201.128. Devices: 21 CFR § 801.4.

<sup>11</sup> 21 CFR § 801.4.

*for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.*  
(emphasis added)

*Black's Law Dictionary* has no definition for “objective intent.” “Objective,” however, is defined as, “[o]f or relating to, or based on externally verifiable phenomena, as opposed to an individual’s perceptions, feelings, or intentions.”<sup>12</sup> There is a distinction in the regulations, then, between the “objective intent,” which determines the intended use of the product, and the subjective knowledge of the manufacturer, which could change the intended use. This is often referred to as the Catch-22 regulation.<sup>13</sup> As one commentator put it, “[u]pon a strict reading of this regulation, a manufacturer must relabel its device to accord with extra-label uses if the manufacturer knows, or has knowledge of facts that would lead it to know, that a device introduced into interstate commerce by the company is to be used for conditions, purposes, or uses other than those for which the company offers it.”<sup>14</sup> It is a Catch-22 because if a manufacturer labels its product to reflect the off-label use it knows about the product becomes misbranded and subject to FDA enforcement action. However, if it does not label the product to reflect the off-label use, it is also misbranded or adulterated—since it is being shipped for an intended use not contained in the labeling.<sup>15</sup>

### III. INTENT IN TORT AND CRIMINAL LAW

Part of the problem is that “objective intent” is a phrase unique to FDA law, with no direct parallels in either tort law or criminal law. Indeed, on its face, “objective intent” appears almost an oxymoron. “Objective” is defined as “[o]f or relating to, or based on externally verifiable phenomena, as opposed to an individual’s verifiable perceptions, feelings, or intentions.”<sup>16</sup> Intent, by contrast, is subjective. In tort law, for example, as Dobbs on Torts explains, “[s]ince intent is a state of mind, it is necessarily subjective. That is, the relevant state of mind is that of the person whose intent is in question. . . . [H]e is not necessarily acting intentionally merely because other people acting in like circumstances would harbor an intent.”<sup>17</sup> However, since there is no “mind reading machine” to determine the subjective intent of the actor, the “subjective intent is necessarily determined from external or objective evidence.”<sup>18</sup>

The closest analogue in tort law comes from product liability and is the concept of the reasonable foreseeable use to which a product can be put. In product liability law, a product must be reasonably safe for both foreseeable uses and misuses.<sup>19</sup> For example, children often use products in dangerous ways, and if a safer design is feasible, a manufacturer should utilize it to protect against a child’s misuse.<sup>20</sup>

<sup>12</sup> BLACK’S LAW DICTIONARY, 7th ed., 1101.

<sup>13</sup> Kahan, J., *Extra-Label Use*, J. MED. DEVICE & DIAG. IND., (Apr. 1990), 47, 48.

<sup>14</sup> *Id.*

<sup>15</sup> *Id.*

<sup>16</sup> BLACK’S LAW DICTIONARY, 7th ed. P. 1101.

<sup>17</sup> LAW OF TORTS, Dobbs, § 25, 49.

<sup>18</sup> *Id.*

<sup>19</sup> Dobbs, § 370, p. 1027, *see also*, *Ellsworth v. Sherne Lingerie, Inc.*, 303 Md. 581, 495 A.2d 348 (1985); *Reid v. Spadone Mach. Co.*, 119 N.H. 457, 404 A.2d 1094 (1979) overturned on other ground, *Daigle v. City of Portsmouth*, 129 N.H. 561, 534 A.2d 689 (1987).

<sup>20</sup> Dobbs, § 370, p. 1027, *see also*, Phillips, Jerry J., *Products Liability for Personal Injury to Minors*, 56 VA. L. REV. 1223 (1970).

This definition, however, cannot be imported directly into FDA regulation, since that would conflict with FDA's acknowledged inability to regulate off-label use as opposed to off-label promotion. For example, in 1982, FDA said:

[O]nce a [drug] product ... has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in the approved labeling.... "unapproved" or more precisely "unlabeled" 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....<sup>21</sup>

Indeed, the Federal Food Drug and Cosmetic Act (FDCA) forbids the regulation of off-label use saying, "Nothing in this Act shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship."<sup>22</sup> It is demonstrated below that the courts have found these same problems in FDA's attempted expansion of the intended use regulations.

Similarly, there is no clear analogue to "objective intent" in criminal law. Intentional crimes, as opposed to crimes with a *mens rea* of knowledge, negligence or recklessness, are divided at common law into general and specific intent crimes. General intent requires that an actor intended the physical act in question.<sup>23</sup> One needs no further intention or purpose. Assault, for example, requires only that the actor intended the touching in question, and the law assumes that the actor knows the reasonably likely consequences of that action. In that sense, criminal law considers intent objectively. However, the law of criminal intent, even here, is subjective in the sense that one can negate the intent by proving insanity, involuntariness,<sup>24</sup> hypnotism<sup>25</sup> or somnambulism,<sup>26</sup> among other things.

This seemingly self-contradictory phrase, "objective intent," causes great consternation in the pharmaceutical and medical device industry. As one article asked, "What are companies to do when they learn that, *contrary to their wishes*, their

<sup>21</sup> 12 FDA Drug Bulletin 4-5 (1982) cited in 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994).

<sup>22</sup> 1994 - Pub. L. No. 105-115, § 214, 111 Stat. at 2348 (codified at 21 U.S.C. § 396 (FDCA § 906)). See also, *Buckman v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350-351 (2001) ("Would-be applicants may be discouraged from seeking §510(k) approval of devices with potentially beneficial off-label uses for fear that such use might expose the manufacturer or its associates (such as petitioner) to unpredictable civil liability. In effect, then, fraud-on-the-FDA claims could cause the agency's reporting requirements to deter off-label use despite the fact that the FDCA expressly disclaims any intent to directly regulate the practice of medicine, see 21 U.S.C. § 396 (1994) ed., Supp. IV), and even though off-label use is generally accepted.")

<sup>23</sup> See, for example, Massachusetts Criminal Model Jury Instructions, 3.120, "Intent," "In determining whether the defendant acted 'intentionally,' you should give the word its ordinary meaning of acting voluntarily and deliberately, and not because of accident or negligence. It is not necessary that the defendant knew that he (she) was breaking the law, but it is necessary that he (she) intended the act which constitutes the offense."

<sup>24</sup> *People v. Newton*, 8 Cal. App. 3d 359 (1970) ("Where not self-induced, as by voluntary intoxication or the equivalent, ... unconsciousness is a complete defense...")

<sup>25</sup> See, Model Penal Code and Commentaries, Comment to §2.01 at 221 (1985) ("The widely held view that the hypnotized subject will not follow suggestions which are repugnant to him was deemed insufficient to warrant treating his conduct while hypnotized as voluntary; his dependency and helplessness are too pronounced."); Comment (Mary C. Bonnema), "Trance on Trial": An Exegesis of Hypnotism and Criminal Responsibility, 39 WAYNE L. REV. 1299 (1993).

