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# ONE-HALF PHEN IN THE MORNING/ ONE FEN BEFORE DINNER: A PROPOSAL FOR FDA REGULATION OF OFF- LABEL USES OF DRUGS\*

Jaime A. Wilsker\*\*

*When a nearly untested drug combination enters the obesity market in a country where people are willing to try almost anything that promises to help them shed pounds, you have a potential disaster on your hands.<sup>1</sup>*

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\* The term "off-label" refers to the practice of prescribing drugs for uses that have not been approved by the Federal Drug Administration ("FDA"). Marlene Cimon, *Public Policy: FDA's Approval Process Faces Challenge in New Senate Bill Finding the Proper Balance Between Protecting and Overburdening Americans is at the Heart of Renewed Debate Over the Agency's Mission*, L.A. TIMES, July 22, 1997, at A5. Fen-phen, for example, is a two-drug combination that was not FDA approved. *Id.* (noting that some 40-60% of all prescriptions are off-label uses). See also *Fen/Phen: Unapproved Drug-2: Bill Seen Helping Cancer Doctors*, DOW JONES NEWS SERVICE, July 21, 1997, at 18:15:00; Kathleen Kerr, *Drug Makers Seek Return of Redux*, N.Y. NEWSDAY, Nov. 12, 1997, at A24 (noting another example of off-label dispensing, namely, the drug Redux (dexfenfluramine)). Although available in Europe for a long time, the FDA approved Redux only last year "after what some researchers believe was a shallow review of the adverse effects." Terence Monmaney, *Diet Drugs Said To Kill Off Some Brain Cells*, AUSTIN AMER.-STATESMAN, Aug. 27, 1997, at A1. Similar to fen-phen, Redux is another controversial diet pill that has been recently removed from pharmacies as a result of widespread concern with heart valve problems. Kerr, *supra*, at A24. Manufacturers are seeking to put Redux back on the market for treatment of psychiatric disorders. Kerr, *supra*, at A24.

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<sup>1</sup> Gina Kolata, *Millions Flock to Diet Drugs, But Risks Are Emerging*, PITTSBURGH POST-GAZETTE, July 20, 1997, at A3. Not since the 1970's craze with amphetamines have diet pills gained such popularity. *Id.* Yet, this craze begs the

## INTRODUCTION

Desperation leads people to the "miracle" bottle for a quick fix weight loss drug like fen-phen.<sup>2</sup>

It's not just being able to wear shorts in public. It's being able to squat down to the bottom drawers of the file cabinet. It's being able to bend her leg enough to work the parking brake in her blue Chevy pick-up. It's being able to fit through the turnstile at Blockbuster.<sup>3</sup>

For many, "[t]he promise of a thinner, happier life was contained in two little syllables—Fen-phen."<sup>4</sup> However, the advent of the so-called "fen-phen cocktail" makes it ever more apparent that

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question, "[w]hat are people willing to risk to be slim?" *Id.*

<sup>2</sup> See Thomas N. Tiedt, et al., *Pharmacotherapy in The Management Of Obesity*, 277 JAMA 1201, 1201 (1997). "Diet pills are at best only signals to stick to required diet and exercise." *Id.*

<sup>3</sup> Roger Bull, *Fen-phen Fear: Is Weight Loss Worth the Health Risk?*, FLA. TIMES-UNION, Aug. 26, 1997, at D1. Fen-phen has become a last resort for many obese people. *Id.* In the past Kim Fraley had tried Weight Watchers, Nutrisystem, Jenny Craig and the Mayo Diet and lost a few pounds which she eventually gained back. *Id.* The battle over weight gain began for Fraley in high school when she became unable to participate in sports due to a knee injury. *Id.* Two years later she became pregnant and gained an additional sixty-five pounds. *Id.* Earlier this year, at age twenty-five, Fraley weighed over 324 pounds. *Id.* She has currently dropped to 250 pounds by taking fen-phen. *Id.* Ann Diamond, another fen-phen user, was satisfied with the results (losing nine pounds in seven weeks), but has quit taking the diet drug due to reports linking fen-phen to pulmonary hypertension. *Id.*

<sup>4</sup> Jennifer Brett, *Dieters Hear Fen-phen Warnings*, ST. PETERSBURG TIMES, Aug. 3, 1997, at 1. Dana Reuter tried almost every diet, none of which helped her lose weight and keep it off. *Id.* "Then something that seemed almost magical came along: pills she could take that would stamp out her appetite and boost her energy. The pounds would melt off. Slim jeans were in her future." *Id.* At age 47, after taking half a pill at a time for close to three months, Reuter claims that she had no appetite which resulted in a loss of 30 pounds. *Id.* Like Ann Diamond, Reuter quit taking fen-phen because of concern over the development of deformed heart valves in others who ingested the drug. *Id.*

"succumbing to the allure of diet pills as a quick fix for excess weight may be courting disaster."<sup>5</sup>

In the age of a "wonder drug" for just about everything, the battle between the health and safety needs of society and the rights of the drug industry to sell its products with as little governmental intrusion as possible becomes far more serious when a third element is added—off-label prescriptions. Off-label prescriptions allow for the dispensing of drugs for uses that have not been approved by the Federal Drug Administration ("FDA").<sup>6</sup> Fen-phen, for example, is a combination of two appetite suppressants, each individually approved by the FDA for short-term use,<sup>7</sup> but the concomitant use of both drugs is neither approved nor recommended by either the FDA or the manufacturers.<sup>8</sup> Still, it is legal

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<sup>5</sup> Robert Langreth, *Medicine: Eminent Journal Urges Moratorium on Diet Drug Use*, WALL ST. J., Aug. 28, 1997, at B1. The FDA has begun gathering information on the rate of occurrence of adverse side effects with fen-phen in order to decide what steps, if any, should be taken. *Id.* For example, more warnings, changes in recommended dosages or length of time the drugs should be prescribed for are under consideration. *Id.* Meanwhile, a few patients are ceasing their use of the drug in light of possible heart valve side effects. *Id.*

<sup>6</sup> Cimon, *supra* note \*, at A5. See also Robert Langreth & Bruce Ingersoll, *Pharmaceuticals: Diet-Drug Mix May Damage Heart Valves*, WALL ST. J., July 9, 1997, at B1 (noting that absent FDA approval of the combined use of fenfluramine and phentermine, doctors have been prescribing their concomitant use in recent years).

<sup>7</sup> *Heart Disease Link to Diet Drugs Prompts FDA Action*, MARKETLETTER, July 21, 1997, available in 1997 WL 11870685, at ISSN 0951-3175. Both drugs are approved as "monotherapies for severe obesity." *Id.* Fenfluramine Hydrochloride is implicated in the management of exogenous obesity as a short term (a few weeks) adjunct in a weight reduction regimen based on caloric restriction. See PHYSICIANS' DESK REFERENCE: PRODUCT INFORMATION, ISBN: 1-56363-151-2, at 1288-89 (1996) [hereinafter PDR]. Phentermine has the identical indications with the additional language, "the limited usefulness of agents of this class should be measured against possible risk factors inherent in their use." PDR, *supra*, at 2464-66.

<sup>8</sup> Murray M. Lumpkin, M.D., *Public Health Advisory: Reports of Valvular Heart Disease in Patients Receiving Concomitant Fenfluramine and Phentermine*, (last modified Aug. 28, 1997) <<http://www.fda.gov/cder/phenfen.html>>. This public health advisory provides:

We strongly encourage all health care professionals to report any cardiac valvular disease or other serious toxicities associated with the

and quite common for doctors to prescribe a drug to be used for an indication which was never FDA approved.<sup>9</sup> Physicians who prescribe fen-phen and other off-label prescriptions are, in effect, creating a new drug that has not been proved generally safe and effective for human consumption.<sup>10</sup> As concerns over side-effects grow and as new reports begin to link these drugs to primary pulmonary hypertension, rare heart valve disorders, and even brain damage,<sup>11</sup> will no one stop to ask: who will regulate doctors when

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use of fenfluramine, dexfenfluramine, or phentermine to the FDA's MEDWATCH program at 1-800-FDA-1088/fax 1-800-FDA-1078, or to the respective pharmaceutical manufacturers. Of particular interest in such cases would be the dosage and duration of therapy with the drug product(s), whether there were any other medications being taken by the patient on a chronic basis, whether there was any history of pre-existent cardiac disease, the results of the patient's cardiac examination, and the degree of obesity at the time of the initial therapy with the drug(s).

*Id.* Dr. Lumpkin is the Deputy Center Director for Drug Evaluation and Research for the FDA. *Id.* Fenfluramine is sold by American Home Products Corporation as Pondimin. *See* Langreth, *supra* note 5, at B1. Phentermine is sold by Smith Kline Beecham PLC and several smaller manufacturers. *See* Langreth, *supra* note 5, at B1. American Home Products asserted that the reports linking heart valve damage to fen-phen are "inconclusive." Langreth, *supra* note 5, at B1.

<sup>9</sup> Kathleen Kerr, *New Heart Cases Spur Fen-phen Label Move*, N.Y. NEWSDAY, Aug. 28, 1997, at A52. "The combination was tested by millions of Americans who decided it was the easy answer to their weight-loss woes based on the sales pitches of diet centers, doctors, Internet ads, and fliers on lamp-posts." Nancy Shute, *Pills Don't Come With A Seal Of Approval*, U.S. NEWS & WORLD REP., Sept. 29, 1997, at 7475.

<sup>10</sup> Robert Kushner, M.D., *The Treatment of Obesity: A Call for Prudence and Professionalism*, 157 ARCHIVES OF INTERNAL MEDICINE 602, 603 (1997). The physician's greatest asset is the ability to seize on the drug frenzy to lose weight that is popularized in women's magazines, on television and almost inescapable in modern-day society. *Id.* The physicians appear as superheros, ready to conquer the evil of obesity, armed with the perfect panacea. *Id.* Not too far behind, the commercial weight loss programs are starting to incorporate pharmacotherapy into their diet regimens. *Id.*

<sup>11</sup> Robert Langreth, *Pressure in U.S. Builds to Restrict Diet Drugs*, WALL ST. J. (Europe), Aug. 28, 1997, at 3. The most recent side-effect report tells of a 29-year-old woman who died of pulmonary hypertension after taking fen-phen for only 23 days. *Id.* The autopsy revealed lung damage similar to that caused by Aminorex, which was banned in the late 1960's in Europe after it was

they are free to prescribe approved drugs for any and all uses they desire?

This Note examines the best way to protect society against the desire and, with the advent of fen-phen, ability to self-medicate in an effort to attain the American ideal that beauty and thinness are one in the same. In particular, this Note argues that off-label uses of such prescription drugs must fall under FDA supervision. Part I will examine the development of the FDA's supervisory role in the regulation of prescription drugs. Part II will address the manufacturers' liability for prescription drugs under the Restatement (Second) of Torts, section 402A, comment k and current case law. Part III will discuss Fenfluramine and Phentermine. Part IV provides a proposal which would grant the FDA authority to oversee off-label dispensing of drugs. This Note concludes that the FDA must take an active role in the regulation of off-label dispensing of drugs to ensure greater consumer safety.

## I. THE DEVELOPMENT OF THE FDA'S SUPERVISORY ROLE

Drugs and medical devices are the most heavily regulated consumer products in our society.<sup>12</sup> As set forth by statute,<sup>13</sup> the FDA is the primary agency concerned with the regulation of pharmaceuticals.<sup>14</sup> Congress delegated to the FDA the power to protect individuals by regulating which drugs will be deemed safe and effective.<sup>15</sup> Since the "drug" category is broad, generalizations

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implicated in many deaths. *Id.*

<sup>12</sup> Richard J. Crout, *The Drug Regulatory System: Reflections and Predictions*, 36 FOOD DRUG COSM. L.J. 106, 113 (1981).

<sup>13</sup> See 21 U.S.C. §§ 301-393 (1938).

<sup>14</sup> *Id.* See also MARDEN DIXON & FRANK WOODSIDE III, 1 DRUG PRODUCT LIABILITY: GOVERNMENT REGULATIONS § 8.01 (1997) (providing an overview of the regulation of prescription drugs). The FDA oversees the process from the initial testing of the product through post-marketing surveillance. *Id.* at 8-3. The FDA also controls drug labeling, advertising and communications between manufacturers and practitioners who prescribe pharmaceutical products. *Id.*

<sup>15</sup> JAMES T. O'REILLY, 1 FOOD AND DRUG ADMINISTRATION: OVERVIEW § 13.01 (1995) (referring to 21 U.S.C. §§ 301-393). Marketers and manufacturers of prescription drugs are primarily responsible for the safety and effectiveness of the drug. *Id.* at 13-2. The FDA evaluates the empirical data provided by these

about the risks and benefits of drugs should only be made with caution. Accordingly, it is of import to note that drugs are different than most other products because they have the potential to be toxic.<sup>16</sup> Therefore, drugs deserve stricter governmental regulation.

From the time of the original Food, Drug & Cosmetic Act ("FDCA"),<sup>17</sup> legislation has always been intended to set standards of quality while promoting technological advancement in the development of new drugs.<sup>18</sup> Yet, as time passes, the problem of "finding the proper balance between protecting and overburdening the public" remains virtually unchanged.<sup>19</sup>

Initially, the Secretary of Agriculture had the primary responsibility to investigate the safety of new drugs prior to entering commerce.<sup>20</sup> However, when Sulfanilamide was distributed

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two entities to ascertain whether the drug is safe for human consumption. *Id.* at 13-2, 13-3. It is important to keep in mind that any and all procedures that are designed to assess safety cannot guarantee a total absence of harm. *Id.* at 13-3.

<sup>16</sup> See MARDEN DIXON & FRANK WOODSIDE III, 2 DRUG PRODUCT LIABILITY: MANUFACTURERS LIABILITY § 14.01 (1997) (reviewing pharmaceutical agents). "[A] drug can cause a catastrophe even when the most elaborate precautions known to medical science have been carefully followed." *Id.* at 14-2, 14-3.

<sup>17</sup> Act of June 30, 1906, ch. 3915, 34 Stat. 768 (amended 1938). See also O'REILLY, *supra* note 15, at 13-4 (noting that "the 1906 Act was superior to scattered state and federal enactments which predated it, but by the time of the New Deal it was evident that drug regulation required more explicit prohibitions and broader powers of enforcement"); DIXON & WOODSIDE, *supra* note 14, at 8-5 (noting that the original FDCA "officially approved the prescription system of drug distribution").

<sup>18</sup> DIXON & WOODSIDE, *supra* note 14, at 8-4. As technological advancements emerge, Congress seeks to protect the public. DIXON & WOODSIDE, *supra* note 14, at 8-4. This desire may directly conflict with the ability to make more drugs available to the public in a rather short time period. DIXON & WOODSIDE, *supra* note 14, at 8-4.

<sup>19</sup> Cimons, *supra* note \*, at A5 (noting that lawmakers, on one side, seek to accelerate the approval process, while consumer groups, on the other, argue that such acceleration will inevitably weaken the FDA and ultimately leave the public vulnerable to potentially dangerous pharmaceutical products).

<sup>20</sup> See DIXON & WOODSIDE, *supra* note 14, at 8-5 (citing Act of June 25, 1938, ch. 675, § 1, 52 Stat. 1040).

without ever being tested,<sup>21</sup> more than one hundred people died around the country.<sup>22</sup> The resulting public outcry led to the passage of the FDCA in 1938 which allowed for federal regulation of new drugs.<sup>23</sup> Pre-1938 drugs were generally recognized as safe ("GRAS") and did not require further clearance.<sup>24</sup> All new drugs, however, would require clearance by the FDA via a safety process which was precipitated by the submission of a new drug application by the drug manufacturer.<sup>25</sup>

By the early 1960's, it became clear that due to the sheer number of prescription drugs which were inevitably accompanied by potential for abuse in the face of technological advancement, greater governmental control was needed.<sup>26</sup> The 1962 amendment to the FDCA additionally required proof of efficacy for all new drugs.<sup>27</sup> Prior to this amendment, the FDA's role was simply to

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<sup>21</sup> Sulfanilamide is a diethylene glycol that was used as an antibiotic in the mid-1930's. See DIXON & WOODSIDE, *supra* note 14, at 8-5. Diethylene glycol, a substitute solvent, became a deadly poison when ingested in the doses recommended by physicians. See O'REILLY, *supra* note 15, at 13-5.