<sup>26</sup> Norval Morris, *Somnambulist Homicide: Ghosts, Spiders, and North Koreans*, 5 RES JUDICATAE 29 (1951).

own device is being used for an extra-label indication? Companies may fear FDA regulatory sanctions ... if their device becomes widely used for an extra-label indication."<sup>27</sup> (emphasis added)

It could be argued that this is a similar situation to willful blindness, where, for example, a person sells spray paint to a known vandal. It may be contrary to the vendor's wishes that the purchaser uses it for vandalism. However, it should be noted that in situations like this, the actor is willfully blind to the probability of an *illegal* action. Some courts, in fact, disallow willful blindness jury instructions unless the evidence establishes both 1) that the defendant was subjectively aware of a high probability of illegal conduct, and 2) that the defendant purposefully contrived to avoid learning of the illegal conduct.<sup>28</sup> One struggles to find a parallel where a *lawful* act becomes unlawful because the actor has knowledge of a high probability that a third party will act in a *lawful* manner. That the courts have struggled with it as well and that FDA still holds to this definition are seen below.

#### IV. EVOLUTION OF INTENDED USE DEFINITION

The intended use regulation came into existence in 1952.<sup>29</sup> Under this regulation, and under prior regulations, FDA and its predecessor agency looked solely at the actual statements made by a manufacturer in the marketplace about its product. It was not until 1995, when FDA attempted to regulate tobacco, that its interpretation of intended use changed. This article now tracks the changes in the regulatory position of FDA and its predecessor agency through these three periods.

##### A. 1906-1952

In 1906, in response to very public criticisms by the American Medical Association of patent medicine abuses and vivid descriptions of filthy meat-packing conditions in Upton Sinclair's *The Jungle*,<sup>30</sup> Congress passed the Pure Food and Drugs Act.<sup>31</sup> It defined "drug" as "all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals." The act was designed to promote honest labeling and to prevent cheats.<sup>32</sup> It looked only at the difference between labeled composition and the actual composition of the drug.<sup>33</sup> As the Supreme Court found in 1911, the act covered only false claims about identity, not false therapeutic claims.<sup>34</sup> To overcome this ruling, Congress passed the Sherley Amendment, which "prohibited [claims about] curative or therapeutic effect[s]...which [are] false and fraudulent."<sup>35</sup>

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<sup>27</sup> Kahan at p. 49.

<sup>28</sup> *United States v. Farfan-Carreón*, 935 F.2d 678, 680 (5th Cir. (1991)).

<sup>29</sup> 21 CFR § 200.128 (1993). See also Elson, Eugene M., *The Expanded Meaning of "Adequate Directions for Use,"* 7 FOOD DRUG COSM. L.J. 743 (1952).

<sup>30</sup> *The Long Struggle for the 1906 Law*, FDA Consumer (1981) at <http://www.foodsafety.gov/~lrd/history2.html> (last visited May 18, 2009).

<sup>31</sup> Pub. L. No. 59-384, 34 Stat. 768 (1906).

<sup>32</sup> H.R. REP. NO. 59-2118, at 7 (1906)

<sup>33</sup> Pub. L. No. 59-384, §§ 8, 10, 34 Stat. at 770-771. Peter Barton Hutt & Peter Barton Hutt II, *A History of Government Regulation of Adulteration and Misbranding of Food*, 39 FOOD DRUG COSM. L.J. 2 (1984); Peter Barton Hutt, *Criminal Prosecution for Adulteration and Misbranding of Food at Common Law*, 15 FOOD DRUG COSM. L.J. 382 (1960).

<sup>34</sup> *United States v. Johnson*, 221 U.S. 488, 497 (1911).

<sup>35</sup> Pub. L. No. 62-301, 37 Stat. 416 (1912).

Both the original statute in 1906 and the statute as amended in 1912 looked at the statements made to the marketplace in order to classify substances as drugs. As the agency said in 1914 about tobacco:

Under the Food and Drugs Act, a drug is defined as any substance or mixture of substances, intended to be used for the cure, mitigation, or prevention of disease of either man or other animals. It, therefore, follows that tobacco and its preparations, when labeled in such a manner as to indicate their use for the cure, mitigation, or prevention of disease, are drugs within the meaning of the act, and, as such, are subject to the provisions thereof. On the other hand, tobacco and its preparations which are not so labeled and are used for smoking or chewing or as snuff and not for medicinal purposes are not subject to the provisions of the act.<sup>36</sup>

In 1938, Congress passed the FDCA.<sup>37</sup> It expanded misbranding to include claims in "labeling" as well as the "label."<sup>38</sup> Specifically, this expanded jurisdiction to promotional material, such as circulars and pamphlets.<sup>39</sup> So, in addition to the actual label on the drug, FDA jurisdiction was extended to manufacturer claims communicated in the marketplace. Additionally, the definition of a drug was expanded to include "articles ... intended to affect the structure or any function of the body,"<sup>40</sup> because the prior definition related only to treating diseases and did not encompass physiological conditions such as obesity or shortness, and consumers were vulnerable to fanciful claims of medical cure for such conditions. Medical devices were regulated for the first time. But, as the legislative history makes clear, the manufacturer controlled the classification of its product by the claims it made, "The use to which a product is to be put will determine the category into which it will fall ... The manufacturer of the article through his representations in connection with its sale can determine the use to which the article is to be put."<sup>41</sup> This was made clear in an exchange between W.G. Campbell, the then head of the FDA and Senator Copeland, the sponsor of the FDCA. Campbell first explained that a chiropractor's table would not be a drug unless the manufacturer "was to ship that table into interstate commerce, and say that that table would cure various ills."<sup>42</sup> Later:

Senator COPELAND. This is true, too, is it not, Mr. Campbell, that if such devices were shipped without advertising to a legitimate practitioner, and if he chose in his practice, legalized as he is under the law, to use that device, that is his privilege.

Mr. CAMPBELL. Quite right. There is no interference at all with the manufacture, with the marketing, with the use of such product. This is

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<sup>36</sup> U.S. Dept. of Agriculture (USDA), Bureau of Chemistry, Service and Regulatory Announcements, "No. 13: The Status of Tobacco and its Preparations Under the Food and Drug Act," at 24 (1914) (Bulletin)

<sup>37</sup> Pub. L. No. 75-717, 52 Stat. 1040 (1938).

<sup>38</sup> *Id.* § 201(m), 52 Stat. at 1041 (codified at 21 U.S.C. § 321(m)).

<sup>39</sup> *Kordel v. United States*, 335 U.S. 345, 348 (1948).

<sup>40</sup> *Id.* § 201(g)(3), 52 Stat. at 1041 (codified at 21 U.S.C. § 321(g)(1)(C)).

<sup>41</sup> S. REP. NO. 73-493, at 2-3, (1934), cited in 56 Fed. Reg. 60,537, 60,546 (1991).

<sup>42</sup> Foods, Drugs, and Cosmetics: Hearings on S. 2800 Before the Senate Comm. on Commerce, 73d Cong., 2d Sess. (1934) at 517.

only when someone goes to the extreme of converting that thing into a drug, according to this definition, and making preposterous and ridiculous representations about it that there would be any jurisdiction under this law, and I cannot conceive of that occurrence.<sup>43</sup>

It was clear, therefore, that the manufacturers' representations were determinative of their intent.<sup>44</sup> As the Second Circuit noted in *United States v. An Article ... Sudden Change*:

The legislative history provides firm support for this rule. See S.Rep.361, 74 Cong., 1st Sess. (Dunn p. 240):

The use to which the product is put will determine the category into which it will fall. If it is to be used only as a food it will come within the definition of food and none other. If it contains nutritive ingredients but is sold for drug use only, as clearly shown by the labeling and advertising, it will come within the definition of drug, but not that of food. If it is sold to be used both as a food and for the prevention or treatment of disease, it would satisfy both definitions and be subject to the substantive requirements for both. *The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put.* For example, the manufacturer of a laxative which is a medicated candy or chewing gum can bring his product within the definition of drug and escape that of food by representing the article fairly and unequivocally to be a drug product."<sup>45</sup>

It should be noted that these characterizations deal specifically with the threshold question of whether something is a drug or device or not, not with a new intended use arising after a drug or device has been approved. In the early 1950s, to address the problem of manufacturers circumventing the FDCA's labeling requirements by providing the information to consumers in communications falling outside the traditional labeling definition, FDA began to reach beyond the actual label of a product.<sup>46</sup> FDA would seek to designate a product misbranded if it failed to have adequate directions for *all* intended uses communicated to the marketplace.<sup>47</sup>

## B. 1952 - 1992

In 1950, the Ninth Circuit sustained an FDA claim that a product was misbranded because its labeling failed to bear a description of therapeutic uses that

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<sup>43</sup> *Id.*, at 518.

<sup>44</sup> *Action of Smoking and Health v. Harris*, 655 F.2d 236, 238 (D.C. App., (1980)), *see also*, *National Nutritional Foods Association v. Mathews*, 557 F.2d 325, 333 (2nd Cir. (1977)) (“(t)he vendors’ intent in selling the product to the public is the key element in this statutory definition.”) *and see* the Trade Correspondence of 1940 issued by the Administration quoted in Erlebacher, *When Is a “Cosmetic” Also a “Drug” Under the Federal Food, Drug and Cosmetic Act*, 27 FOOD DRUG COSM.L.J. 740, 759-760 (1972). *and* Adams, *Cosmetic or Drug?*, 35 FOOD DRUG COSM.L.J. 98, 102 (1980).

<sup>45</sup> *US v. An Article ... “Sudden Change,”* 409 F.2d 734, 739 n. 3 (2d Cir. (1969)). *See also* cases cited in text at 739.

<sup>46</sup> David G. Adams, *FDA Regulation of Communications on Pharmaceutical Products*, 24 SETON HALL L. REV. 1399, 1403 (1993).

<sup>47</sup> *See* Eugene M. Elson, *The Expanded Meaning of “Adequate Directions for Use,”* 7 FOOD DRUG COSM. L.J. 743 (1952).

were suggested in newspaper advertisements.<sup>48</sup> Amplifying this and other rulings, FDA issued a new regulation defining intended use. That definition is the one that is still operative.<sup>49</sup>

In 1962, Congress required manufacturers to provide a premarket showing of effectiveness, as well as safety, for each “use ... prescribed, recommended or suggested in the labeling thereof.”<sup>50</sup> This law made it a crime to market any new drug with any use “prescribed, recommended or suggested in the labeling thereof” which was not approved by FDA.<sup>51</sup> In the Congressional testimony, “intended use” and “claimed use” were used synonymously. Chairman Harris of the House Commerce Committee described his bill, which had identical language about uses, as requiring “a showing that new drugs and biologicals are effective for their *intended use*—as well as safe—before they may be marketed.”<sup>52</sup> The Secretary of Health, Education and Welfare (HEW), FDA’s parent agency, testified that Chairman Harris’ bill, which contained a provision concerning conditions claimed in labeling, would operate “by requiring that new drugs be shown effective for their intended uses, as well as safe, before they are marketed.”<sup>53</sup> As FDA made clear, “The committee has heard testimony about the alleged difficulties of establishing whether a drug will or will not accomplish its intended purpose.... The drug companies routinely assert through promotional material, in labeling and by other means what they believe their products will accomplish. They do not hesitate to make claims. The only question is whether they should justify those claims or show the facts upon which they are based.”<sup>54</sup>

In 1976, Congress passed the Medical Device Amendment,<sup>55</sup> which allowed, among other things, devices which were substantially equivalent to devices on the market before 1976 to be approved through an abbreviated process—the co-called 510(k) process.<sup>56</sup> In order to be approved under the 510(k) procedure, a device could claim *only* the intended uses of a predicate device. In evaluating the claims made by a manufacturer, FDA testified it was allowed to look at how the device was marketed:

[A] manufacturer of a device that is banned [for human use cannot] escape the ban by labeling the device for veterinary use. The Secretary may consider the ultimate destination of a product in determining whether or not it is for human use, just as he may consider actual use of a product in determining whether or not it is a device.<sup>57</sup>

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act.<sup>58</sup> It authorized an “abbreviated new drug application” (ANDA) which

<sup>48</sup> *Alberty Food Products v. United States*, 185 F.2d 321 (9th Cir. (1950)).

<sup>49</sup> 21 CFR § 200.128. *see note 30 supra*.

<sup>50</sup> Pub. L. No. 87-781, § 102(c), 76 Stat. 781-781 (codified at 21 U.S.C. § 355(d)(1)).

<sup>51</sup> 21 USC §§ 321(p), 331(d), and 355(a).

<sup>52</sup> 108 CONG. REC. h7714 (Daily Ed. (May 3, 1962)) (Chairman Harris’ remarks on H.R. 11581, Title I, Part A, § 102 (as reported). *See also id.* At H10839 (Daily ed. (June 18, 1962)) (Statement of Rep. Sullivan).

<sup>53</sup> Drug Industry Act of 1962: Hearings on H.R. 11581 before the House Comm. On Interstate and Foreign Commerce, 87th Cong. 61 (1962) (State of HEW Secretary Ribicoff) (1962 House Hearings).

<sup>54</sup> 1962 House Hearings, at 571-2.

<sup>55</sup> Pub. L. No. 94-295, 90 Stat. 539 (1976).

<sup>56</sup> 21 U.S.C. §§ 360(k), 360c(f) (identifying premarket notification process and associated substantial equivalence mechanism).