<sup>22</sup> Tests conducted by both the FDA and the American Medical Association ("AMA") thereafter showed that a few simple animal experiments would have revealed the deadly solvent. See O'REILLY, *supra* note 15, at n.15. The complete report is available in MEMORANDUM OF SENATOR COPELAND ON INTRODUCTION OF S1944 in C. DUNN, FEDERAL FOOD DRUG & COSMETIC ACT (1938).

<sup>23</sup> See DIXON & WOODSIDE, *supra* note 14, at 8-5. The Secretary's recommendation was to license control of new drugs to protect against general distribution prior to experimental and clinical tests proving them safe and effective. *Id.* See 21 U.S.C. §§ 301-393 (1938).

<sup>24</sup> O'REILLY, *supra* note 15, at 13-6.

<sup>25</sup> O'REILLY, *supra* note 15, at 13-6.

<sup>26</sup> DIXON & WOODSIDE, *supra* note 14, at 8-6 (stating that Congress was particularly concerned with the efficacy of numerous products marketed by the pharmaceutical industry).

<sup>27</sup> O'REILLY, *supra* note 15, at 13-7 (citing Pub. L. No. 87-781, 76 Stat. 780 (amending 21 U.S.C. §§ 321(p), 355 (1962))). See Jurow, *Effect on the Pharmaceutical Industry of "Effectiveness" Provisions*, 19 FOOD DRUG COSM. L.J. 110 (1964) (noting Senator Kefauver's objective was to insure that all drugs are of adequate and acceptable quality, yet he conceded that the accomplishments of the amendments were "relatively modest where the need is greatest"); S. REP. NO. 87-1744 (1962) (noting that the standard for both safety and effectiveness requires that there be evidence consisting of adequate tests by all methods reasonably applicable).



perform a risk/benefit analysis whereby if the value of the drug outweighed its potential risk, the FDA did not preclude the drug's marketing.<sup>28</sup>

Unfortunately, as a result of the AIDS crisis, drug product approvals are once again on the "fast track."<sup>29</sup> Under President Ronald Reagan's administration, there was minimal interference with the drug market as evidenced by an ineffective regulation that required Patient Package Inserts ("PPIs")<sup>30</sup> to accompany most commonly prescribed drugs.<sup>31</sup> Manufacturers send PPIs to drug prescribers in an effort to inform them of risks associated with the drug's use.<sup>32</sup> This action was applauded by the drug industry as a barrier against intrusion into the practice of medicine.<sup>33</sup> However, FDA regulation becomes much more onerous when off-label dispensing effectively serves to keep potential dangers well hidden.<sup>34</sup>

The process by which a new drug is discovered involves various elements of the unknown in understanding the pharmacology of a particular drug. A new drug is often heralded simply by showing a desirable effect. An extensive experimental process occurs in an effort to prove and to replicate the effect that was

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<sup>28</sup> DIXON & WOODSIDE, *supra* note 14, at 8-7. Furthermore, if a drug was deemed innocuous prior to 1962, policy dictated that the FDA approve the product even though its effectiveness could not be proven via scientific inquiry. DIXON & WOODSIDE, *supra* note 14, at 8-7.

<sup>29</sup> O'REILLY, *supra* note 15, at 13-8.

<sup>30</sup> PPIs provide warnings directly to the users of the product about the potential for the drugs to cause certain known adverse and serious side effects. See 9 HEALTH NEWS DAILY 162, Aug. 21, 1997, available in WESTLAW, Health & Medicine Database, HND File [hereinafter HEALTH NEWS DAILY]. This procedure is used in addition to, not in place of, warnings on the drugs' labels. *Id.*

<sup>31</sup> See DIXON & WOODSIDE, *supra* note 14, at 8-11 (citing 47 Fed. Reg. 39,249 (1982)).

<sup>32</sup> See HEALTH NEWS DAILY, *supra* note 30, at 162.

<sup>33</sup> DIXON & WOODSIDE, *supra* note 14, at 8-11.

<sup>34</sup> See Langreth & Ingersoll, *supra* note 6, at B1 (stating, in reference to fenphen, that the FDA "never approved the combined use of the appetite suppressants because the health risks were unknown").

originally observed.<sup>35</sup> As more information develops, a New Drug Application ("NDA") is filed with the FDA.<sup>36</sup> Thereafter, it is the FDA's obligation to oversee the process by which a new drug can be marketed in interstate commerce.<sup>37</sup>

### A. *New Drug Defined*

All new drugs must have the following characteristics: (1) classification as a drug; (2) absence of general recognition of safety and efficacy for the drug or absence as to such recognition regarding a particular use for which it is proposed to be used and prescribed; and (3) absence of recorded pre-1938 uses for that drug which match identically the uses for which the drug is now represented to be useful.<sup>38</sup> The FDA is given broad discretion in determining whether these characteristics exist and a new drug can be declared.<sup>39</sup> For example, combinations of well-known drug substances where such combinations have not become generally recognized as safe and effective are included under the rubric of new drugs.<sup>40</sup> Absent sufficient evidence regarding efficacy of the final product and a detailed report describing the tests employed to assess the safety of the product, any change or introduction of a new product must await FDA approval.<sup>41</sup> Moreover, newness of

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<sup>35</sup> DIXON & WOODSIDE, *supra* note 14, at 8-13 (noting that scientists are not only searching for that desirable effect, but also for any side effects and adverse reactions which may occur).

<sup>36</sup> DIXON & WOODSIDE, *supra* note 14, at 8-14. The FDCA provides that "no person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval application . . . is effective with respect to such drug." 21 U.S.C. § 355 (1938). Without the NDA, a potential competitor cannot learn of clinical test results of a product; in turn, it cannot be marketed. See also Edmund W. Kitch, *The Patent System and the New Drug Application: An Evaluation of the Private Investment in New Drug Research and Marketing*, in REGULATING NEW DRUGS 101 (Richard Landau, ed., 1973).

<sup>37</sup> See DIXON & WOODSIDE, *supra* note 14, at 8-13.

<sup>38</sup> Act of June 25, 1938, ch. 675, 52 Stat. 1040, 75th Cong., (1938).

<sup>39</sup> DIXON & WOODSIDE, *supra* note 14, at 8-15 (noting that water may even be construed as a drug when it is represented as having a curative effect).

<sup>40</sup> S. Res. 194, 74th Cong., 2d Sess. (1937).

<sup>41</sup> 21 U.S.C. § 355(b)(1) (1962). The regulations establishing procedures for

the drug's uses does not relate to past history; rather it relates to the chemical composition which has not been recognized among experts as safe and effective for a specific purpose.<sup>42</sup> Essentially, it is an expert decision to be made by the FDA subject to deferential judicial review.<sup>43</sup> It has been held that the court cannot enter the realm of FDA expertise and decide a product's safety and efficacy because the FDA's superior expertise mandates deference on factual issues.<sup>44</sup> Therefore, the courts broadly defer to the

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implementation of 21 U.S.C. § 355 are at 21 C.F.R. §§ 312 and 314.

Any person may file with the Secretary an application with respect to any drug . . . . The application should include: (a) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (b) a full list of the articles used as components of such drug; (c) a full statement of the composition of such drug; (d) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug; (e) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (f) specimens of the labeling proposed to be used for such drug.

21 U.S.C. § 355(b)(1).

<sup>42</sup> DIXON & WOODSIDE, *supra* note 14, at 8-15.

<sup>43</sup> Farquhar v. FDA, 616 F. Supp. 190, 193 (D.D.C. 1985). "The FDA has the established procedures and expertise as well as the statutory authority to make this difficult determination. Judicial review will of course be available at a later time, but [an individual] must first exhaust his administrative remedies." *Id.*

<sup>44</sup> Premo Pharm. Labs, Inc. v. United States, 629 F.2d 795, 801 (2d Cir. 1980). New drug issues are "particularly suited to initial determination by the FDA." *Id.* (quoting Weinberger v. Bentex Pharm., Inc., 412 U.S. 645, 653-54 (1973)).

Whether a particular drug is a "new drug," depends in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by substantial support in scientific literature. One function is not peculiar to judicial expertise, the other to administrative expertise. The two types of cases overlap and strongly suggest that Congress desired that the administrative agency make both kinds of determinations.

*Id.* at 803 (quoting Weinberger v. Bentex Pharm. Inc., 412 U.S. 645, 652 (1973)).

FDA's authority so that when a drug is reconstituted and declared a new drug, courts generally agree.

### B. Drug Categories

Products that become "drugs" are open to strict regulation by the FDA. New drugs are divided into four statutory categories: (1) articles recognized by the United States Pharmacopoeia and other official formularies consisting of learned experts in the medical field; (2) articles intended to be used in diagnosis, cure, prevention, mitigation or treatment of disease in man or animals by chemical action; (3) articles intended to affect the structure or any function of the body of man or animals by chemical action; and (4) articles intended to become a component of any of these three types of articles.<sup>45</sup> Categories 1, 2 and 3 contain both the finished drug product and active ingredient components; category 4 includes the active and inactive components of the drug.<sup>46</sup> When determining the statutory category of a new drug, the FDA and courts look to the intent of the vendor.<sup>47</sup> Throughout the process there is great deference given to the FDA in reading such intent.<sup>48</sup>

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<sup>45</sup> 21 U.S.C. § 321(g) (1994).

<sup>46</sup> *United States v. Generix Drug Corp.*, 460 U.S. 453, 454 (1983) (noting that active ingredients in the majority of prescription drugs constitute only 10% of the end product). For example, in treating hypertension, there are eight active ingredients in chlorothiazide: allopurinol, spironolactone with hydrochlorothiazide, furosemide, diethylpropion hydrochloride, chlorothiazide with reserpine, amitriptyline with perphenazine, prochlorperazine maleate, and chlorthalide. *Id.* at 455.

<sup>47</sup> *United States v. Midwest Pharm. Inc.*, 825 F.2d 1238, 1246 (8th Cir. 1987) (concluding that the generic over-the-counter products were intended to be sold as controlled substances). The drug in *Midwest* was advertised as "357 Magnum," "20/20," "30/30," "White Mole," "Mini-White" and "Incense." *Id.* at 1242. Midwest evinced knowledge that the practice of marketing or selling misbranded drugs was apparent, endorsed and encouraged. *Id.* at 1247. Furthermore, intent of this illegal activity was inferred via markings on the capsules that were similar to that found on amphetamine capsules and quaaludes. *Id.*

<sup>48</sup> See generally *Action on Smoking and Health v. Harris*, 655 F.2d 236 (D.C. Cir. 1980). The court cited two rationales for deference on the administrative interpretation of statutes—administrative expertise and congressional acquies-

### C. *Experimental Procedures*

The ability of the FDA to declare a product a "new drug" and thereafter regulate it gives rise to a complex procedural system. The first step is the pre-marketing investigation which involves animal testing and various phases of clinical testing.<sup>49</sup> Once a correlation has been noted with a specific compound and a desired result, the drug is tested on animals in an effort to avoid human exposure to toxic materials.<sup>50</sup> Common sense dictates that, with reasonable exceptions, evidence of animal toxicity would serve as toxicity in humans. Thus, animal testing determines the potential margin of safety in humans at the preliminary stages of research.<sup>51</sup>

Clinical investigation is the next step in the FDA's process and entails the administration of the drug to human subjects.<sup>52</sup> This step is comprised of three separate phases. Phase one recruits volunteer human subjects in order to gain early information about

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cence. *Id.* at 238.

<sup>49</sup> DIXON & WOODSIDE, *supra* note 14, at 8-20.

<sup>50</sup> DIXON & WOODSIDE, *supra* note 14, at 8-20.

<sup>51</sup> DIXON & WOODSIDE, *supra* note 14, at 8-13. *See also* 21 C.F.R. § 314.50(d)(2)(iv) (1985) (requiring a new drug application to include studies of "the absorption, distribution, metabolism, and excretion of the drug in animals").

<sup>52</sup> 21 C.F.R. § 314.50 (d)(3). Clinical investigation means "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice." 21 C.F.R. § 312.3(b) (1987). The section, relating to human pharmacokinetics and bioavailability, requires a description of the studies of the drug when administered to humans. 21 C.F.R. § 314.50 (d)(3)(i). Bioavailability has been defined as "the degree to which a drug or other substance becomes available at the physiological site of activity after administration." AMERICAN HERITAGE COLLEGE DICTIONARY 139 (3d ed. 1993). Pharmacokinetics has been defined as "the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body." AMERICAN HERITAGE COLLEGE DICTIONARY, *supra*, at 1024. A statement of the analytical and statistical methods employed must accompany the application, whether the studies were performed in compliance with the institutional review board regulations and whether there was informed consent on the part of the human subject. 21 C.F.R. § 314.50 (d)(3)(i).

the product's pharmacological and pharmacokinetic effects.<sup>53</sup> Phase two involves the dispensing of the drug to supervised patients for the unique purpose of treating the disease for which it was intended to determine the drug's safety and effectiveness.<sup>54</sup> Phase three examines rarer side effects, drug efficacy and drug interaction to better evaluate the overall risk-benefit relationship and develop physician labeling.<sup>55</sup>

Upon completion of the clinical trials, the manufacturer must submit an NDA to the FDA.<sup>56</sup> The NDA is a compilation of all the studies performed, including all noted benefits and adverse effects of the products.<sup>57</sup> These reports must also contain an affirmation that each study conducted was in compliance with applicable regulations.<sup>58</sup> The FDA requires all reports of clinical tests to be attached to the NDA.<sup>59</sup> The FDA further mandates that the NDA have copies of case reports annexed thereto for patients who died or could not finish the testing due to adverse reactions.<sup>60</sup>

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<sup>53</sup> DIXON & WOODSIDE, *supra* note 14, at 8-21.

<sup>54</sup> DIXON & WOODSIDE, *supra* note 14, at 8-21.

<sup>55</sup> DIXON & WOODSIDE, *supra* note 14, at 8-22.

<sup>56</sup> Each NDA submitted must contain a detailed summary of its contents as set forth in 21 C.F.R. § 314.50(c). *See* 21 C.F.R. § 314.50(c) (1985) (requiring that the summary include (1) the proposed text for labeling the drug; (2) the pharmacologic class of the drug; (3) marketing history, if any, of the drug outside of the United States; (4) chemistry, manufacturing and controls of the application; (5) nonclinical pharmacology and toxicology; (6) human pharmacokinetics and bioavailability; (7) microbiology for anti-infective drugs; (8) clinical data; and (9) benefit and risk considerations). In addition, 21 C.F.R. § 314.50(d) outlines the "technical parts" of the NDA. *See* 21 C.F.R. § 314.50(d) (requiring that the application contain "data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application").

<sup>57</sup> DIXON & WOODSIDE, *supra* note 14, at 8-22.

<sup>58</sup> 21 C.F.R. § 314.50(d)(2)(v) ("For each nonclinical laboratory study, a statement that it was conducted in compliance with the good laboratory practice regulations [is required].").

<sup>59</sup> 21 C.F.R. § 314.50(d)(3) (requiring a summary of the pharmacokinetics and metabolism of the active ingredients).

<sup>60</sup> 21 C.F.R. § 314.50(f)(2) ("The application is required to contain copies of individual case report forms for each patient who dies during a clinical study or who did not complete the study because of an adverse event, whether believed

In addition, an amendment to the NDA is available via an abbreviated application to correct any misinformation.<sup>61</sup>

Upon a showing that the drug is safe and effective for its proposed use or uses, the NDA is approved by the FDA.<sup>62</sup> However, such approval does not extend to other uses.<sup>63</sup> Therefore, a manufacturer is not permitted to promote a drug for a purpose other than that approved.<sup>64</sup> After approval, the manufacturer must file periodic briefs regarding ongoing clinical study of the product.<sup>65</sup> Post-marketing requirements include an Alert report to be filed within fifteen days of the time the manufacturer learns of new side-effects.<sup>66</sup> Moreover, a manufacturer must maintain records concerning the safety and efficacy of the drug.<sup>67</sup> Periodic reports addressing studies in the medical and scientific literature must also be filed.<sup>68</sup> Once an adverse reaction associated with the

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to be drug related or not.”).