<sup>57</sup> H.R. Rep. No. 94-853, at 14 (1976)

<sup>58</sup> Pub. L. No. 98-417, 98 Stat. 1585 (1984).

allowed a manufacturer of a generic version of a pioneer drug to avoid a “new drug application” (NDA). In order to qualify for this approval, the drug must have the same labeling as that approved for the pioneer drug.<sup>59</sup> It was clear by 1984, however, that many drugs were used in an off-label manner, yet generics could simply copy the label of the pioneer drug, without labeling their drug for off-label uses, regardless of how pervasive those uses were. Presumably, a generic manufacturer would have the subjective intent that their product reaches as great a market as possible, even if this market were predominately, or even exclusively, for off-label uses. This suggests that Congress was content to regulate only a manufacturers’ stated intended use for its products and not the subjective intentions of that manufacturer.

### C. 1995 - Present

Despite extensive jurisprudence finding that intended use was determined by the statements of manufacturers in the marketplace,<sup>60</sup> FDA changed course around 1995, interpreting the intended use regulation to mean that a manufacturer’s statements would be evidence of intended use, along with other factors, such as consumer use of the product.

The first such attempt was FDA’s move to regulate tobacco.<sup>61</sup> In their argument that it was proper to look at internal corporate statements and the way consumers used products in the marketplace to determine intended use, FDA cited many opinions interpreting similar statutory provisions, but none that interpreted “objective intent” as it appeared in the intended use regulation. For example, it cited court cases<sup>62</sup> interpreting the Federal Hazardous Substances Act,<sup>63</sup> which defined a hazardous substance as “[a]ny toy or other article intended for use by children which the [Consumer Product Safety] Commission by regulation determines ... presents an electrical, mechanical, or thermal hazard.”<sup>64</sup> Interestingly, in *Baby Rattles*, the manufacturer was arguing for a subjective intent standard which said that *regardless* of what the manufacturer said in the marketplace (it had advertised its rattles in the toy section of a catalog) a product should not be considered a toy

<sup>59</sup> 21 U.S.C. § 355(j)

<sup>60</sup> *United States v. Hohensee*, 243 F.2d 367, 370 (3d Cir. (1957)), cert. den., 353 U.S. 976, 77 S.Ct. 1058, 1 L.Ed.2d 1136 (1957) (intended use proved by promotional claims in graphic material as well as oral representations); *United States v. Millpax, Inc.*, 313 F.2d 152, 154 (7th Cir. (1963)), cert. den., 373 U.S. 903, 83 S.Ct. 1291, 10 L.Ed.2d 198 (1963) (intended use proved by form “disclaimer letter” and magazine testimonials implying that iron tonic was a cancer cure); *Nature Food Centres, Inc. v. United States*, 310 F.2d 67, 69 (1st Cir. (1962)), cert. den., 371 U.S. 968, 83 S.Ct. 552, 9 L.Ed.2d 539 (1963) (intended use proved by claims made in lectures and “Class Notes on Health and Nutrition”); *United States v. Articles of Drug \* \* \* Foods Plus, Inc.*, 362 F.2d 923, 926 (3rd Cir. (1966)) (intended use proved by broadcast claims); *United States v. 354 Bulk Cartons \* \* \* Trim Reducing-Aid Cigarettes*, 178 F. Supp. 847, 851 (D.N.J.(1959)) (cigarettes held to be a drug where they were claimed to be effective in reducing weight); *United States v. 46 Cartons \* \* \* Fairfax Cigarettes*, 113 F.Supp. 336, 337-338 (D. N.J. (1953)) (cigarettes claimed to be effective in preventing respiratory and other diseases held to be a drug); *United States v. 250 Jars \* \* \* “Cal’s Tupelo Blossom U. S. Fancy Pure Honey,”* 344 F.2d 288, 289 (6th Cir. (1965)) (honey held to be a drug because of claims that it was “a panacea for various diseases and ailments”); *Bradley v. United States*, 264 F. 79, 82 (5th Cir. (1920)) (mineral water a drug where claims “that it possesses certain elements or ingredients which are curative, or at least alleviative, for the diseases named in the label”); *United States v. 3 Cartons \* \* \* “No. 26 Formula GM etc.”* 132 F.Supp. 569, 573-574 (S.D. Cal. (1952)) (therapeutic claims for animal heart held to bring it within the definition of drug in 21 U.S. C. § 321(g) (2)).

<sup>61</sup> 60 Fed. Reg. 41,314, 41,471-41,482 (Aug. 11, 1995).

<sup>62</sup> *United States v. Articles of Banned Hazardous Substances... Baby Rattles*, 614 F.Supp. 226, 231 (E.D.N.Y. (1985)).

<sup>63</sup> 15 U.S.C. § 1261 et seq.

<sup>64</sup> 15 U.S.C. § 1261(f)(1)(D) (1985).

if the manufacturer “did not intend, based on his knowledge of the marketplace and the objects’ foreseeable use, that they would be used as toys or otherwise used by children.”<sup>65</sup> The district court accepted FDA’s theory that more than a manufacturer’s statements determined intended use—FDA could look to consumer use, for example—but the court held that internal manufacturer documents never communicated to the marketplace cannot be invoked as evidence of an intended use.<sup>66</sup> Neither the appeals court nor the Supreme Court decided this issue in finding that FDA’s regulation outstripped its power.<sup>67</sup>

FDA’s rationale for regulating tobacco played a part in the *Washington Legal Foundation* cases.<sup>68</sup> In these cases, the Washington Legal Foundation was successful, initially, in obtaining a preliminary injunction against the operation of new FDA guidance about the off-label uses of reprints of articles from medical and scientific journals. In their appeal, FDA mooted the controversy but also pressed the point that a manufacturer’s intended use is determined by its subjective intent regarding that product. As one commentator put it:

FDA advanced this theory in order to win a point in the constitutional argument. Under *Central Hudson Gas & Electric Corp. v. Public Service Comm’n*, commercial speech is not protected by the First Amendment if its purpose is to further an unlawful transaction. Since the lawfulness of the speech is what is at issue, the unlawfulness that defeats First Amendment protection cannot be found in the speech, itself, but must be independent of the speech. FDA’s theory in the court of appeals was that it is unlawful for a manufacturer to introduce into interstate commerce a drug that is an unapproved new drug, or that is misbranded, because the manufacturer subjectively intends the drug to be put to an off-label use. Where a manufacturer subjectively intends an off-label use, the manufacturer’s dissemination or support of statements about that off-label use is speech in furtherance of an independently unlawful transaction (i.e., the unlawful introduction into commerce of a new drug that is unapproved and misbranded), and the statements are merely evidence of the unlawfulness.<sup>69</sup>

Since the appeals court found no controversy to adjudicate, it did not pass on FDA’s new theory of intended use, but the new definition was greeted with surprise by the legal community. The commenter above noted that such a definition “if ever adopted by the courts, has the potential to expand FDA’s authority enormously with respect to off-label uses. Moreover, it would render highly questionable the current regime in which widespread, well-known off-label use of a drug is permitted so long as a manufacturer does not promote it.”<sup>70</sup> He pointed to FDA’s pediatric-use rulemaking (discussed next) as well as the products liability potential of such a definition of intended use (*Buckman v. Plaintiff’s Legal Cmte*—discussed below).<sup>71</sup>

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<sup>65</sup> *Baby Rattles*, 614 F.Supp. at 231.