<sup>61</sup> 21 C.F.R. § 314.54 (1992) (prohibiting approval of an abbreviated NDA for a new indication and for other changes if investigations are necessary for such approval).

<sup>62</sup> DIXON & WOODSIDE, *supra* note 14, at 8-25.

<sup>63</sup> DIXON & WOODSIDE, *supra* note 14, at 8-25.

<sup>64</sup> DIXON & WOODSIDE, *supra* note 14, at 8-25.

<sup>65</sup> See 21 C.F.R. §§ 310.303, 314.80 (1974). “The applicant must establish and maintain records and make reports related to clinical experience or other data or information necessary to make or facilitate a determination of whether there may be grounds . . . for suspending or withdrawing approval of the application.” 21 C.F.R. § 310.303(a).

<sup>66</sup> 21 C.F.R. § 314.80(c)(1)(1985) (“The applicant shall promptly investigate all adverse drug experiences that are the subject of these 15-day Alert reports and shall submit follow-up reports within 15 working days of receipt of new information or as requested by [the] FDA.”).

<sup>67</sup> 21 C.F.R. § 314.80 (“The applicant shall maintain, for a period of 10 years, records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.”).

<sup>68</sup> 21 C.F.R. § 314.81. Such literature includes reports of experiences, investigations or studies involving any property of the drug; copies of unpublished reports regarding toxicological findings in animal studies and in vitro studies; prepublication manuscripts conducted by the applicant; and published clinical trials that include tabulations or summaries of the data. *Id.*

use of the drug is noted, the manufacturer must file an FDA-1639, Drug Experience Report.<sup>69</sup>

An NDA application will be approved by the FDA upon a sufficient showing that the drug meets statutory standards for safety and effectiveness, labeling, manufacturing and controls.<sup>70</sup> It should always be kept in mind that the FDA may refuse to approve an NDA on the basis of insufficient information to determine if the product is safe for use under the conditions prescribed.<sup>71</sup> Upon approval for marketing, the manufacturer has a continuing obligation to monitor clinical experience with the drug and report all adverse reactions to the treating physicians and the FDA.<sup>72</sup> Often, warnings are to be inserted by the manufacturer in the package insert and the Physician's Desk Reference.<sup>73</sup> On other

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<sup>69</sup> 21 C.F.R. § 314.80. Each form should refer to only one patient or a single publication. 21 C.F.R. § 314.80 (f)(2). Copies of the FDA-1639 form may be acquired from the Division of Epidemiology and Surveillance (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. *See* 21 C.F.R. § 314.80(f)(4).

<sup>70</sup> 21 C.F.R. § 314.105(c) (1992) ("[The] FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.").

<sup>71</sup> 21 C.F.R. § 314.125(b) (1985) (noting that the FDA may refuse approval because of the absence of well-controlled investigations documenting that the drug will indeed have its purported effect, inadequate labeling or improper testing protocol).

<sup>72</sup> 21 U.S.C. § 355 (1962); 21 C.F.R. §§ 310.303, 310.305 (1986). "Each manufacturer, packer, and distributor shall maintain for a period of 10 years records of all adverse drug experiences required under this section to be reported, including raw data and any correspondence relating to the adverse drug experience . . . ." 21 C.F.R. § 310.305(f)(1).

<sup>73</sup> *See* 21 C.F.R. § 201.56 (1979) (requiring that labels contain a summary of scientific information, must be informative and accurate and shall be based, whenever possible, on data derived from human experience); 21 C.F.R. § 201.57 (1979) (requiring that labels for human prescription drugs contain the following information: (1) a "description" including the proprietary name, type of dosage, pharmacological class and chemical name and structure of the formula; (2) a "clinical pharmacology" section containing a summary of the clinical activity of the drug in humans; (3) an "indications and usage" section requiring the label to state that the drug is implicated in the treatment or prevention of a disease or condition; (4) a "contraindications" section requiring the label to describe



occasions, a "Dear Doctor" letter may be required.<sup>74</sup> Furthermore, the FDA Bulletin has proven a reliable source of information on the approval of new drugs and the discovery of adverse reactions with these drugs.<sup>75</sup> If the danger is of such a magnitude that it requires immediate withdrawal from the market, federal authorities are empowered to suggest and negotiate such action.<sup>76</sup>

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situations in which the drug should not be used; (5) a "warnings" section requiring the label to state serious side effects and potential safety hazards; and (6) a "precautions" section requiring the label to provide information addressing special care guidelines, information for patients, laboratory tests, drug interactions, pregnancy, pediatric use and geriatric use).

<sup>74</sup> This letter is an advisory to the physician directly that adverse effects have been noted with the drug's use. See DIXON & WOODSIDE, *supra* note 14, at 8-40.

<sup>75</sup> DIXON & WOODSIDE, *supra* note 14, at 8-44. The FDA bulletin was founded in 1971 by Dr. Henry E. Simmons, Director of the Bureau of Drugs. DIXON & WOODSIDE, *supra* note 14, at 8-45. Dr. Simmons reasoned that since physicians rarely saw the package inserts and heavily relied on information in medical journal articles for their prescriptions, this would be the most effective means of reaching and educating the physician about new drugs. DIXON & WOODSIDE, *supra* note 14, at 8-45.

<sup>76</sup> See 21 U.S.C. § 355(e).

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed [w]as not filed within thirty days after the receipt of written notice for the Secretary specifying the failure to file

The FDA also maintains extensive regulations concerning current good manufacturing practice.<sup>77</sup> Specifically, a manufacturer must maintain records and establish production and control procedures.<sup>78</sup> Furthermore, the manufacturer is also required to keep a complaint file for one year after the expiration date of the drug.<sup>79</sup> The intent is to provide authority to correct faulty operations prior to the production of defective drugs.<sup>80</sup> Despite these many stringent regulations, defective drugs inevitably find their way into the drug market.<sup>81</sup>

## II. MANUFACTURER LIABILITY FOR PRESCRIPTION DRUGS

It is not surprising that the rise in the number of drug-related injuries has led to a marked increase in litigation.<sup>82</sup> The majority

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such information; or (5) that the application contains any untrue statement of material fact . . . .

*Id.*

<sup>77</sup> 21 C.F.R. §§ 210-211 (1978). For example, the regulations address requirements with respect to personnel, equipment and components. 21 C.F.R. § 211.80.

<sup>78</sup> 21 C.F.R. § 211.180. Additionally, all records must be made readily available for authorized inspection at the establishment where the activities described in the records takes place. 21 C.F.R. § 211.180(c).

<sup>79</sup> 21 C.F.R. § 211.180(b) ("Records shall be maintained for all components, drug product containers, closures, and labeling for at least one year after the expiration date . . . ."); 21 C.F.R. § 211.180 (e) ("Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.").

<sup>80</sup> DIXON & WOODSIDE, *supra* note 14, at 8-51 (noting that a drug is deemed adulterated "if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets [the appropriate safety and quality standard]") (citing THE CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS (1963) and section 501 (a)(2)(B) of the KEFAUVER-HARRIS DRUG AMENDMENTS (1963)).

<sup>81</sup> See DIXON & WOODSIDE, *supra* note 14, at 8-52.

<sup>82</sup> See Patty Coleman Selker, Note, *An Escape from Strict Liability: Pharmaceutical Manufacturers' Responsibility for Drug-Related Injuries Under*

of courts have held that in the case of pharmaceutical products, the principle of strict liability is qualified by a special rule derived from comment k to section 402A of the Restatement (Second) of Torts.<sup>83</sup> Specifically, sellers of "unavoidably unsafe" products are not held strictly liable to injured consumers as long as they warn consumers of known or reasonably discoverable risks.<sup>84</sup>

Comment k provides that strict liability is not applicable to the sale of a product that is incapable of being made safe for its intended use so long as its utility outweighs its apparent risks and

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*Comment K to Section 402A of the Restatement (Second) of Torts*, 23 DUQ. L. REV. 199 (1984).

<sup>83</sup> See, e.g., *Brown v. Superior Court*, 751 P.2d 470, 476 (Cal. 1988).

[C]omment k would impose liability on a drug manufacturer only if it failed to warn of a defect of which it either knew or should have known. This concept focuses not on a deficiency in the product—the hallmark of strict liability—but on the fault of the producer in failing to warn of dangers inherent in the use of its product that were either known or knowable—an idea which "rings of negligence."

*Id.* The court further stated that

[T]here is an important distinction between prescription drugs and other products such as construction machinery, the producers of which were held strictly liable. In the latter case, the product is used to make work easier or to provide pleasure, while in the former it may be necessary to alleviate pain and suffering or to sustain life.

*Id.* at 478-79. Furthermore, public policy favors the development of new drugs because the potential for the greater good far exceeds the risks that may accompany the drug's introduction. *Id.* at 479.

<sup>84</sup> RESTATEMENT (SECOND) OF TORTS § 402A cmt. k (1979).

a warning is supplied.<sup>85</sup> Such products are labeled “unavoidably unsafe.”<sup>86</sup> While this term is not defined, all of the examples of “unavoidably unsafe” products in comment k refer to prescription drugs.<sup>87</sup> Therefore, a reasonable inference is that the drafters intended to limit the scope of this provision to drugs and similar products.<sup>88</sup>

Courts generally assume that the therapeutic benefits of prescription drugs outweigh any risks associated with their use.<sup>89</sup> For example, in *Brown v. Superior Court*, a unanimous court reasoned that since prescription drugs are products with indispensable uses, “a manufacturer is not strictly liable for injuries caused by a prescription drug so long as the drug was properly prepared and accompanied by warnings of its dangerous propensities that

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<sup>85</sup> *Id.*

[T]here are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of prescription drugs. . . . [T]he seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.

*Id.*

<sup>86</sup> W. PAGE KEETON ET AL., PROSSER AND KEETON ON THE LAW OF TORTS 695 (5th ed. 1984) (hereinafter PROSSER & KEETON). See also Raymond Paul Johnson & Mike Eidson, *Product Liability History*, in DEFECTIVE PRODUCT: EVIDENCE TO VERDICT § 1-4(j) (1995) (noting that “manufacturers need not warn of dangers inherent in the use of unavoidably unsafe products because theoretically these products cannot be made absolutely safe for intended uses, even when properly prepared and accompanied by appropriate warnings”).

<sup>87</sup> See Richard C. Ausness, *Unavoidably Unsafe Products And Strict Products Liability: What Liability Rule Should Be Applied To The Sellers Of Pharmaceutical Products?*, 78 KY. L.J. 705, 714 (1990).

<sup>88</sup> See Victor E. Schwartz, *Unavoidably Unsafe Products: Clarifying The Reasoning And Policy Behind Comment K*, 42 WASH. & LEE L. REV. 1139, 1141 (1985).

<sup>89</sup> See, e.g., *DeLuryea v. Winthrop Lab.*, 697 F.2d 222, 228-29 (8th Cir. 1983); *Basko v. Sterling Drug, Inc.*, 416 F.2d 417, 425-26 (2d Cir. 1969); *Gaston v. Hunter*, 588 P.2d 326, 338-41 (Ariz. Ct. App. 1978).

were either known or reasonably scientifically knowable at the time of distribution.”<sup>90</sup> Furthermore, “if drug manufacturers were subject to strict liability, they would be reluctant to undertake research programs to develop some pharmaceuticals that would prove beneficial.”<sup>91</sup>

Once a drug is properly prepared and meets FDA approval, the product cannot, as a matter of law, be “defective.”<sup>92</sup> In *Grundberg v. Upjohn Co.*, the court opined that the benefits to society in promoting the development, availability and reasonable price of drugs justify this conclusion.<sup>93</sup> The court held that

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<sup>90</sup> 751 P.2d 470, 482-83 (Cal. 1988).

<sup>91</sup> *Id.* at 479 (“Public policy favors the development and marketing of beneficial new drugs, even though some risks, perhaps serious ones, might accompany their introduction, because drugs can save lives and reduce pain and suffering.”)

<sup>92</sup> *Grundberg v. Upjohn Co.*, 813 P.2d 89, 97 (Utah 1991). The court acknowledged that by characterizing all FDA-approved prescription medications as “unavoidably unsafe,” it was inevitably expanding the literal interpretation of comment k. *Id.* at 90. The court held that “a drug approved by the United States Food and Drug Administration (FDA), properly prepared, compounded, packaged, and distributed, cannot as a matter of law be defective in the absence of proof of inaccurate, incomplete, misleading, or fraudulent information furnished by the manufacturer in connection with FDA approval.” *Id.* In strict liability, the plaintiff need not impugn the conduct of the manufacturer or retailer, but is required to impugn the product. See PROSSER & KEETON, *supra* note 86, at 695. Defect is an element of strict liability whereby a plaintiff has to establish that: (1) a defect in the product was a cause of the plaintiff’s harm; and (2) the product was defective when it left the hands of the defendant in order to make out a prima facie case for liability. JAMES A. HENDERSON & AARON D. TWERSKI, *PRODUCTS LIABILITY: PROBLEMS AND PROCESS* 17 (3d ed. 1997). “The product must be defective in the kind of way that subjects persons or tangible property to an unreasonable risk of harm.” PROSSER & KEETON, *supra* note 86, at 695.

<sup>93</sup> 813 P.2d at 96 (noting that “drugs are our most cost-effective input in supplying the demand for health . . . [and] if we are serious about minimizing costs, our best bet is to increase the number of drug innovations”).

in light of the strong public interest in the availability and affordability of prescription medications, the extensive regulatory system of the FDA, and the avenues of recovery still available to plaintiffs, [a] broad grant of immunity from strict liability claims based on design defects should be extended to FDA-approved drugs.<sup>94</sup>

Thus, according to the courts, comment k was intended to afford a special protection to drug products and in so doing to limit the scope of products liability.<sup>95</sup>

Many jurisdictions have applied comment k to cases involving the liability of drug manufacturers, reasoning that it is counter-intuitive to hold manufactures strictly liable for a failure to warn of risks of which they were unaware and could not have been aware of by the reasonable application of scientific knowledge available at the time of distribution.<sup>96</sup> Even if a new drug proves less valuable than initially perceived, the manufacturer may still be exempt from strict liability under comment k provided it was unaware of the drug's risks.<sup>97</sup> Therefore, a manufacturer that acts

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<sup>94</sup> *Id.* at 99.

<sup>95</sup> *Pollard v. Ashby*, 793 S.W.2d 394, 406 (Mo. Ct. App. 1990). Although holding that comment k provides only an affirmative defense for drug manufacturers charged with a design defect, Judge Smith noted that "Comment k therefore provides freedom from liability to prescription drugs where they are properly prepared and adequate warnings are given. Such products are not under those circumstances defective or unreasonably dangerous." *Id.*

<sup>96</sup> *See, e.g., DeLuryea v. Winthrop Lab.*, 697 F.2d 222, 228-29 (8th Cir. 1983) (noting that the standard for liability under strict liability and negligence are essentially the same in the realm of drug products); *McKee v. Moore*, 648 P.2d 21, 24 (Okla. 1982) (noting that in the absence of FDA regulations to the contrary, the manufacturer has no obligation to warn a consumer if the prescribing physician has been adequately warned of any adverse side effects); *Chambers v. G.D. Searle & Co.*, 441 F. Supp. 377, 380-81 (D. Md. 1975) (noting that "[w]hile there may be a distinction drawn between a negligent failure to warn and the warning requirements for strict liability insofar as other products are concerned, comment k itself indicates that where new drugs, sold only under the prescription of a physician, are involved, the standard is essentially the same").