<sup>66</sup> *Coyne Beahm v. FDA*, 966 F.Supp. 1374, 1392 (M.D.N.C. (1997)).

<sup>67</sup> See *FDA v. Brown & Williamson Tobacco Corp.*, 520 U.S. 120 (2000) and *FDA v. Brown & Williamson Tobacco Corp.*, 153 F.3d 155 (4th Cir. (1998)).

<sup>68</sup> *Washington Legal Foundation v. Kessler*, No. Civ 1:94CV01306 (RCL) (D.D.C. filed (June 13, 2004)) and its subsequent decisions and appeals.

<sup>69</sup> Richard M. Cooper, *The WLF Case Thus Far: Not with a Bang, But a Whimper*, 55 *FOOD & DRUG L.J.* 477, 485 (2000).

<sup>70</sup> *Id.*

<sup>71</sup> *Id.*

The next major attempt to expand the meaning of the “intended use” regulation came in 1998, when FDA issued its “Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients.”<sup>72</sup> Citing the paucity of research about the safety and effectiveness of drugs in children, FDA noted that when physicians were forced “to choose between prescribing drugs without well-founded dosing and safety information or utilizing other, potentially less effective therapy,” they often respond by prescribing adult-approved drugs to children, but in smaller doses.<sup>73</sup> This common off-label use of medications exposes children to unique risks:

Correct pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight ... or on body surface area. ... Potentially significant differences in pharmacokinetics may alter a drug’s effect in pediatric patients. The effects of growth and maturation of the immune system, alterations in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes may result in significant differences in the doses needed by pediatric patients and adults.<sup>74</sup>

Additionally, physicians may prescribe older, less effective drugs, as opposed to newer, more effective medication that has not been subjected to rigorous study in the pediatric population.<sup>75</sup> An example of this may be found in anti-depressants. Prozac, one of the oldest selective serotonin re-uptake inhibitors (SSRI) was approved for children in 2003.<sup>76</sup> Until 2009, this was the only antidepressant approved for use in children. In March of 2009, FDA approved Celexa for use in the pediatric population.<sup>77</sup> For six years, then, psychiatrists had no FDA-approved alternative to Prozac.

New FDA rules required any drug manufacturer submitting a new drug for approval to study the safety and effectiveness of its drug in the pediatric population. This mandated study requirement replaced the voluntary option provided by Congress in the Food and Drug Modernization Act of 1997<sup>78</sup> (FDAMA), which provided six months of market exclusivity for their products before generics could enter the market in exchange for studying their drug in children. A manufacturer could seek a complete waiver of this requirement if it could show that the necessary studies were impossible or highly impractical or if it could point to strong evidence that the product would be ineffective or unsafe in all pediatric age groups.<sup>79</sup> Alternatively, a manufacturer could seek a *limited* waiver if it could certify that the product: 1) does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments; and 2) is not likely to be used in a substantial number of

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<sup>72</sup> 21 C.F.R. §§ 201, 312, 314, 601, 63 Fed. Reg. 66,632 (Dec. 2, 1998).

<sup>73</sup> Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,900.

<sup>74</sup> 62 Fed. Reg. at 43,901.

<sup>75</sup> *Assoc. of Amer. Phys. And Surg. v. FDA*, 226 F.Supp.2d 204, 207 (D.D.C., October 17, 2002).

<sup>76</sup> FDA, *FDA Approves Prozac for Pediatric Use to Treat Depression and OCD*, (Jan. 3, 2003) at <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01187.html> (last visited May 18, 2009).

<sup>77</sup> Reuters, *Depression Pill OK’d for Kids But Probe Goes On*, (Mar. 20, 2009) at <http://www.reuters.com/article/rbssBiotechnology/idUSN2032438520090320?pageNumber=1&virtualBrandChannel=0> (last visited May 18, 2009) and see, *Forest Laboratories, Inc. Announces FDA Approval of Lexapro(R) for the Treatment of Major Depressive Disorder in Adolescents*, at <http://www.frx.com/news/PressRelease.aspx?ID=1268211> (last visited July 1, 2009)

<sup>78</sup> Pub. L. No. 105-115, 111 Stat. 2296 (1997).

<sup>79</sup> 21 C.F.R. §§ 314.55(c)(2), 601.27(c)(2).

pediatric patients.<sup>80</sup> For already marketed products, FDA could have required a manufacturer to conduct studies of pediatric uses, but only if it could show that such testing was required.<sup>81</sup> The rule did not apply to unlabeled indications, so if a use, even a wide-spread use, of a drug was off-label, that use did not need to be studied in children.<sup>82</sup> If a manufacturer refused to conduct the appropriate studies, FDA could have sought a federal court injunction to declare the product “misbranded or an unapproved new drug or unlicensed biologic.”<sup>83</sup>

The Association of American Physicians and Surgeons challenged the new rules in the District Court of DC. In defending its rule, FDA argued that pediatric use was a use that was “prescribed, recommended, or suggested” by the product’s label,<sup>84</sup> even if the label specifically disclaimed use on children in compliance with another FDA regulation.<sup>85</sup> The two sides spent a large amount of time on the issue of whether FDA could look beyond the manufacturer’s label in determining intent. Plaintiffs cited *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. (1998)) aff’d on other grounds, 529 U.S. 120 (2000) (“[N]o court has ever found that a product is ‘intended for use’ or ‘intended to affect’ within the meaning of the [FDCA] absent manufacturer claims as to that product’s use.”) FDA, by contrast, cited cases supporting a broader view: that it can look to “promotional claims, advertising, and any other relevant sources.”<sup>86</sup> This line of cases suggested that the courts could look to “evidence that the vendor is aware that his product is being offered or used by others for a purpose for which it is neither labeled nor advertised.”<sup>87</sup> Even consumer intent could be relevant to the inquiry.<sup>88</sup> The court rejected both arguments, however, finding that the question of whether FDA could regulate claims not made in the labeling was a different question than whether a product was a drug or not. It did, however, indicate that the notion that FDA could regulate unclaimed uses of drugs based solely on the knowledge of the manufacturer flew in the face of tradition. It pointed to the statement by then-FDA Commissioner David Kessler regarding drug testing on pediatric populations:

I need to acknowledge the limits of FDA’s authority. It is our job to review drug applications for the indications suggested by the manufacturer. We do not have the authority to require manufacturers to seek approval for indications which they have not studied. Thus, as a matter of law, if an application contains indications only for adults, we’re stuck.<sup>89</sup>

The court further noted that if FDA had the authority it claimed—to regulate labels based on a manufacturer’s knowledge of widespread off-label use—that

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<sup>80</sup> §§ 314.55(c)(2), 601.27(c)(2); 63 Fed. Reg. at 66,634.