<sup>97</sup> *See Gaston v. Hunter*, 588 P.2d 326, 340 (Ariz. Ct. App. 1978) (interpreting comment k to mean that for experimental drugs, the manufacturer has a duty to explicitly advise that the drug is experimental and must warn of known or knowable risks).

reasonably in manufacturing and distributing an unavoidably unsafe product will not be subject to strict liability for harm caused by this product.<sup>98</sup>

Drug manufacturers, however, sell knowledge as well as products.<sup>99</sup> Therefore, the information that drug manufacturers provide is of great importance. "A manufacturer of a prescription drug has a legal duty to warn the medical profession, not the patient, of any risks inherent in the use of the drug which the manufacturer knows or should know to exist."<sup>100</sup> However, a violation of a duty to warn does not render the manufacturer liable for injuries absent a showing that the product is defective.<sup>101</sup> A manufacturer's duty is to adequately warn the attending physician, but it has no duty to warn the lay public regarding prescription

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<sup>98</sup> See *Kociemba v. G.D. Searle & Co.*, 695 F. Supp. 432, 435 (D. Minn. 1988). "The manufacturer of a desirable yet unavoidably unsafe product is protected in that it will not be held liable if it uses reasonable care in manufacturing an inherently dangerous product." *Id.* According to Minnesota Jury Instruction Guide ("JIG") 117, "the reasonable care to be exercised by a manufacturer when designing a product will depend on all facts and circumstances, including, among others, the likelihood and seriousness of harm against the feasibility and burden of any precautions which would be effective to avoid the harm." See JIG 117, MINNESOTA DISTRICT JUDGES ASS'N, MINN. PRACT., CIVIL (3d ed. 1986).

<sup>99</sup> Dixon & Woodside reason that many drugs are accompanied by unavoidable dangers that may result in future complications. DIXON & WOODSIDE, *supra* note 16, at 14-7. Therefore, drugs can be used safely only with accurate and complete disclosure regarding safety and effectiveness from the manufacturer. DIXON & WOODSIDE, *supra* note 16, at 14-7.

<sup>100</sup> *Smith v. E.R. Squibb & Sons*, 273 N.W.2d 476, 479 (Mich. 1979) (citing *McEwen v. Ortho Pharm. Corp.*, 528 P.2d 522, 530 (Or. 1974)). See also *Sterling Drug, Inc. v. Yarrow*, 408 F.2d 978, 991 (8th Cir. 1969); *Love v. Wolf*, 38 Cal. Rptr. 183, 184 (1964).

<sup>101</sup> *Spuhl v. Shiley, Inc.*, 795 S.W.2d 573, 580 (Mo. Ct. App. 1990). A necessary element of a strict liability claim under Section 402A is that the product be in a defective condition. *Id.*; RESTATEMENT (SECOND) OF TORTS § 402A(1) (1979). "A product is in a defective condition where the condition is one not contemplated by the ultimate consumer, which condition caused the product to fail to perform in the manner reasonably to be expected in light of its nature and intended function." *Richardson v. Holland*, 741 S.W.2d 751, 754 n.3 (Mo. App. 1987) (citing RESTATEMENT (SECOND) OF TORTS § 402A cmt. g (1965)).

drugs.<sup>102</sup> Furthermore, there is a continuing duty on the part of the manufacturer to provide post-sale warnings to physicians of any deficiencies that it learns exist in the product.<sup>103</sup>

The duty to warn of drug dangers is particularly important because drug dangers are not open and obvious.<sup>104</sup> A manufacturer is deemed an expert in his/her particular field and is under a continuous duty to keep abreast of scientific developments relating to the manufacturer's product and to notify the medical profession of any additional adverse effects discovered from its use.<sup>105</sup>

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<sup>102</sup> *Pierluisi v. Squibb*, 440 F. Supp. 691, 694 (D.P.R. 1977). It is the prevailing general rule that the duty to adequately warn of a drug's propensity for harm is discharged by a manufacturer's warning to doctors. *Id.* See also *Parke Davis & Co. v. Stomosodt*, 411 F.2d 1390, 1401 (8th Cir. 1969) (noting that the warning should be sufficient to appraise a general practitioner of the dangerous propensities of the drug); *Gravis v. Parke Davis & Co.*, 502 S.W.2d 863, 870 (Tex. Civ. App. 1973) (finding that it is unreasonable to demand that the manufacturer of drugs specifically warn each and every patient that receives drugs prescribed by the physician or other authorized persons).

<sup>103</sup> See, e.g., *Braniff Airways, Inc. v. Curtiss-Wright Corp.*, 411 F.2d 451, 453 (2d Cir.), *cert. denied*, 396 U.S. 959 (1969).

It is clear that after such a product has been sold and dangerous defects in design have come to the manufacturer's attention, the manufacturer has a duty either to remedy these or, if complete remedy is not feasible, at least to give adequate warnings and instructions concerning methods for minimizing the danger.

*Id.*

<sup>104</sup> *Tampa Drug Co. v. Wait*, 103 So. 2d 603, 607 (Fla. 1958).

When a distributor of an inherently dangerous commodity places it in the channels of trade, then by the very nature of his business, he assumes the duty of conveying to those who might use the product a fair and adequate warning of its dangerous potentialities to the end that the user, by the exercise of reasonable care on his own part, shall have a fair and adequate notice of the possible consequences of use or even misuse.

*Id.*

<sup>105</sup> *McEwen v. Ortho Pharm. Corp.*, 528 P.2d 522, 528 (Or. 1974) (citing *Schenebeck v. Sterling Drug Inc.*, 423 F.2d 919, 922 (8th Cir. 1970)). "To satisfy this duty, the manufacturer must utilize methods of warning which will be reasonably effective, taking into account both the seriousness of the drug's adverse effects and the difficulties inherent in bringing such information to the attention of a group as large and diverse as the medical profession." *Id.* at 529.



Therefore, the issue becomes "whether the manufacturers met their duty of promulgating warnings commensurate with their actual knowledge gained from research and adverse reaction reports as well as commensurate with their constructive knowledge as measured by scientific literature and other available means of communication."<sup>106</sup>

FDA regulations require only that package inserts, the advertising and the labeling be changed when a new defect has been discovered,<sup>107</sup> and adverse experiences be reported promptly.<sup>108</sup> The FDA's concern is purely regulatory in nature. However, there is no implication that a manufacturer is strictly liable for failure to warn the medical community of possible injury absent a showing of proximate causation that an adequate warning would have prevented the injury.<sup>109</sup> If such injury has never occurred before and,

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<sup>106</sup> *Dalke v. Upjohn Co.*, 555 F.2d 245, 248 (9th Cir. 1977).

<sup>107</sup> See 21 C.F.R. § 201.57 (1979). The label must state the limitations associated with a particular drug's use. 21 C.F.R. § 201.57(3)(i). If the drug should be reserved for certain situations, this information shall also be stated in the labeling section. 21 C.F.R. § 201.57(3)(ii). If indications for long term use are different from that of short term use, the label shall specifically assert such. 21 C.F.R. § 201.57(3)(iii).

<sup>108</sup> See 21 C.F.R. § 314.80(a) (1985).

Adverse drug experience means any adverse event associated with the use of a drug in humans . . . including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; and adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

*Id.*

<sup>109</sup> See, e.g., *Stanback v. Parke, Davis & Co.*, 657 F.2d 642, 644-45 (4th Cir. 1981) (noting that there is a distinction between a failure to warn case in which the physician might have responded to a warning and one in which he would not have done so because in the former there is evidence of causation); *Chambers v. G.D. Searle & Co.*, 441 F. Supp. 377, 385 (D. Md. 1975) (finding that adequate warnings associated with the use of oral contraceptives would not have affected the physician's treatment of the patient and therefore lacked causation); *Vaughn v. G.D. Searle & Co.*, 536 P.2d 1247, 1251 (Or. 1975) (finding no proof of causation because even if the physician had been properly warned, the patient would have been treated in the identical manner).

with the exercise of due care, the manufacturer could not have foreseen such an injury, there can be no duty to warn.<sup>110</sup>

A manufacturer is not liable for the "unfortunate consequences attending use of a prescription drug merely because the manufacturer had undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk."<sup>111</sup> Accordingly, if the manufacturer gives proper warnings of potential hazards of the drug and the warnings are read by a prescribing physician, "the company has fulfilled its duty and there is no liability."<sup>112</sup> Moreover, there can be no liability if the prescribing physician relies on his own knowledge when prescribing a drug.<sup>113</sup> Therefore, similar to the act of firing a loaded weapon in a crowded room, liability must fall on the physicians who are dispensing off-label drug combinations absent adequate empirical evidence regarding safety, because someone will surely be harmed.

### III. THE FEN-PHEN COCKTAIL

Under current FDA statutes, drug manufacturers cannot distribute off-label information because it is considered illegal

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<sup>110</sup> See *Johnston v. Upjohn Co.*, 442 S.W.2d 93, 97 (Mo. Ct. App. 1969). "One factor which conditions the taking of precaution is the knowledge or means of knowledge of the danger. If the maker is justifiably ignorant of a danger in his product there is no negligence in a failure to guard against it." *Id.* (quoting 2 FOWLER V. HARPER & FLEMING JAMES JR., *THE LAW OF TORTS*, § 28.7 (1956)).

<sup>111</sup> *Demmler v. SmithKline Beecham Corp.*, 671 A.2d 1151, 1155-56 (Pa. Super. Ct. 1996). The law requires a reasonable connection between the act or omission on the part of the manufacturer and the injury suffered by the complainant. *Id.*

<sup>112</sup> *Parke, Davis & Co. v. Mayes*, 183 S.E.2d 410, 410 (Ga. Ct. App. 1971). The court held that the manufacturers of Chloromycetin gave a sufficient warning to the medical profession regarding the possibility of causing anemia. *Id.* The prescribing doctor read the warnings and was made aware of possible dangers associated with the drug's use. *Id.* Accordingly, the company fulfilled its duty. *Id.*

<sup>113</sup> See *Formella v. Ciba-Geigy Corp.*, 300 N.W.2d 356, 358 (Mich. Ct. App. 1980) (noting that the physician knew that Tandearil could cause blood dyscrasia after prolonged use but failed to conduct a blood test prior to dispensation).

promotion.<sup>114</sup> Physicians, though, are free to prescribe approved drugs for off-label purposes without the protection of long-term studies and FDA approval for the new use.<sup>115</sup> This freedom is particularly dangerous with respect to diet drugs due to the willingness of society to try anything to find the "magical relief" for obesity.<sup>116</sup> Coupling such a desire with a physician's unfettered prescription tactics relegates fen-phen to be labeled an inevitable tragedy.

### A. Obesity As A Major Public Health Concern

Obesity is a harmful condition and a major public health issue. Obesity is the most common and costly nutritional problem in the United States, affecting approximately thirty-three percent of adults.<sup>117</sup> However, the vast amount of money spent in an effort to lose weight is often for naught because the weight is usually gained back.<sup>118</sup> Weight reduction strategies such as food restric-

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<sup>114</sup> See Cimon, *supra* note \*, at A5.

<sup>115</sup> See Cimon, *supra* note \*, at A5 ("Doctors appropriately rely on journal articles all the time, but there are two problems associated with [relying on small studies]: Companies lose the incentive to do the [larger] studies and, occasionally, you'll have a medical disaster.").

<sup>116</sup> See James J. Cerda, M.D., *The Pharmacologic Management of Obesity*, 84 J. FLA. MED. ASS'N 89 (1997). The article concluded that: (1) obesity is not cosmetic; (2) the weight loss industry is lucrative and must be watched closely; and (3) until the FDA revises labeling and until long-term studies are available, the use of unapproved anorectic medications for extended periods of time must be presented to the patient in such a manner so that he or she is made aware that the drug is unapproved and still in its investigational phase. *Id.* at 91.

<sup>117</sup> R.J. Kuczmarski, et al., *Increasing Prevalence of Overweight Among U.S. Adults*, 272 JAMA 205, 205-11 (1994). See also Robert M. Russell, *Nutrition (contempo)*, 277 JAMA 1876, 1876 (1997) (noting that The National Health and Nutrition Examination Survey, a cross-sectional sampling of surveys that are performed periodically and provide national health reference data, found that Americans gained an average of 3.6kg [approx. 7.9 lbs.] between 1980 and 1991, with an eight percent increase in the prevalence of obesity).

<sup>118</sup> T.A. Wadden, *Treatment of Obesity By Moderate and Severe Caloric Restriction: Results of Clinical Research Trials*, 229 ANNALS OF INTERNAL MED. 688, 688-93 (1993). Ninety to ninety-five percent of persons who lose weight subsequently regain it. *Id.* Furthermore, health care costs attributable to obesity

tion, exercise and behavior modification are well established treatments for the obese population. The obesity problem arises, however, because these weight reduction practices have very poor long-term outcomes attributable primarily to a lack of compliance.<sup>119</sup>

The chronic nature of obesity coupled with the prevalent perception of lack of willpower, laziness and inferiority that accompanies the disease makes the treatment frustrating.<sup>120</sup> Literature has shown that obese people are often referred to as "morally defective" and "gluttonous," making weight management suspect at reputable institutions.<sup>121</sup> Many patients accept the myth

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amount to approximately \$68 billion per year, and an additional \$30 billion per year is spent on weight-reduction programs and special foods. *Id.* See also *Long-term Pharmacotherapy in the Management of Obesity: National Task Force on the Prevention and Treatment of Obesity*, 276 JAMA 1907, 1907-15 (1996); Danya Harpster, *What Have You Got To Lose?*, NEW ORLEANS TIMES, Oct. 14, 1997, at F1.

A dieter invests money and time, whether he or she enrolls in a Weight Watchers group, is one of the estimated 8 million people who annually buy into a commercial diet program such as Jenny Craig - with its frozen food, vitamins and walking tapes- or simply plunk down \$12.95 for the Sugar Busters book and overhaul the pantry.

*Id.*

<sup>119</sup> B. Guy-Grand, *Pharmacological Approaches to Intervention*, 21 SUPP. 1 INT'L J. OF OBESITY & RELATED METABOLIC DISORDERS S22 (1997). Studies have shown that pharmacotherapy, combined with classical treatment strategies, have improved the long-term maintenance of weight loss. *Id.* at S24. "Pharmacotherapy appears to be the key to effective anti-obesity therapy. Drugs have utility for inducing weight loss in refractory obesity when classical techniques have failed. Drugs also have [the] potential for preventing regain of weight, so aiding long-term maintenance of weight loss." *Id.*

<sup>120</sup> Russell, *supra* note 117, at 1876. This stereotype is based on the assertion that so many people are trying to lose weight, but so few engage in the recommended amount of at least 30 minutes of physical activity that raises the heart-rate for at least four days per week. Russell, *supra* note 117, at 1876. Not only does exercise burn calories, but it also reduces the likelihood of obesity-related conditions such as heart disease and high blood pressure. Russell, *supra* note 117, at 1876.

<sup>121</sup> Cerda, *supra* note 116, at 89 (noting that many physicians avoid obesity treatment as part of their practice for fear of being labeled "quacks" and that "pandering to patients' desires with anorectic medications automatically renders

that obesity is "a social disease and live in shame and frustration."<sup>122</sup> Hence, it is not surprising that "[s]truggling dieters may be willing to take the risk of unlikely and unconfirmed ailments in exchange for a sure way to lose weight."<sup>123</sup> Recently, the "traditional methods of weight loss, involving a decrease in caloric intake, increase in exercise, and behavior modification" have been expanded to include the concept of pharmacologic management of obesity.<sup>124</sup>

### B. The Creation of Fen-Phen

For decades, appetite-suppressant drugs have cycled in and out of popularity with the medical profession and patients alike, each group desperate for treatment answers. "Current evidence suggests that drugs for the treatment of obesity, either alone or in combination, may produce short-term weight loss."<sup>125</sup> Hailed as a major

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a clinician as a second class practitioner").

<sup>122</sup> Cerda, *supra* note 116, at 90. Obesity is defined as a "body mass index" ("BMI") greater than 27 where the weight is expressed in kilograms and height in meters. Cerda, *supra* note 116, at 90. The BMI is the weight in kilograms divided by the square of the height in meters. Cerda, *supra* note 116, at 90. Often the cause of obesity is dismissed as the patient's compulsive eating lifestyle. Cerda, *supra* note 116, at 90. While this habit aggravates obesity, psychiatric and biological infirmities play an equally important role. Cerda, *supra* note 116, at 90.

<sup>123</sup> Laura Fraser, *The New Diet Drugs, They Really Do Help Some People Lose Weight: But Are They Worth the Risk?*, 10 HEALTH 52 (1996). However, fen-phen has not proven more effective than other diet regimens. In the Weintraub study, only 26 out of the 121 patients lost more than 10% of their body weight from taking fen-phen. See Weintraub, *infra* note 130, at 581-646 (revealing that the risks outweigh the potential benefits). Furthermore 19 dieters dropped out of the study because of side effects. Weintraub, *infra* note 130, at 581-646. Lastly, none of the patients maintained the weight loss once off the fen-phen "cocktail." Weintraub, *infra* note 130, at 581-646.

<sup>124</sup> Cerda, *supra* note 116, at 90 (stating that diet drugs act centrally, peripherally, or via a combination of these methods).

<sup>125</sup> Eugene V. Biosaubin, *Treatment for Obesity*, 276 JAMA 445, 445 (1996). However, the National Institute of Health called for additional long-term studies. *Id.* A weight-loss regimen should include exercise and behavior modification. *Id.* A "mission statement" should also be established setting reasonable, attainable

advance for managing obesity, fen-phen seemed to be a panacea for people who are thirty percent above their ideal weight.<sup>126</sup>

It was hypothesized that fenfluramine combined with phentermine would enhance weight loss over and above what could be achieved with the best behavior modification, exercise and nutrition program.<sup>127</sup> Accordingly, in a 1992 medical study, Dr. Weintraub, a professor of clinical pharmacology at the University of Rochester, administered the combination of fenfluramine at sixty milligrams and phentermine at fifteen milligrams in addition to behavior modification for 190 weeks in 121 obese females.<sup>128</sup> This combination drug therapy resulted in significant weight loss sustained over 210 weeks.<sup>129</sup> Weintraub and coworkers,<sup>130</sup> (fellow researchers and pharmacologists) concluded that anorexiant medications<sup>131</sup> can help one lose weight and maintain the weight

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goals for the individual. *Id.*

<sup>126</sup> 4 HARVARD WOMEN'S HEALTH WATCH, Feb. 1997, *available in* WESTLAW, Health & Medicine Database, HVD-WHW File [hereinafter HARVARD WOMEN'S HEALTH WATCH]. However, "[b]ecause the drugs are used to treat a condition that affects 58 million people, experts are concerned that indiscriminate use of these medications will lead to an increase in the number of people who suffer serious and potentially fatal side effects." *Id.*

<sup>127</sup> See M. Weintraub et al., *Long-term Weight Control Study: I-VII*, 51 CLINICAL PHARMACOLOGY & THERAPEUTICS 581-646 (1992).

<sup>128</sup> See Cerda, *supra* note 116, at 90-91 (noting that "[a]s expected, when the drugs were stopped in some patients they slowly regained weight despite continued diet, exercise and behavior modification"). Other patients, who were administered fen-phen on an intermittent basis, lost weight while on the medication and increased weight while not on the medication. Cerda, *supra* note 116, at 91. Hence, the implication is that treatment for obesity, similar to other chronic diseases, should be continuous. Cerda, *supra* note 116, at 91.

<sup>129</sup> Cerda, *supra* note 116, at 90.

<sup>130</sup> These researchers reasoned that patients might obtain better results and/or have fewer side effects if sub-maximal doses of a drug from each group were combined in a study. M. Weintraub et al., *Long-term Weight Control Study: I-VII*, 51 CLINICAL PHARMACOLOGY & THERAPEUTICS 581-646 (1992). Furthermore, the drugs might act synergistically to produce a positive effect on weight loss. *Id.* In addition, using two drugs with opposing adverse side effects might potentially offset each other and result in a lower incidence of both. *Id.*

<sup>131</sup> Anorexiant is defined as "producing anorexia." 1 THE NEW SHORTER OXFORD ENGLISH DICTIONARY 83 (1993). Anorectic means "characterized by a lack of appetite." *Id.*

loss for prolonged periods of time with little fear of developing abuse patterns associated with drug ingestion.<sup>132</sup> This study proved to be the beginning of a craze that would end with many questioning how physicians could prescribe such a drug with little empirical data to support such dispensing.

Fenfluramine (Pondimin),<sup>133</sup> a serotonergic agent,<sup>134</sup> acts to

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<sup>132</sup> For example, drug addiction is a serious and widespread problem facing prescription drug users. See NEIL R. CARLSON, *PHYSIOLOGY OF BEHAVIOR* 582 (5th ed. 1994). Similar to the use of "designer drugs," users of off-label prescription drugs are exposed "to unknown dangers of untested and often contaminated products." *Id.* at 583.

<sup>133</sup> Fenfluramine is manufactured by A.H. Robins, a subsidiary of American Home Products, Inc. See ANDREWS PHARMACEUTICAL LITIGATION REPORTER 12321 (June 1997). See also Paul D. Rheingold, *Fen-Phen/Redux Diet Drugs*, MEALEY'S LITIGATION REPORTS: DRUGS AND MEDICAL DEVICES, Aug. 1, 1997, at 22 (noting that "fen" is sold under a number of trade names by A.H. Robins, a subsidiary of American Home Products, Inc.).

<sup>134</sup> A neurotransmitter is an "endogenous chemical released by one neuron that alters the electrical activity of another neuron." See ROBERT M. JULIEN, M.D., PH.D., *A PRIMER OF DRUG ACTION: A CONCISE Nontechnical Guide To The Actions, Uses, And Side Effects Of Psychoactive Drugs* 495 (7th ed. 1995). At the most basic level, the brain cannot process information without neurotransmitters. Michael D. Lemonick, *The Mood Molecule Serotonin Drugs Treat Everything From Depression To Overeating, But As We Learned Last Week, Tinkering With The Chemistry Of The Brain Can Be Risky*, TIME, Sept. 26, 1997, at 74. This situation exists because neurons are separated by gaps (synapses). *Id.* The communication process is as follows: an electrical impulse is released into the nervous system. *Id.* This "signal" reaches the "home" of the neurotransmitters (vesicles) and the neurotransmitters are released. *Id.* These chemicals navigate across the synapse and lock into receptors. *Id.* The locking in at postsynaptic receptors produces "an action equivalent to flipping on a light switch." *Id.* That is "the locations in the nervous system at which a neurotransmitter or drug binds to exert its characteristic effect." JULIEN, *supra* at 496. The neurotransmitters are then reabsorbed or destroyed. Lemonick, *supra*, at 74. Serotonin is a special neurotransmitter in that it gives the message "an emotional tone." Lemonick, *supra*, at 74. "A person's mood is like a symphony and serotonin is like the conductor's baton." Lemonick, *supra*, at 74.

Fenfluramine is structurally related to amphetamine but acts on serotonin as opposed to norepinephrine. JULIEN, *supra*, at 150. As a serotonergic agent, fenfluramine prevents this neurotransmitter from leaving the synaptic cleft and, therefore, the chemical remains in the bloodstream longer and creates a prolonged reaction. JULIEN, *supra*, at 150. This results in a heightened response,

“partially inhibit reuptake of serotonin (5-HT) and to release 5-HT from nerve endings. This increased 5-HT in the synaptic cleft is believed to indirectly reduce food intake [by evoking a feeling of satiety].”<sup>135</sup> “Serotonin is an inhibitor of activity and behavior” particularly involved in the functions of “sleep, wakefulness, mood, temperature regulation, feeding, and sexual activity.”<sup>136</sup> The action of fenfluramine has not been clearly defined. It appears that by inhibiting the reuptake of serotonin, fenfluramine “increase[s] fat mobilization, decrease[s] absorption of dietary fat, and increase[s] cellular glucose uptake.”<sup>137</sup> Additionally, the medica-

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as evidence through mood, physiology and behavior. JULIEN, *supra*, at 150. Drug molecules must attach to specific receptors (like a lock and key relationship) which thereby change the functional property of the cell and produce a pharmacological response. JULIEN, *supra*, at 36. See also CARLSON, *supra* note 132, at 72-73.

[M]olecules of the transmitter substance are destroyed by an enzyme or taken back into the terminal button through the process of reuptake. Drugs can interfere with either of these processes; because they prolong the presence of the transmitter substance in the synaptic cleft (and hence in a location where they can stimulate postsynaptic receptors).

CARLSON, *supra* note 132, at 72-73.

<sup>135</sup> G.A. Bray, *Use and Abuse of Appetite-Suppressant Drugs in the Treatment of Obesity*, 119 ANNALS OF INTERNAL MEDICATION 708-09 (1993). A blockade of reuptake results in an agonist action whereby the neurotransmitter spends a greater amount of time available for interaction with postsynaptic receptors. *Id.* at 708. See generally PDR, *supra* note 7, at 1288-89 (finding that the action of such drugs in treating obesity is primarily one of appetite suppression).

<sup>136</sup> JULIEN, *supra* note 134, at 479. In the brain, “significant amounts of serotonin are found in the upper brain stem, with a large collection in the pons and medulla.” JULIEN, *supra* note 134, at 479. “Other neurotransmitters help us know our stomachs are full; serotonin tells us whether we feel satisfied. Other chemicals help us perceive the water level in a glass; serotonin helps us decide whether we think of it as half empty or half full.” Lemonick, *supra* note 134, at 74.

<sup>137</sup> See AMERICAN HOSPITAL FORMULARY SERVICE: FENFLURAMINE HYDROCHLORIDE, CAS REGISTRY NO: 404-82-0, American Society of Health Systems PHA (1997) [hereinafter FORMULARY SERVICE- FENFLURAMINE] (on file with *Journal of Law and Policy*). Fenfluramine hydrochloride is a “white, crystalline powder and is soluble in water.” *Id.* Its appetite-inhibiting action most likely



tion is thought to relieve hunger by altering nerve impulses to the appetite control center of the brain.<sup>138</sup>

Phentermine (Ionamin)<sup>139</sup> is an amphetamine-like drug,<sup>140</sup> used as an anorexic agent, which is secondary to central nervous system stimulation.<sup>141</sup> More specifically, phentermine inhibits the uptake of norepinephrine (Ne)<sup>142</sup> and dopamine (Da).<sup>143</sup> Essen-

results from stimulation of the ventromedial nucleus of the hypothalamus. *Id.* The hypothalamus is involved in visceral and autonomic changes along with the regulation of hormonal release. *Id.*

<sup>138</sup> CONSUMER GUIDE TO PRESCRIPTION DRUGS: THE MOST COMPLETE, AUTHORITATIVE, AND CURRENT BOOK OF ITS KIND 169-70 (1990) [hereinafter CONSUMER GUIDE]. Fenfluramine's effectiveness lasts only for short periods of time (3-12 weeks). *Id.* at 169. Treatment involves taking the drug "with a full glass of water one hour before meals." *Id.* Side effects include blurred vision, constipation, diarrhea, dizziness, dry mouth, euphoria, fatigue, insomnia, irritability, nausea, nervousness, restlessness, stomach pain, sweating, unpleasant taste in the mouth and vomiting. *Id.* at 170.

<sup>139</sup> Phentermine is sold under various trade names including Fastin, Apidex, Obe-Nix and Ionamin. *See* CONSUMER GUIDE, *supra* note 138, at 326. Numerous manufacturers are involved in the sale of this drug. *See* CONSUMER GUIDE, *supra* note 138, at 326.

<sup>140</sup> Amphetamines act as behavioral stimulants. JULIEN, *supra* note 134, at 489. Similar to the action of cocaine, amphetamines block the reuptake of dopamine, which is the neurotransmitter implicated in movement, attention and learning. CARLSON, *supra* note 132, at 585.

<sup>141</sup> *See* AMERICAN HOSPITAL FORMULARY SERVICE: PHENTERMINE HYDROCHLORIDE, CAS REGISTRY NO: 122-09-8, American Society of Health Systems PHA (1997) [hereinafter FORMULARY SERVICE- PHENTERMINE] (on file with *Journal of Law and Policy*). Phentermine is available as a "hydrochloride salt and as a cation exchange resin complex of sulfonated polystyrene." *Id.* It is used as an adjunct to caloric restriction in the short-term treatment of obesity. *Id.* Phentermine is designed to be most effective in controlling appetite during the first few weeks of dieting. CONSUMER GUIDE, *supra* note 138, at 326. The drug is also available in a time-release form which must be swallowed whole or side effects may increase. CONSUMER GUIDE, *supra* note 138, at 326. The side effects are almost identical to that of fenfluramine with the addition of a false sense of well-being. CONSUMER GUIDE, *supra* note 138, at 327.

<sup>142</sup> CARLSON, *supra* note 132, at 64. Produced in the adrenal glands, this neurotransmitter is primarily involved in alertness and wakefulness. CARLSON, *supra* note 132, at 65.

<sup>143</sup> FORMULARY SERVICE- PHENTERMINE, *supra* note 141. The cell bodies of Ne are located in the brain stem. JULIEN, *supra* note 134, at 477. Large amounts

tially, among other things, phentermine "indirectly suppresses appetite by inhibiting Da receptors."<sup>144</sup>

### C. Problems With The "Fen-Phen Cocktail"

Off-label dispensing of drugs cannot become an uncontrolled experiment on millions of Americans. Yet it is evidently becoming an invitation for people to self-medicate in an effort to shed a few pounds. One problem that immediately developed from the dispensing of fen-phen was the number of prescriptions written for people of lesser girth.<sup>145</sup> One reason for this is that local Nutri/System weight-loss centers highlight the fact that a physician will give a quick check-up and then a prescription for diet pills.<sup>146</sup> More astonishingly, one can just log on to the internet and get a

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of Da are found in the basal ganglia, the frontal cortex and the limbic system. JULIEN, *supra* note 134, at 478. "The release of Ne produces an alerting, focusing, orienting response (similar to the fight/flight/fright syndrome)" and "positive feelings of reward." JULIEN, *supra* note 134, at 478. The release of Da is associated with emotion and reward systems. JULIEN, *supra* note 134, at 478-79.

<sup>144</sup> Cerda, *supra* note 116, at 90 (noting that as the length of time that a person is on the drug increases, the effect on weight decreases).

<sup>145</sup> HARVARD WOMEN'S HEALTH WATCH, *supra* note 126. The number of prescriptions written for fen-phen increased from 60,000 in 1992 to 1.1 million by 1995. HARVARD WOMEN'S HEALTH WATCH, *supra* note 126. Patients received 18 million new prescriptions and refills last year alone. See *Heart Disease: Valvular Heart Disease Associated With Commonly Prescribed Diet Pills*, BLOOD WEEKLY, July 28, 1997, available in 1997 WL 10931944 [hereinafter BLOOD WEEKLY].

<sup>146</sup> Fraser, *supra* note 123, at 52. Last fall Nutri/System became the first major diet center in the country to give clients appetite suppressants under a pilot program referred to as NutriRx. Fraser, *supra* note 123, at 52. When asked what she would do if the NutriRx doctor stopped prescribing fen-phen for her, a patient responded, "I'll just find another center and another doctor." Fraser, *supra* note 123, at 52.

prescription for fen-phen.<sup>147</sup> Dr. Piotr Hitzig advertises on the web that if you cannot make it to his office, he will prescribe drugs via other means.<sup>148</sup> Despite little training in obesity, many physicians have begun overnight fen-phen treatment programs with promises of a more slender you that will not fade in time.<sup>149</sup>

Certainly, one can find safer and more effective means for such a serious health problem. "The bottom line is what have diet pills produced other than hundreds of millions of dollars of sales and hundreds of thousands of adverse events a year?"<sup>150</sup> A quick glimpse into current litigation makes this statement far more alarming: Thomas and Mary Linnen contend that their thirty-year-old daughter died because of primary pulmonary hypertension as a direct result of using fen-phen.<sup>151</sup> Additionally, in a class action complaint, plaintiffs seek to represent persons nationwide who have

<sup>147</sup> See, e.g., Piotr Hitzig, *The Fen/Phen Protocol: Frequently Asked Questions* (last modified May 10, 1996) <<http://techno.king.net/jmay/faq.txt.html>>.