<sup>81</sup> 21 C.F.R. § 201.23(a). FDA had to demonstrate that the absence of adequate labeling could pose significant risks to pediatric patients; and either 1) the drug is “used in a substantial number of pediatric patients for the labeled indication;” or 2) there is “reason to believe that the drug product would represent a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications.” 21 C.F.R. § 201.23(b).

<sup>82</sup> See 63 Fed. Reg. 66,658; FDA Denial at 7.

<sup>83</sup> § 201.23(d); 63 Fed. Reg. at 66,636.

<sup>84</sup> 21 U.S.C. § 355(d)(1).

<sup>85</sup> 21 C.F.R. § 201.57(f)(9)(vi).

<sup>86</sup> *Hanson v. United States*, 417 F.Supp. 30, 35 (D.Minn) *aff’d* 540 F.2d 947 (8th Cir. (1976)).

<sup>87</sup> *United States v. Kasz Enters., Inc.*, 855 F.Supp. 534, 539 (D.R.I. (1994)).

<sup>88</sup> *United States v. Travia*, 180 F.Supp.2d 115, 119 (D.D.C.(2001)).

<sup>89</sup> David Kessler, Speech of FDA Commissioner to the American Academy of Pediatrics (Oct. 14, 1992).

would conflict with clear Congressional will to condone off-label use,<sup>90</sup> and to allow the manufacturer, “through his representations in connection with its sale, [to] determine the use to which his article is to be put.”<sup>91</sup> Despite the District Court’s rejection of FDA’s authority to regulate unclaimed uses, the agency has continued to apply this interpretation of the intended use regulation as seen below.

The issue next arose in *Buckman Co. v. Plaintiffs’ Legal Comm.*,<sup>92</sup> with the plaintiffs’ legal committee (respondents) arguing that Acromed submitted a fraudulent 510(k) submission through Buckman Corporation (petitioner), a regulatory consulting firm, for its plate and screw system. The devices were a variable screw placement (VSP) plate and the screws required to attach that plate to bone. They were described in premarket notifications as “Nested Bone Plates,” and “Cancellous Bone Screws.” A letter from FDA on January 10, 1986 asked for clarification on the intended use of the devices.<sup>93</sup> AcroMed responded that the components were “intended for use in appropriate fractures of long bones of both the upper and lower extremity.”<sup>94</sup> It was this intended use that was at the core of the dispute, with respondents claiming it was a fraud on FDA. They claimed that AcroMed never intended the screws to be used in the long bones and from the start the screws were only going to be marketed and sold for use in the spine. Petitioners argued that use in the long bones was, indeed, one possible intended use. “Intended use,” then, formed a key part of the briefing in this case. As the respondents stated in their merits brief:

“Intended use” is at the heart of the FDCA regulatory scheme. It determines whether a product is a drug or device, the character of the product, the regulatory requirements to which it is subject, and the extent of the requirements. Thus, for example, a screw that is intended for use in constructing a car is not a medical device subject to regulation under the FDCA. The same screw, if intended for use in constructing crutches, would be a Class I medical device subject to minimal regulation. If that screw were intended for use in the human spine, it would be a Class III medical device subject to premarket approval.<sup>95</sup>

Petitioners argued, among other things, that a civil case alleging fraud on FDA based on an allegedly fraudulent “intended use” statement was expressly preempted because it imposed a new definition of “intended use” that was different than that employed by FDA.<sup>96</sup> They characterized respondents’ claims against them as stating that they needed to disclose to the FDA that they *subjectively* “desired or hoped that the bone screws ... although labeled for use only in bones other than the spine—would be used by physicians for spinal fixation.”<sup>97</sup> By contrast, according to petitioner, federal law imposes no such requirement that 510(k) submissions

<sup>90</sup> See H.R. CONF. REP. NO. 105-399, at 97 (1997), *reprinted in* 1997 U.S.C.C.A.N. 2880-2887 (“The off-label use of a medical device by a physician using his or her medical judgment in determining how and when to use the medical product for the care of a particular patient is not the province of the FDA.”).

<sup>91</sup> S. REP. NO. 73-493, at 3 (1934), *See also* *Action on Smoking & Health v. Harris*, 655 F.2d 236, 243 (D.C. Cir. (1980)) (quoting the report and stating: “These comments reveal the understanding even in 1934 that the crux of FDA jurisdiction over drugs lay in manufacturers’ representations as revelatory of their intent.”).

<sup>92</sup> 531 U.S. 341 (2001).

<sup>93</sup> Resp. Br., *Buckman Corp. v. Plaintiffs Legal Cmte*, No. 98-1768, at 8.

<sup>94</sup> *Id.*

<sup>95</sup> Resp. Br. At 4.

<sup>96</sup> Pet. Br. At 17.

<sup>97</sup> *Id.* at 20.

disclose how a manufacturer subjectively intends that a device will be used because subjective intent is irrelevant under the Medical Device Amendments. "So long as a device's labeling and a manufacturer's marketing refer only to cleared uses, the manufacturer has complied with the federal statutes even if it hopes (as would any rational manufacturer) that physicians engage in off-label uses."<sup>98</sup>

They note that substantial equivalence would be an unworkable standard if the subjective intent of manufacturers was at issue.<sup>99</sup> A device only qualifies for substantial equivalence if it has an identical intended use as the predicate (pre-1976) device. There is no way to determine the subjective intent of the pre-1976 manufacturer, which might not be the current manufacturer of a particular device.<sup>100</sup> Further, since the 510(k) process was designed to encourage competition with grandfathered devices, allowing an inquiry into the subjective intent of the manufacturers would defeat that purpose. If the off-label use of a product has become the standard of care for a particular condition, for example, it would be almost impossible for a manufacturer to come to market with a device for 510(k) clearance and *not* have that use in mind. By 1992, for example, that was the case for pedicle screws.

Respondents disputed the idea that they were putting forward a requirement that FDA look into the purely subjective intents of manufacturers.<sup>101</sup> Their understanding of "intended use" did not forbid a manufacturer from bringing a product to market with a hope or desire that it would be used off-label, but that it cannot lie about the way it will classify the device in the marketplace. As they characterized their interpretation:

This interpretation of the law doesn't mean one can't request a 510(k) with the hope, or even the expectation that it will be used "off label," nor does it mean that a 510(k) clearance must list every potential use of a device. However, it does mean that if someone requests marketing clearance under section 510(k), they must, at a minimum, truthfully describe the manner in which they expect that the device will be characterized by its sellers and distributors—the "objective" intended use of the product. ... Plaintiffs do not allege that Buckman merely submitted a 510(k) notification to the FDA with the subjective hope, knowledge or expectation that the device at issue would be used "off label" for spinal fixation and failed to disclose this to the FDA. Rather, plaintiffs have alleged and proven that Buckman affirmatively told the FDA that the device at issue was intended for use in repairing arm and leg fractures when it had no expectation that the device would actually be described that way by anyone and specifically intended that the device would be characterized in the marketplace and used solely as a spinal fixation device.<sup>102</sup>

Respondents put forward a comprehensive picture supporting the notion that AcroMed knew and actively promoted its products in the marketplace to be used in the spine and not in the long bones of the arms and legs as they had applied for

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<sup>98</sup> *Id.*

<sup>99</sup> *Id.* at 24.