<sup>148</sup> Kolata, *supra* note 1, at A3. "Piotr Hitzig, M.D., an internist, had practiced general medicine for 20 years before devoting himself to the exclusive treatment of patients using the Fen/Phen protocol." Piotr Hitzig, *The Fen/Phen Protocol: Frequently Asked Questions*, (last modified May 10, 1996) <<http://techno.king.net/jmay/faq.txt.html>>.

<sup>149</sup> Kushner, *supra* note 10, at 603. These physicians have seized on the drug frenzy that has been revered in magazines and tabloids and have made it a profitable enterprise. A Chicago program featuring fen-phen in a newspaper advertisement offered patients half-off on the first visit merely "as an incentive to try the program." Kushner, *supra* note 10, at 603. As a result of advertisements such as this, sales for phentermine have increased 442% and sales for fenfluramine are up 6,390%. Kushner, *supra* note 10, at 603. "Like a palooka prizefighter, the pharmaceutical industry keeps coming at overweight Americans with one basic strategy . . . [a]ppetite suppression." See Rick Ansorge, *Experts Call Appetite-Suppressing Drugs Sure Losers*, CINCINNATI ENQUIRER, Oct. 17, 1997, at D02.

<sup>150</sup> Tiedt, *supra* note 2, at 1201. "Diet pills are at best only signals to stick to required diet and exercise. Certainly, we can find safer and more effective signals for such a serious health problem. The use of these drugs only adds to the unhealthy societal attraction to synaptic stimulants." Tiedt, *supra* note 2, at 1201.

<sup>151</sup> See *Highlights*, ANDREWS PHARMACEUTICAL LITIGATION REPORTER, June 1997, at 12321. (noting Linnen v. A.H. Robins, Inc., No. 97-2307, (Mass. App. Ct. 1997)). This wrongful death suit is brought against the manufacturers and distributors of fen-phen and the doctor who prescribed it, alleging a failure to warn of the risks involved. *Id.*

taken fen-phen which resulted in alleged dangerous side effects including valvular heart disease.<sup>152</sup> Moreover, a Brooklyn woman filed a ten million dollar lawsuit alleging that fen-phen led to two surgeries for heart valve replacements.<sup>153</sup> Lastly, a wrongful death action in Orange County asserts that a doctor prescribed fen-phen which eventually led to a patient's blocked heart artery and death in August 1996.<sup>154</sup>

In January 1997, Wyeth-Ayerst, a manufacturer of fenfluramine, sent letters to 470,000 medical professionals advising that the concomitant use of fen-phen is not recommended.<sup>155</sup> On July 8, 1997, the Mayo Clinic reported a clinical observation of valvular heart disease in twenty-four patients who had ingested fen-phen.<sup>156</sup> In light of the Mayo Clinic's findings, Jenny Craig Inc. said it was recommending that doctors stop prescribing the drug

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<sup>152</sup> See *Gardner v. Gate Pharmaceuticals*, No. 97-2542, (N.D. Cal. 1997). The complaint was filed on July 9, 1997, alleging that the manufacturers failed to adequately warn that the FDA had not approved the concomitant use of the drugs. *Id.*

<sup>153</sup> Kathleen Kerr, *B'klyn Woman Files \$10 million Fen-Phen Suit*, N.Y. NEWSDAY, Aug. 15, 1997, at A33. The complaint alleges that "drug companies failed to ensure safety for consumers when they tested, manufactured and marketed fen-phen." *Id.*

<sup>154</sup> *Lawsuit Says Faulty Advice on Fen-Phen Led to Death*, ORANGE COUNTY REGISTER METRO, Aug. 15, 1997, at B02. Autopsies by the county coroner's office revealed that at least seven people died of heart disease in the past year with fen-phen in their system. *Id.*

<sup>155</sup> *Valvular Heart Disease in 33 Fen-Phen Patients Spurs FDA "Dear Doctor" Letter: Agency Will Meet With Manufacturers of Obesity Drugs to Discuss Labeling Changes*, 9 HEALTH NEWS DAILY 131, July 9, 1997, available in WESTLAW, Health & Medicine Database, HND File. The letter stated that the "safety and effectiveness of the use of fenfluramine and phentermine in combination have not been established." *Id.*

<sup>156</sup> Shelly Plutowski, *Valvular Heart Disease Associated With Commonly Prescribed Diet Pills: Mayo Clinical Observation Raises Questions About Fenfluramine-Phentermine Therapy* (last modified Aug. 29, 1997) <<http://www.mayo.edu/news/mayo%20ROCHES..97/07-Jul-97/fenphen/fen-phennews.html>>. "All 24 patients had cardiovascular symptoms or a heart murmur." *Id.* Subsequent testing revealed that heart valves were thickened and blood was leaking backwards. *Id.*

combination of fenfluramine and phentermine.<sup>157</sup> That same day, an FDA Public Health Advisory was issued to remind health care practitioners that the safety and efficacy of the concomitant use of fen-phen has not been established.<sup>158</sup> The FDA recommended that physicians follow their patients closely with periodic and thorough

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<sup>157</sup> *Diet Centers Rethink Prescribing Fen-Phen Combo*, STAR TRIB. (St. Paul, Minn.), July 20, 1997, at 05E. However, Nutri-System continues to promote herbal fen-phen as a natural alternative to other diet drugs. *Id.* This product contains ephedrine, an herbal stimulant, which has been involved in more than a dozen deaths. *Id.* The FDA has proposed banning any marketing of such products. *Id.*

Over the counter, \$23.99 will buy a 15-day supply of "herbal fen-phen," priced at General Nutrition Centers at Oakwood mall. The active ingredient- St. John's wort, which works like fenfluramine, and ma huang, which is also sometimes called ephedra and works like phentermine- are becoming medically suspect for the same reason as their prescription counterparts.

Harpster, *supra* note 118, at F1. St. John's wort contains the active ingredient hypericin which is used to treat mild to moderate depression by elevating the body's level of serotonin. See Barbara Russi Sarnataro, *Herb Found To Suppress Appetite, Too*, CHI. SUN-TIMES, Oct. 15, 1997, at 60. "In the United States, it has been available in vitamin and health food stores for years but was not widely known. All that changed [on] June 28- the day the ABC program 20/20 aired a glowing report on the plant's anti-depressant qualities." Peter Larsen, *A More Natural Prozac? St. Johns Wort Users Want To Get To The Root Of Their Depression*, FORT WORTH STAR-TELEGRAM, Nov. 19, 1997, at 5.

<sup>158</sup> Lumpkin, *supra* note 8. The Summary of Reports reads:

As of July 8, 1997, there have been 33 cases reported to [the] FDA of unusual valvular morphology and regurgitation involving the mitral, aortic, and/or tricuspid valves, usually being multivalvular. About half of the women were reported to have pulmonary hypertension with their valvular disease. All 33 patients were American women with a mean age of 43.3 years (range: 35-72), all of whom had received combined fenfluramine and phentermine therapy for between 1 and greater than 16 months (mean 10) before presentation with their valvular disease. Echocardiographic confirmation of valvular disease was seen in nearly all of these patients. To date, surgical intervention has been required in six patients; the histopathology of the diseased valves resembled that seen in carcinoid syndrome or ergotamine toxicity. The course of the cardiac valvulopathy in individuals after the drugs are stopped is presently unknown.

Lumpkin, *supra* note 8.

cardiac evaluation.<sup>159</sup> Also, the findings prompted the FDA to send out "Dear Doctor" letters warning physicians of the potential for heart problems.<sup>160</sup>

Fen-phen, widely and aggressively advertised as "the medication that would allow you to eat and live like a 'normal' person,"<sup>161</sup> has proven to be a prime example of the potential danger of off-label uses of drugs. As of July 21, 1997, ten patients needed open-heart surgery as a result of taking fen-phen.<sup>162</sup> Some six million Americans are estimated to have tried fen-phen last year prior to doctors finding heart valve side effects.<sup>163</sup> By July 22, 1997, an additional seventeen cases of heart disorder were reported.<sup>164</sup>

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<sup>159</sup> Furthermore, "as signs and symptoms of cardiopulmonary disease develop, further cardiac evaluation should be pursued." Lumpkin, *supra* note 8.

<sup>160</sup> Langreth & Ingersoll, *supra* note 6, at B1. In January 1997, American Home notified doctors that appetite suppressants that were used for more than three months were linked to a 23-fold increase in the risk of pulmonary hypertension. Langreth & Ingersoll, *supra* note 6, at B1. "Proponents of the drug[s] counter that there is ample evidence that obesity [itself] causes high blood pressure and heart disease." Langreth & Ingersoll, *supra* note 6, at B1.

<sup>161</sup> MARKETLETTER, *supra* note 7. A class action lawsuit was recently filed against the manufacturers of fenfluramine and phentermine focusing on both primary pulmonary hypertension and the heart valve abnormalities. MARKETLETTER, *supra* note 7. The suit alleges that the manufacturers and distributors both knew of and encouraged the off-label use of the drugs. MARKETLETTER, *supra* note 7.

<sup>162</sup> *Fen/Phen Critics Fight Bill That Would Push Unapproved Drugs*, DOW JONES NEWS SERVICE, July 21, 1997, at 18:11:00. The Senate is preparing legislation called the "killer fen-phen" amendment to allow drug salesmen to provide doctors with studies promoting unapproved uses of medicines. *Id.* The FDA's concerns with the bill include: (1) doctors may not necessarily take the time out of their busy schedules to read further research to ensure that the company promoting the drug is adequately portraying all aspects of it; (2) small-scale studies are ineffective because they do not involve a larger subject pool that would more adequately represent the likelihood of side effects; and (3) the company will not have an incentive to do more thorough research. *Critics Seize on Fen-Phen Scare to Fight Senate Drug Legislation*, STAR-TRIB. (St. Paul, Minn.), July 22, 1997, at 07A.

<sup>163</sup> See Laura Johannes, *Significant Heart-Valve Leaks Found in Large-Scale Study of Diet Pill Users*, WALL ST. J. (Europe), Nov. 13, 1997, at 8.

<sup>164</sup> *FDA Finds 17 More Cases Link Fen/Phen, Heart Ails*, COMMERCIAL APPEAL (Memphis, Ten.), July 22, 1997, at A5. The FDA has yet to evaluate the

Three days later, the diet drug combination was being held accountable for causing heart and lung problems that led to a Fargo woman's death.<sup>165</sup>

Manufacturers then began working with the FDA to develop warning language to reflect concerns over the side effects associated with fen-phen.<sup>166</sup> The revised labeling would include a boxed warning about a possible heart valve disorder associated with the drug's use,<sup>167</sup> although doctors still do not know how fen-phen causes heart valve injuries.<sup>168</sup> For Vicki Thomas, the warnings were too little too late.<sup>169</sup> At age 41, Ms. Thomas was diagnosed with primary pulmonary hypertension and the condition has only worsened.<sup>170</sup> She is in desperate need of a heart-lung transplant, has weakened kidneys, and claims that "the only things

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reports and establish a direct link between the consumption of fen-phen and heart valve problems. *Id.* However, Dr. Mehmood Khan, chief of endocrinology at Hennepin County Medical Center in Minneapolis, studied 307 echocardiograms and found a "[c]lear association between [diet] drug therapy and heart-valve problems." Johannes, *supra* note 163, at 8.

<sup>165</sup> *Hospital: Fen-Phen Didn't Cause Fargo Death*, STAR-TRIB. (St. Paul, Minn.), July 25, 1997, at 03B. The autopsy showed that the patient suffered from pulmonary hypertension. *Id.* However, the hospital claims this condition did not contribute to her death. *Id.*

<sup>166</sup> *Wyeth-Ayerst to Add Information to Labeling of Antiobesity Therapies*, PR NEWswire, July 25, 1997, at 14:14:00.

<sup>167</sup> *Id.* The boxed warning is a method used to prominently display information of a critical nature. *Id.* The warning will also contain language regarding the risk of primary pulmonary hypertension. *Id.* However, doctors also note that the link between the treatment of obesity with fen-phen and valvular heart disease is inconclusive. *Id.*

<sup>168</sup> BLOOD WEEKLY, *supra* note 145. Dr. Heide Connolly, Mayo cardiologist, stated: "We believe that these cases raise significant concern that this combination of appetite suppressants can have important implications regarding valvular heart disease, but more comprehensive stud[ies], which we are planning, [are] needed to make a definitive statement about the association." BLOOD WEEKLY, *supra* note 145.

<sup>169</sup> Anne Marie O'Neill & Michele Keller, *Bitter Pills: Vicki Thomas Lost Far More Than Pounds on the Diet Drugs Fen-Phen*, PEOPLE, Aug. 18, 1997, at 105. Vicki Thomas was 5 feet, 6-1/2 inches and 157 pounds and wanted to lose 15 pounds. *Id.*

<sup>170</sup> *Id.*

that don't hurt are the tip of my nose and my eyeballs. It has been hell."<sup>171</sup>

Primary pulmonary hypertension is "increased blood pressure in the blood vessels of the lungs."<sup>172</sup> Fen-phen has been linked to this condition due to ties to the increased level of serotonin in the synaptic clefts which occurs after ingesting fen-phen.<sup>173</sup> This increased level of serotonin constricts the veins, raising the blood pressure and resulting in a restriction of blood flow.<sup>174</sup> Heart valve damage is evidenced by a "glistening white or wax appearance" on the leaflets and chords of the valve and induces symptoms including shortness of breath, fatigue and extreme swelling in the lower extremities.<sup>175</sup> Additionally, switching to natural forms of fen-phen may not be a safer alternative because herbal fen-phen, diet-phen and fen-chi contain ephedra which has been implicated in more than 800 reports of adverse events, among them twenty to thirty deaths.<sup>176</sup> Nevertheless, neighborhood drug stores will stock

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<sup>171</sup> *Id.* While it is not possible to prove that the drugs caused her condition, her cardiologist, Dr. Bruce Brundage, thinks that no physician should advocate fen-phen for people who want to lose a few pounds. *Id.*

<sup>172</sup> Rheingold, *supra* note 133, at 22. The term "primary" implies no known cause. Rheingold, *supra* note 133, at 22.

<sup>173</sup> Rheingold, *supra* note 133, at 22.

<sup>174</sup> Rheingold, *supra* note 133, at 22 (citing <<http://www.netmedicine.com/pt-PTINFO/Prim-ph.html>>). A world-wide group known as the International Pulmonary Primary Hypertension Study "found a 23 times increase of PPH in those who used fen-phen for more than three months over non-users." Rheingold, *supra* note 133, at 22.

<sup>175</sup> Rheingold, *supra* note 133, at 22. Patients developing these symptoms or a new heart murmur throughout the course of therapy should consult a physician and request a complete cardiac evaluation. See Charles W. Henderson, *Information Added to Anti-Obesity Therapy Labeling*, DISEASE WEEKLY PLUS, Aug. 11, 1997, available in 1997 WL 11421558.

<sup>176</sup> Lisa Jennings, *It's Still A Drug: 'Natural' Forms of Fen/Phen Can Produce Damaging Side Effects*, COMMERCIAL APPEAL (Memphis, Ten.), Aug. 3, 1997, at F1. Reports ranged from unpleasant side effects to more serious ones including seizures, heart attacks and strokes. *Id.* Under the Dietary Supplement Health and Education Act of 1994, dietary supplements are not required to be tested for safety and efficacy prior to shelving. *Id.* However, a current FDA proposal seeks to limit Ephedrine alkaloids in dietary supplements to no greater than eight milligrams per serving. *Id.* It could be almost two years before the



their shelves with herbal fen-phen simply due to high consumer demand.<sup>177</sup>

Unfortunately, no animal studies or good clinical testing has been done on the effects or adverse reactions of fen-phen.<sup>178</sup> It is therefore no wonder that the controversy surrounding the drugs' use continues. As recently as August 20, 1997, doctors asserted that the drugs do not increase serotonin levels in the blood that reaches the heart, but reduces such levels.<sup>179</sup> The National Institute of Mental Health ("NIMH") discovered that the drug works similarly to Prozac by enhancing pleasant emotions while diminishing unpleasant ones.<sup>180</sup> It has been asserted that the problem arises with the

proposed regulation becomes final. Carolyn Poirot, *Herbal Fen-Phen Sales Are Up- As Are Warnings Flags*, FT. WORTH STAR-TELEGRAM, Aug. 21, 1997, at 1. See also U.S. HHS: FDA Warns Against Drug Promotion of "Herbal Fen-Phen", M2 PRESSWIRE, Nov. 7, 1997, available in 1997 WL 15142782. The agency is warning consumers that the herbal form of the drug has not been proved safe and effective for human consumption. *Id.* "The FDA warned that companies are violating federal law by advertising the dietary supplements as weight-loss products-or implying such a benefit by mimicking the prescription drug names . . . [t]he average consumer would look at this product and think, 'Wow, this is the same name as fen-phen, it must provide the same benefit.'" *Government Cracks Down on Diet Supplement "Herbal Fen-Phen,"* SAN DIEGO UNION-TRIB., Nov. 7, 1997, at A9.

<sup>177</sup> Jennings, *supra* note 176, at F1 (noting that "[h]erbal fen-phen is the lesser of two evils").

<sup>178</sup> Rheingold, *supra* note 133, at 22. Hence, the prescribing physician and the patient have none of the scientific support which the FDA requires before a drug is marketed. Rheingold, *supra* note 133, at 22.

<sup>179</sup> *Dieter's Valve Damage Needs More Research*, WALL ST. J., Aug. 20, 1997, at A15. It is argued that fenfluramine blocks the reuptake of serotonin into platelets, leaving them to be destructed by monamine oxidase (MAO). See JULIEN, *supra* note 134, at 495 (noting that MAO is an "[e]nzyme capable of metabolizing norepinephrine, dopamine, and serotonin to inactive products"). However, it is still possible to have increased serotonin levels in brain synapses. *Dieter's Valve Damage Needs More Research, supra*, at A15.

<sup>180</sup> *Risk in a Pill Society: Some New Prescription Drugs Are Only Dimly Understood By Science*, L.A. TIMES, Sept. 1, 1997, at B4. The method by which serotonin works remains a mystery among many individuals in the medical profession. *Id.* For example, William S. Appleton, a Harvard Medical School psychiatrist, stated: "I have begun to regard the serotonin synapse the same way I think of my radio when it does not work—I hit it and it often starts broadcast-

fen-phen cocktail because it not only prevents absorption of serotonin, but also decreases the brain's sensitivity to that neurotransmitter.<sup>181</sup> In other words, it is still under investigation to discover the exact mechanism of action for serotonin and its fluctuating effect on fen-phen users. Not surprisingly, a citizen's petition dated around August 21, 1997 requested the FDA to rescind approval of the drugs because of the "imminent danger to the public safety."<sup>182</sup>

Concerns about the apparent direct causal relationship between ingesting fen-phen and cardiac and respiratory malfunctioning climaxed as a result of the New England Journal of Medicine's publication demanding a moratorium on the use of anorectic drugs for cosmetic purposes.<sup>183</sup> Results of the study indicated that the use of anorectic drugs caused pulmonary hypertension.<sup>184</sup> The affected mitral, aortic and tricuspid heart valves resulted in valve-replacement surgery for five patients.<sup>185</sup> Through examinations, researchers concluded that appetite-suppressant drugs cannot

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ing again. I have begun to believe that is what these antidepressants do to the synapse—they hit it." *Id.*

<sup>181</sup> *Id.* Given the vast quantity of individuals now taking the drugs, the NIMH study should remind us to fight our natural instinct to believe in the curative powers of medicine to the extent that we lose sight of the various complications that accompany the pharmacological products.

<sup>182</sup> HEALTH NEWS DAILY, *supra* note 30. The petition was filed with the FDA by Ronald Benjamin, a Binghamton, New York attorney, on behalf of two patients claiming to have experienced cardiovascular-related side effects from the anti-obesity drugs. HEALTH NEWS DAILY, *supra* note 30.

<sup>183</sup> Gregory D. Curfman, *Diet Pills Redux*, 337 NEW ENG. J. MED. 629, 629-630 (1997). The method by which these drugs cause pulmonary hypertension has not been established conclusively, particularly because it has been impossible to reproduce the disease in animals. *Id.*

<sup>184</sup> *Id.*

<sup>185</sup> *Id.* It is speculated that serotonin was involved with the injuries to the heart valves. *Id.* Because of the severity of the effects, the editors of the New England Journal of Medicine released the finding of the paper "more than seven weeks before publication." *Id.* "The editors believed that doctors and their patients needed to be alerted quickly, so that appropriate decisions could be made and the scope of the problem could be rapidly assessed." *Id.*

maintain weight loss indefinitely.<sup>186</sup> Furthermore, a recent study has found that a dose comparable to that prescribed to reduce weight in humans caused neurotoxicity in monkeys which can result in mood, memory and sleep problems.<sup>187</sup> However, as with every controversial issue, some users continue to advocate the drug's effectiveness. They say exactly what dieters want to hear, and believers hear only these messages of hope and herald these words as the truth in the face of compelling evidence to the contrary.

#### *D. Addressing The Problems Of Fen-Phen*

Even the believers of fen-phen have to start losing hope. It appears that the perils of weight loss pills far outweigh the benefits that are cited few and far between. The big news is that fen-phen does not result in significant weight loss because the average weight loss is approximately five and one-half pounds more than dieting alone.<sup>188</sup> Such a finding begs the question, is the diet-pill craze coming to a close? While "America has clearly not lost its appetite for drugs,"<sup>189</sup> sales of diet pills are diminishing rap-

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<sup>186</sup> *Id.* To date, efficacy only for short-term weight loss has been proven conclusively. *Id.* Safety becomes more doubtful when taking the drug over an extended period of time because the risk of serious toxicity increases with use. *Id.*

<sup>187</sup> *U.S. HHS: Psychiatric Symptoms May Signal Brain Damage From Diet Pills*, M2 PRESSWIRE, Aug. 27, 1997, available in 1997 WL 13653387. This study suggests that fen-phen use may result in irreversible loss of brain serotonin nerve terminals. *Id.* In this study, the monkeys' brains continued to show signs of damage seventeen months after taking fen-phen. *Id.* However, there is no evidence that such harmful changes would occur in humans. *Id.*

<sup>188</sup> Jane E. Brody, *Hard Evidence Building Against Fen-Phen Safety*, PORTLAND OREGONIAN, Sept. 3, 1997, at E12. Also, dieters regain some or all of the weight when they cease taking the drugs. *Id.* Proponents of fen-phen assert that "although the drugs sometimes might be hazardous, obesity itself is a far greater risk." *Id.* Excess weight "results in 300,000 deaths a year from causes such as heart disease, diabetes, kidney disease, and stroke." *Id.*

<sup>189</sup> Andrew K. Skolnick, *Lessons From U.S. History of Drug Use*, 277 JAMA 1919, 1919 (1997). Skolnick notes the irony that while America is passing strict regulations concerning the tobacco industry and no longer sympathizing with the problem drinker, "we are [at the same time] taking Prozac

idly.<sup>190</sup> Furthermore, the National Association to Advance Fat Acceptance and the Council on Size and Weight Discrimination recently filed suit in United States District Court in Washington seeking to compel the government and drug companies to remove fen-phen and redux from the market.<sup>191</sup>

On September 15, 1997, fenfluramine was removed from the market after new evidence linked its use to serious heart valve problems.<sup>192</sup> After analyzing heart tests on 291 fen-phen users and noting that ninety-two had damaged heart valves, the FDA was forced to take prompt action.<sup>193</sup> The FDA concluded that fenflura-

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in record numbers [and] slimming down with Fen-Phen." *Id.*

<sup>190</sup> Laura Johannes & Steve Stecklow, *Trimming the Sales: Diet-Pill Prescriptions Plummet as Concerns Rise Over Side Effects*, WALL ST. J., Sept. 4, 1997, at A1. According to David Crossen, an analyst of Montgomery Securities in San Francisco, Redux "was the fastest launch of a drug ever. In the first 11 weeks it hit an annual sales rate of \$220 million." *Id.* Mr. Crossen sees current annual sales closer to \$70 million. *Id.*

<sup>191</sup> *Advocates For Fat People Sue Over Weight-Loss Drugs*, ST. LOUIS POST, Sept. 6, 1997, at 21. The suit asks for a fund to be established to offset the harm that resulted from the promotional activities that made fen-phen a household term. *Id.* Sally Smith, a member of the Fat Acceptance Group, said that the organization "feels strongly that what's at stake in this lawsuit is the health and well-being of Americans all sizes of large. The FDA has been asleep at the wheel, and drug manufacturers are profiting from the desperation of fat people." *Id.*

<sup>192</sup> Marlene Cimon, *2 Diet Drugs Tied to Heart Problems Taken Off the Market: Action Effectively Ends Fen-Phen Combination*, L.A. TIMES, Sept. 16, 1997, at A1. "Despite the continued availability of phentermine, experts do not expect it to be combined with" other drugs given the problems in the present situation. *Id.* But see Johannes & Stecklow, *supra* note 190, at A1 (noting that Nutri/System is now recommending that clients switch to phen-pro, a combination of Phentermine and Prozac, absent any studies for its safety and efficacy). Phen-pro works differently than fen-phen, but it still suppresses appetite. Johannes & Stecklow, *supra* note 190, at A1. There is no evidence that the concomitant use of the drugs enhances either drugs' effect. Johannes & Stecklow, *supra* note 190, at A1. "Although phentermine . . . was not recalled, it does have the potential to cause some side effects. They include rapid heart rate, insomnia, anxiety, headache, dry mouth, digestive upset, changes in libido and increases in blood pressure." Joe Graedon & Teresa Graedon, Ph.D., *Legal Issues May Make Doctors Leery of Fen-Phen*, BALTIMORE SUN, Nov. 11, 1997, at 5E.

<sup>193</sup> Cimon, *supra* note 192, at A1. Yet this decision does have its critics. Dr.

mine presented an unacceptable risk of heart problems to patients.<sup>194</sup> At this point in time, due to the recall of fen-phen, the biggest problems appear to be the long-term repercussions for post users and determining what steps can be taken to reduce adverse effects.<sup>195</sup>

Approximately one hundred lawsuits have been filed around the country alleging heart-valve problems, primary pulmonary hypertension and brain damage as a result of ingesting fen-phen.<sup>196</sup> Yet the dilemma for the FDA remains virtually un-

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Bernard Ginsberg, a Santa Monica physician with an extensive weight-loss practice, asserts that he "would have preferred an alert to doctors, rather than taking the drugs off the market." Cimons, *supra* note 192, at A1. Dr. Ginsberg continued, "[Patients] didn't know when it was time to eat unless they were told; and when they ate something, they got full right away. I thought it was a panacea, but sometimes some things are too good to be true." Cimons, *supra* note 192, at A1.

<sup>194</sup> John Schwartz, *2 Diet Drugs Are Pulled Off Market: Health Concerns Grow After FDA Links Pills to Rare Heart Problem*, WASH. POST, Sept. 16, 1997, at A01. At least three deaths had been linked to the use of the drug to date. *Id.* "The FDA said the valve problems can cause a backflow into a heart chamber, increasing the risk of bacterial endocarditis, a potentially fatal infection of the heart's lining, during invasive medical and dental surgery." *FDA Says Fen-Phen Users Need Doctor's Examination*, WALL ST. J., Nov. 14, 1997, at B13. The FDA issued the recall after learning that almost one-third of patients studied evinced heart-valve damage. *See Keep the Watchdog Well-fed: Action Against Fen-Phen Shows the Need For a Vigorous FDA*, L.A. TIMES, Sept. 18, 1997, at B8.

<sup>195</sup> *See* John G. Auerbach, *What the Diet-Drug Recall Means to Patients*, WALL ST. J., Sept. 16, 1997, at B1. "Physicians, of all people, might be expected to be skeptical and respect the powerful effects of drugs. . . . You'd think they would wonder at the very least if what they are doing is safe. How do they know they are doing no harm." *See* Gina Kolata, *How Fen-Phen, a Diet 'Miracle,' Rose and Fell*, N.Y. TIMES, Sept. 23, 1997, at F1.

<sup>196</sup> *See* Laura Johannes & Richard Schmitt, *Lawyers Prepare for Deluge of Diet-Drug Suits*, WALL ST. J., Sept. 17, 1997, at B1. Rarely do drug companies confront such a large group of people affected in such a disastrous way. *Id.* Even newspapers are advertising lawyers groups selling memberships to new diet-drug litigation for \$250. *Id.* Desire to become involved in this litigation is readily apparent: analysts estimate that liability could exceed \$4 billion. *Id.* Furthermore, some lawyers are contemplating filing suit against the manufacturers under the Federal Tort Claims Act. *Id.* Class-action suits were filed in New York, Utah, Colorado, California, and Hawaii arguing that "[t]housands of people will now

changed: "It must address public, political and industry pressure to approve promising new drugs quickly and yet protect Americans from unsafe medications."<sup>197</sup> It is clear, after the fen-phen fiasco, that the FDA needs a stricter procedure for the evaluation of new drug uses. However, logic runs amiss as seen by a recent bill which was proposed to Congress that would shorten the approval process by requiring only one clinical trial to prove safety and efficacy.<sup>198</sup> Supervision, as a whole, is virtually absent.<sup>199</sup>

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need regular medical attention for which the drug makers must be held responsible." See *Lawsuits Filed Against Makers of Fen-Phen*, WASH. POST, Sept. 22, 1997, at A11. Moreover, a suit, believed to be the first in Orange County dealing with the effects of fen-phen, was filed recently. See Marcida Dodson, *O.C. Clinic Named in Fen-Phen Lawsuit*, L.A. TIMES, Sept. 30, 1997, at A22. This class-action suit was filed by a woman alleging heart problems as a result of taking the drug combination. *Id.* Also, a Punta Gorda woman filed a federal class action suit against eight drug companies alleging the drug combination damaged her heart and lungs. *Id.* The suit claims that fen-phen "represents an imminent public health danger." See Stephen Nohlgren, *Class-action Lawsuit Challenges Safety of Fen-Phen*, ST. PETERSBURG TIMES, Oct. 1, 1997, at 1B. Additionally, a North Carolina law firm filed a class-action suit against five drug companies in hopes of receiving \$75,000 for each plaintiff to cover continual medical services. See Catherine Clabby, *Class-action Suit Takes Aim at Popular Diet Medications*, NEWS & OBSERVER (Raleigh, N.C.), Oct. 2, 1997, at A3.

<sup>197</sup> Laura Johannes & Steve Stecklow, *Withdrawal of Diet Drug Raises Questions in U.S.*, WALL ST. J. (Asia), Sept. 17, 1997, at J6. The FDA and drug companies continue to assert that they took swift action to protect the public, despite the lack of conclusive proof that the drug combination is directly responsible for the reported adverse effects. *Id.*

<sup>198</sup> *Danger Off the Label*, NEWS & OBSERVER (Raleigh, N.C.), Sept. 22, 1997, at A10. The post-approval regulation, or lack thereof, with off-label uses of drugs appears to pose the greatest risk to the public. *Id.* The bill before Congress, HR 1710, does not address this issue. *Id.* Moreover, it would permit manufacturers to promote off-label uses. *Id.* The only monitoring by the FDA is on a voluntary basis. *Id.* The author argues "either give the agency enough resources to monitor drugs' use and effects thoroughly . . . or create an independent agency analogous to the National Transportation Safety Board to keep an eye on prescription drugs." *Id.*

<sup>199</sup> Kolata, *supra* note 195, at F1. "The tale speaks to the limitations of current methods of evaluating drug safety. It speaks to the willingness of some doctors, who see a quick flow of ready cash free from the constraints of managed care, to lure desperate patients, who will do almost anything to lose weight."