<sup>100</sup> *Id.*

<sup>101</sup> Resp. Br. At 4.

<sup>102</sup> *Id.*, at 28.

in the 510(k) application.<sup>103</sup> In their opinion, therefore, AcroMed had the objective intent to market its products for the spine, so the intended use they disclosed to FDA was fraudulent. Of course, this would have been classic off-label promotion, and properly regulated by FDA.

FDA disagreed with *both* parties' statements about the intended use requirement. It opined that while labeling is important in determining the intended use, so is the manufacturer's knowledge that a product is offered and used for a purpose for which it is neither labeled nor advertised.<sup>104</sup> Also relevant is the manufacturer's knowledge of facts that would give him notice that a product is to be used for purposes other than those for which the manufacturer offered it.<sup>105</sup> That said, FDA was not clear when it would consider a new intended use to arise. When FDA requires a manufacturer to inform it of the intended use of a product, it is asking for more than simply the labeling, but:

It is asking for the intended use that will be revealed by all the manufacturer's "expressions" and "the circumstances surrounding" the device's "distribution." Under the regulations, a manufacturer is not required to disclose every foreseeable use of a device that it secretly desires. Physicians often use medical devices for purposes that are not identified in the labeling, and manufacturers may seek Section 510(k) clearance for the use identified in the labeling without setting forth every possible off-label use to which the device might be put after it reaches the market. But whatever may be the full scope of a manufacturer's duty to disclose the possible uses of the device beyond those stated in the labeling the manufacturer has submitted, when, at the time of the application, a manufacturer plans to promote and distribute a device exclusively for one use, it must disclose to the FDA that intended use. A statement to the FDA that the device has a different intended use would be false and misleading. The intended use stated in the premarket notification must be a bona fide use; it cannot be a pretext calculated to clear the device for distribution for other uses.<sup>106</sup>

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<sup>103</sup> *Id.* at 6-12. Among other things, respondents asserted that Arthur Steffee, MD, formed AcroMed to "manufacture and sell . . . spinal implants and instrumentation." The patent they applied for that covered the screws in question described their use as an adjunct to spinal fusion surgery and consisting of plates affixed to the spines with pedicle screws. AcroMed had submitted premarket notifications for their device twice before for use in spinal fusion surgeries. Both applications were denied as not substantially equivalent to any predicate device. In 1986, shortly after the device was approved, AcroMed's president admitted that the characterization of the devices was "a labeling sleight-of-hand" that "in no way changes the intended uses of the plates and screws." At trial, AcroMed's VP and chief counsel admitted that the only purpose of the screws was spinal fixation. At some point in the proceedings, AcroMed's VP of Operations admitted to FDA enforcement officials that the devices were "always intended for use in the spine and [were] never distributed to parties who were not known to have the skills and training to implant them in the spine." Indeed, it was physically impossible to implant the devices in long bone repair. Respondents also detailed the various ways that the devices had been characterized in the marketplace as spinal fixation devices and marketed exclusively for that use. AcroMed created an advisory panel consisting of a cadre of spinal surgeons who agreed to serve in exchange for stock options. The panel agreed to promote the use of the devices in spinal surgeries and trained surgeons for that use. AcroMed would not ship its plates and screws to anyone unless it was demonstrated that the surgeon had been trained by someone on the advisory panel to implant the device in the spine. The company provided surgeons with video tapes, a technique manual, product catalogs, price lists, and patient booklets, all of which characterized the devices as spinal fixation devices. Indeed, respondents alleged there was no evidence AcroMed ever characterized the devices as long bone fixation devices.

<sup>104</sup> FDA Amicus Brief at 14.

<sup>105</sup> *Id.*

<sup>106</sup> *Id.* at 15.

It is clear from FDA's brief that at a minimum FDA will look to whether the use claimed is a bona fide use of the product.

#### *D. Recent Examples of Enforcement Based on the Expanded Intended Use Definition*

While the attempts to regulate tobacco and to impose pediatric testing requirements are the clearest examples of the government using their newly expanded definition of intended use—a use arising from knowledge of widespread off-label use—there have been some recent suggestions that this definition continues to carry weight.

First, on June 17, 2009, a federal grand jury returned an indictment against Synthes Inc. for conducting clinical trials of its bone cement without FDA approval.<sup>107</sup> Synthes' bone cement, Norian XR, was cleared via a 510(k) premarket notification in 2001 as a general bone void filler.<sup>108</sup> The unapproved use at issue is the use of the cement in load-bearing indications in the spine, for example, to treat vertebral compression fractures (VCF).<sup>109</sup> In addition to felony counts of introducing adulterated and misbranded medical devices with an intent to defraud, Synthes was charged with 45 misdemeanor counts of introducing adulterated and misbranded medical devices. The charges all relate to shipments of their cement on or after August 27, 2003.<sup>110</sup> The allegedly illegal "test market" for the product, by contrast, occurred in the summer and fall of 2002. Also, while the test market constituted 34 cases, the felony and misdemeanor indictments for adulterated or misbranded devices numbered 44 felony and 45 misdemeanor indictments. It is clear that the Department of Justice (DOJ) in this case considered the proposed marketing plan for the cement, to market it for the iliac crest (a part of the hip)<sup>111</sup> was a pretext. Evidently, each shipment of the cement was, therefore, a misbranded or adulterated shipment, whether it was actively promoted for the off-label use or not. Indeed, the plan to market the cement for the iliac crest was noted as a separate fraudulent statement to FDA: "John J. Walsh ... falsely stated that 'at the time of the test market activities,' defendant NORIAN and Synthes 'did not ... intend to market [Norian XR] for the treatment of vertebral compression fractures. Additionally, it was never our intent to suggest, in any way, that the product should be used for such purpose.'" <sup>112</sup> In fact, no amount of warnings to sales people that the cement was never to be marketed for the off-label use was sufficient, apparently, to cure the fact that the company subjectively intended the off-label use of the cement. The indictment details numerous attempts by the company to warn its salespeople that off-label promotion was forbidden and doctors that only the on-label use was intended. Each of these attempts, however, was faulted as being misleading. For example, a presentation to the Spine sales force that stated that Norian XR's approved indications included the spine but not vertebral compression fractures was misleading, according to the government, because that presentation did not direct

<sup>107</sup> Synthes Indicted Over Trials of Cement, WALL STREET JOURNAL, B2, (June 17, 2009).

<sup>108</sup> Indictment found at DOJ website p. 16: (<http://www.usdoj.gov/usao/pae/News/Pr/2009/jun/synthesind.pdf> (last visited June 29, 2009)).

<sup>109</sup> *Id.* at pp. 9-10.

<sup>110</sup> *Id.* at p. 46 & 50.

<sup>111</sup> *Id.* at p. 29. "On or about January 16, 2003, [Defendants] held a meeting ... to approve a market introduction plan for Norian XR ... that described a supposed market for the use of Norian XR in the iliac crest, which is a part of the hip, when, in fact, no such market existed or plan was intended."

<sup>112</sup> *Id.* at pp. 37-38.

the sales force to the label's *specific* warning that the product was "not intended for treatment of vertebral compression fractures."<sup>113</sup> A memo to the sales force specifically telling them that off-label promotion was forbidden, was similarly faulted as was a "dear surgeon" letter telling physicians that using Norian XR to treat VCF was off-label.<sup>114</sup>

One can also see the expanded definition in the deferred prosecution agreement the U. S. Attorney's Office for the Northern District of California entered into with InterMune, Inc., over the alleged shipment of misbranded drugs (Actimmune). InterMune did not contest the facts which the U.S. Attorney believed sufficient to prove the allegation. Those facts included only two allegations of communications with the marketplace by InterMune or its sales force. First, there was a press release which announced the drug's efficacy for the off-label use. Second, it was noted that "several sales force personnel sometimes created and used their own marketing aids in discussions with physicians concerning Actimmune for [idiopathic pulmonary fibrosis—the off-label use]. For example, one former sales representative wrote and distributed an invitation letter to an educational program, which one physician recipient characterized as 'against the spirit of FDA regulations.'" The same set of facts cited two communications by a specialty pharmacy to physicians and patients. These communications were approved by a "former InterMune employee." It is not clear whether this employee was employed by InterMune at the time of the communications or by the pharmacy. Of equal or greater importance, it seems, was the simple fact that InterMune employed salespeople to target the physicians who would prescribe off-label and incentivized these sales people for increased off-label prescriptions—without any evidence that this force ever characterized the drug for the off-label use, other than the two narrow examples.

One can also see the influence of the expanded definition of intended use in FDA's recent activity concerning biliary stents, a plastic or metal tube inserted into the bile duct and typically cleared by FDA for use in the palliative treatment of malignant neoplasms in patients with terminal cancer.<sup>115</sup> In 2003, FDA sent letters to biliary stent manufacturers to remind them to market them only for biliary use, as it had become aware that the vast majority of such stents were being used for vascular stenting.<sup>116</sup> From an article by an FDA employee targeted at endovascular surgeons:

In addition, if [manufacturers] are aware that their devices are being used off-label, they are responsible for addressing the associated regulatory problem—that is, the manufacturer must then secure approval for the other indication or dissuade further off-label use. The FDA recently sent a letter to nonvascular stent manufacturers to remind them of their obligation to ensure that their devices are appropriately labeled for the way they are actually being used. In other words, they have been told to obtain the necessary approvals for the specific vascular indications.<sup>117</sup>

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<sup>113</sup> *Id.* at p. 33.

<sup>114</sup> *Id.* at p. 33-34.

<sup>115</sup> Kenneth Cavanaugh, *Evaluation of Renal Artery Stenting, Endovascular Today*, (Sept. 2006) at 105, 106.

<sup>116</sup> Dorothy Abel, *Off-Label Medical Device Use, Endovascular Today*, (Mar. 2003) (page number not available in internet archive.) (Found at [http://www.evtodayarchive.com/03\\_archive/0303/181.html](http://www.evtodayarchive.com/03_archive/0303/181.html) (last visited May 21, 2009)).

<sup>117</sup> *Id.*

In March, 2007, FDA met with 20 biliary stent manufacturers and warned them about promoting their devices at vascular meetings and requested that they seek approval of the vascular indication.<sup>118</sup> Finally, U.S. Attorneys have suggested that a key indicator of off-label promotion may be the existence of sales representatives devoted to the off-label indication or a large off-label market compared to the market for on-label indications.<sup>119</sup>

## V. CONCLUSION

This new approach of FDA—to view widespread off-label use, and unpublished internal communications as indicative of a new intended use—is inconsistent with the legislative history of the agency, the purpose of the FDCA (to regulate drugs and devices, but leave the practice of medicine to physicians and surgeons) and even FDA's understanding as recently as its brief in *Buckman*. It is reasonable to look at the marketing and promotional activities in determining the intended use of a product. However, FDA should make clear that without affirmative representations by the manufacturers, the widespread off-label use, or even a manufacturer promoting a bona fide use of a product to a physician likely to use the product in an off-label manner, cannot lead to a new intended use. Otherwise, manufacturers will continue to operate in a state of confusion, unsure whether their knowledge of off-label use will impose additional legal risk on them. This is especially important as FDA and DOJ are not the only entities attempting to interpret the intended use regulation. Recently, Michael Loucks, First Assistant U.S. Attorney for the District of Massachusetts, encouraged companies to file off-label promotion suits against their competitors to protect their lawfully-gained labels.<sup>120</sup> Indeed, at least one private litigant has attempted to use civil litigation to enforce its rights through arguing that a drug has a different intended use than labeled.<sup>121</sup> While the court rejected the claim, reaffirming in dicta, that “no court has ever found that a product is ‘intended for use’ or ‘intended to affect’ within the meaning of the [FDCA] absent manufacturer claims as to that product’s use,” FDA could clear up a significant amount of ambiguity by amending its regulation. Without this clarification, the question remains, “What are companies to do when they learn that, *contrary to their wishes*, their own device is being used for an extra-label indication?”<sup>122</sup>

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<sup>118</sup> Daniel Schultz, Director of the Center for Devices and Radiological Health, Statement before the Special Cmte on Aging, United States Senate, found at <http://www.fda.gov/ola/2008/deviceads091708.html> (last visited May, 21, 2009).

<sup>119</sup> Michael K. Loucks, First Assistant U.S. Attorney, District of Mass., Trends in Prosecutions in the Health Care Industry, p. 20, found at [http://law.hamline.edu/files/Michael%20Loucks%20Presentation.Jan\\_2009%5B1%5D.ppt](http://law.hamline.edu/files/Michael%20Loucks%20Presentation.Jan_2009%5B1%5D.ppt) (last visited May 21, 2009).

<sup>120</sup> Paul Greenberg & Tamar Sisitsky, *Off Label Marketing Investigations in the Pharmaceutical Industry*, 4, (2006). (found at [http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/Forum\\_Fall06\\_Off-Label\\_Investigations.pdf](http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/Forum_Fall06_Off-Label_Investigations.pdf) last visited May 22, 2009).

<sup>121</sup> *Sigma Tau Pharmaceuticals v. Schwetz*, 288 F.3d 141 (4th Cir. (2002)).

<sup>122</sup> See footnote 27 above.