On September 24, 1997, the Senate approved legislation that effectively made FDA approval of new drugs an easier and faster process.<sup>200</sup> Consumer groups reacted to this new legislation by saying, "the senators who voted for this bill voted for more drug disasters like fen-phen."<sup>201</sup> Others responded, "[t]he world sometimes can't appreciate a new idea."<sup>202</sup> It is difficult to accept this new legislation when as recently as October 4, 1997, the FDA

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Kolata, *supra* note 195, at F1. The result of the off-label prescription practice is "fen-phen mills." Kolata, *supra* note 195, at F1. The solution may be to require long-term follow-up studies so that serious side effects could be brought to light. Kolata, *supra* note 195, at F1. The process, as it now stands, allows doctors to practice witchcraft. Kolata, *supra* note 195, at F1.

<sup>200</sup> See Helen Dewar & John Schwartz, *Senate Votes to Speed FDA Approval Process for Drugs; Medical Devices*, WASH. POST, Sept. 25, 1997, at A15. The bill was approved by a vote of 98 to 2. *Id.* The two members opposing the bill, Senators Edward M. Kennedy (D-Mass.) and Jack Reed (D-R.I.) voiced their concerns regarding endangering consumers by false labeling products. *Id.* The bill, *inter alia*, (1) requires the FDA to speed approval of new drugs and devices aimed at treating serious illnesses for which there is no therapeutic cure; (2) allows the FDA more discretion over the number of clinical trials that drug companies conduct to test the effectiveness of the drug, which would make it easier to gain drug approval after a single trial; and (3) provides companies with a greater ability to supply doctors with information regarding off-label uses for prescription drugs. *Id.* Companies must commit to further research and agree to seek FDA approval when promoting new and expanded uses. See Marilyn Chase, *FDA Reform May Open A Door to Abuses In Drug Promotions*, WALL ST. J., Sept. 29, 1997, at B1. Therefore, it is not necessarily "[t]urning regulatory red tape into green lights for new drugs." *Id.*

<sup>201</sup> Dewar & Schwartz, *supra* note 200, at A15. Yet advocates contend that the approval of the bill is one of the most important steps forward in recent years. Dewar & Schwartz, *supra* note 200, at A15. Others note that the pressure for approval was substantial because the Prescription Drug User Fee Act, which allows for the prescription drug industry to underwrite the cost of reviews of drugs and enables the FDA to reduce its review time for drugs, was up for renewal. Dewar & Schwartz, *supra* note 200, at A15.

<sup>202</sup> Michael James & Dail Willis, "Father of Fen-Phen" Brushes Off Office Raid; *Timonium Doctor Will Still Prescribe Drug*, BALTIMORE SUN, Oct. 2, 1997, at 1A. Dr. Piotr Hitzig, who prescribes fen-phen (from accrued supplies) to treat obesity, claims that he is providing quality health care. *Id.* However, investigators have seized his records and argue that his practice of prescribing fen-phen over the internet may violate a federal statute which requires that prescriptions be written "in the usual course of professional treatment." *Id.*

confirmed that a woman who was taking fen-phen during her pregnancy caused heart damage to her newborn son.<sup>203</sup> It is rather ironic that President Clinton's Administration continues to assert that, "the final bill represents a significant step toward accomplishing the mutual goal of assuring the agency's optimum performance while protecting the health of the U.S. people."<sup>204</sup>

When given the opportunity, people will seek help for their over-weight condition and find the answer they are looking for in a product on the market.<sup>205</sup> The FDA had many options to choose from to effectively address the adverse side effects attributed to

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<sup>203</sup> Sallie Han & Whitney Walker, *Fen-Phen & Birth Defects*, N.Y. DAILY NEWS, Oct. 4, 1997, at 3. A \$67 million lawsuit was filed in Manhattan by a woman claiming that her son was born with a heart defect due to his exposure to fen-phen in the womb. *Id.* Her baby was born with "blue baby syndrome" (lacking a pulmonary artery) forcing him to undergo open-heart surgery. *Id.* For more information on the effects of fen-phen, pregnant women are invited to call the California Teratogen Information Service at the University of California, San Diego/UCSD Medical Center at (619) 543-2070. *See Diet Pills' Prenatal Effects Studied*, PRESS ENTERPRISE (Riverside, Cal.), Oct. 14, 1997, at C01.

<sup>204</sup> *Progress on U.S. Senate and House FDA Reform Bills*, MARKETLETTER, Oct. 6, 1997, available in 1997 WL 14509968. It becomes increasingly apparent that the Senate values industry profits over public health. *Id.* The House of Representatives and Senate have each passed different bills which attempt to streamline the FDA. *See Undermining the FDA Series: Editorials*, ST. PETERSBURG TIMES, Oct. 14, 1997, at 10A. The House version of the bill would allow companies to promote off-label uses of the drugs that they manufacture. *Id.* The Senate version restricts the government's ability to protect patients from certain medical devices. *Id.* "Under the compromise, drug companies will be able to circulate medical journal articles on unapproved uses of drugs, but only after obtaining FDA clearance. In addition, the companies will be required to study the safety of specific off-label uses and seek FDA approval for them within three years." *See* Bruce Ingersoll, *Congress Clears Bipartisan Bill To Speed FDA Review of New Drugs and Devices*, WALL ST. J., Nov. 10, 1997, at B12.

<sup>205</sup> Sandy Banks, *The Dire Consequences of Pursuing Beauty*, NEWS & OBSERVER (Raleigh, N.C.), Oct. 2, 1997, at E4. "Forget the health risks and get out of our way; we're chasing a dream . . . magic pills with the power to melt away pounds without making you hungry or grumpy or sick." *Id.* Fen-phen has become the tragedy of the times. *Id.* Our society is, without a doubt, weight-obsessed. *Id.* "[W]e've bet on Jenny Craig and Nutri-System, Slim Fast and Dexatrim, Weight Watchers and Overeaters Anonymous. And in the absence of fen-phen, we'll continue to search for that magic bullet." *Id.*



fen-phen use. The agency could have labeled the drugs and limited the dispensing of the drugs in such a way as to prohibit their use in combination or could have limited the dispensing of the drugs to the "morbidly obese."<sup>206</sup> Instead, the FDA approved each drug and blindly allowed their combined use.<sup>207</sup> Granted, FDA approval of a drug does not mean that the user is ensured safety and protected from all possible resulting harm.<sup>208</sup> However, such approval provides some comfort to the user in knowing that the drug has passed numerous animal and clinical studies. Thereafter, the consumer can make a more informed and educated decision regarding use.<sup>209</sup>

Pick your poison as the cycle continues: if it's not one drug, it's another. All of them promise to make one's dream a reality, yet one must realize that the answer to trimming down is not found in a bottle. Despite the widespread use of pharmacologic therapies, the

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<sup>206</sup> Henry I. Miller, *Fen-Phen Flap No Cause For New Regulatory Fat*, WALL ST. J., Sept. 23, 1997, available in 1997 WL-WSJ 14167245. Morbid obesity is defined as "when the patient is more than double his ideal weight and subject to life-threatening complications." *Id.* The FDA might also have required a boxed-warning to patients using either fenfluramine or phentermine. *Id.*

<sup>207</sup> *Phen-Fen Dreams*, BANGOR DAILY NEWS, Sept. 24, 1997, available in 1997 WL 11882815. "[S]o many people blithely gave over their bodies to these serious drugs with the idea of dropping a few pounds." *Id.*

<sup>208</sup> Shute, *supra* note 9, at 7475. Since 1980, 13 drugs have been recalled because they have proven to be unsafe. Shute, *supra* note 9, at 7475. Additionally, an estimated 51% of FDA-approved drugs have major adverse effects that are not detected until used by the general public. Shute, *supra* note 9, at 7475. Nearly 140,000 people each year die from an adverse reaction to prescription drug use. Shute, *supra* note 9, at 7475. For example, Roche Holding Ltd. withdrew its application from the FDA after noting a link between Xenical and precancerous lesions of the breast. See Robert Langreth, *Roche Seeks U.S. Approval For Xenical*, WALL ST. J. (Europe), Nov. 17, 1997, at 3. If it had been approved, Xenical would have been the first "fat-blocker" drug in the United States. See Lawrence G. Proulx, *Diet Drugs At A Glance*, WASH. POST, Nov. 18, 1997, at Z07.

<sup>209</sup> Kathleen Kerr, *Fen-Phen Records: FDA Knew Of Risks-Reports Were Filed On Adverse Reaction*, SUN-SENTINAL, (Ft. Lauderdale, Fla.), Oct. 20, 1997, at 3A. Frighteningly enough, fen-phen was labeled as a suspect medication "in at least 70 deaths reported to the FDA between 1974 and 1997, but those reports were never disclosed" to the public. *Id.*

prevalence of obesity continues to increase, and the results of treatment remain unsatisfactory.<sup>210</sup> In general, maintaining a reduced weight requires exercise and a diet, not necessarily medical supervision or drugs. "Hopefully, doctors, Congress and weight-obsessed Americans will learn [fen-phen's] powerful lesson: There is no magic potion."<sup>211</sup> In an effort to protect the public, the FDA must take an affirmative step to regulate off-label dispensing of drugs.

#### IV. A PROPOSAL TO INCORPORATE OFF-LABEL USES OF DRUGS UNDER FDA REGULATION

The standard for safety and efficacy requires experts to evaluate scientific data in an effort to ascertain if the potential benefits of a new drug outweigh the potential harms.<sup>212</sup> It becomes increasingly apparent that restricting a company's ability to disseminate information about off-label uses of drugs does nothing more than invite other means to achieve the same end. All it really takes is one crafty salesperson to find a loophole in what it means to "distribute" information, and the cycle starts again.

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<sup>210</sup> *Long-term Pharmacotherapy in the Management of Obesity: National Task Force on the Prevention and Treatment of Obesity*, 276 JAMA 1907, 1907-15 (1996).

<sup>211</sup> *The Cult of Thinness*, ST. LOUIS POST-DISPATCH, Sept. 20, 1997, at 30. Although intended only for the obese, weight-loss programs and diet gurus showcased the drug. *Id.* Yet, upon the Mayo Clinic's findings, the drugs were recalled. *Id.* The disastrous effects should be a warning to the Senate that drug companies should be required to market drugs [via FDA approval] which are to be used for off-label purposes. *Id.* The practice has proven far too dangerous to allow drug companies and doctors to effectuate inappropriate prescriptions without empirical evidence to reveal potential negative consequences. *Id.*

<sup>212</sup> See DIXON & WOODSIDE, *supra* note 14, at 8-7. Drug product litigation involving determinations of safety and effectiveness can reasonably be said to be a forum for evaluating methodologies which will have a profound effect, good or bad, upon the health of citizens. See 21 U.S.C. §355(d) (1962) ("If the Secretary finds . . . the reports do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof, he shall issue an order refusing to approve the application.").

The power to distribute off-label drugs effectively makes human beings guinea pigs. While it is somewhat pedantic, it must be reiterated over and over again: physicians are dealing with life and death. Eager consumers are dealing with doctors who are creating miracle drugs without the slightest inkling of any clinical studies to support their hunch. These consumers are hoping that this time will be different, but should we not wonder if there will be a next time? Society relies on the power of medicine and believes in the "magic pills," but our trust is being betrayed by our willingness to abide by a doctor's commands. The stakes are high and the pot is surely not sweet enough to risk life. The need for new regulation becomes increasingly apparent when consumers are offered drug combinations that could ultimately cause them irreparable harm.

*A. An Off-Label Use Of A Drug Should Be Regarded As A New Drug That Falls Under FDA Regulation*

While it is impossible to guarantee either the safety or efficacy of a given drug, a new drug may not be marketed or administered to human beings without FDA approval.<sup>213</sup> A drug may be regarded as "new" if:

- (1) it contains a new chemical substance for medical use;
- (2) it is an established drug offered in new dosage form;
- (3) it is an established drug offered with new medical claims; (4) it is an established drug offered at new dosage levels; and (5) it is an established drug packed in new or novel packaging materials.<sup>214</sup>

The combination of two distinct drugs logically falls under the "new drug" label which requires additional testing on the new pharmacologic compound.

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<sup>213</sup> See *Id.* § 355(a).

<sup>214</sup> DIXON & WOODSIDE, *supra* note 14, at 8-16; See 21 U.S.C. § 321(p) (1994) (stating that in particular, if either the composition of a drug product is not generally recognized as safe and effective among experts qualified by experience and training to deem the item such or a composition is used under such circumstances and according to such conditions that the approval is no longer for that drug product then the combination of two distinct drugs can no longer be regarded as safe and effective without clinical investigations).

It is counter-intuitive to allow doctors to combine potent medications without prior investigations having established that the new product is fit for human consumption. Just as a product must meet U.C.C. guidelines for merchantability,<sup>215</sup> prescription drugs must rise to that standard, if not a higher one, in an effort to protect society from the unknown. Moreover, if a doctor purports to *know of a particular purpose for which the goods are required and there is reliance on his or her skill and judgment*, there is an implied warranty that the goods shall be fit for such purposes.<sup>216</sup> Therefore, the FDA must regulate a doctor's unfettered power to dispense any number of combinations of pills on nothing more than a premonition. If a seller's skill or judgment can be held accountable when the buyer relies on such in accepting goods which later proved ineffective for the specific purpose they were purchased for, should not a doctor be held liable for his or her indiscriminate dispensing of medications when reassuring patients of their effectiveness?

It is common sense that while two distinct entities may separately be legal and pose no substantial danger to anyone, the combination of these two seemingly benign entities can prove deadly. An example for clarification is drinking and driving. Both activities are legal if you are of a certain age and, for the latter, pass state-mandated tests. When combined, the results are disas-

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<sup>215</sup> While the dispensing of prescription drugs does not involve a seller or merchant, the analogy is still applicable. For example, U.C.C. § 2-314 provides that

[g]oods to be merchantable must be at least such as (a) pass without objection in the trade under the contract description; and (b) in the case of fungible goods, are of fair average quality within the description; and (c) are fit for the ordinary purposes for which such goods are used; and (d) . . . [be] of even kind, quality and quantity; and (e) are adequately contained, packaged, and labeled as the agreement may require; and (f) conform to the promise or affirmations of fact made on the container or label if any.

U.C.C. § 2-314 (1977).

<sup>216</sup> See *Id.* § 2-315. The Implied Warranty Of Fitness for a Particular Purpose, while pertaining to sales of goods, appears to be equally applicable to off-label uses of drugs.

trous. Such an outcome is equally applicable to off-label uses of drugs.<sup>217</sup>

The policies discussed earlier in this Note support drastic limitations on the dispensing of drugs for unapproved purposes. A proposal for stricter regulation of off-label uses of drugs would read as follows:

- (1) The manufacturers of a pharmacologic drug licensed by the FDA for sale by prescription shall not be subject to liability for harm caused by the dispensing of drugs for off-label uses.
- (2) Any two drug products, previously FDA approved as separate pharmaceutical agents, that are being dispensed for concomitant use shall be termed a "new drug."
- (3) New drug status will imply the absence of familiarity with the chemical and the expert's inability to assess the safety and effectiveness of the product absent extensive scientific evaluations.
- (4) The NDA will specify in bold letters that THE COMBINATION OF THE DRUGS FOR CONCOMITANT USE IS NOT APPROVED FOR THE NEW INDICATION.
- (5) Any and all combinations of pre-approved drug substances, where that combination has not become generally recognized as safe, are "new drugs." Generally recognized as safe will be defined as: having been exposed to both animal testing and clinical investigations which result in a compilation of studies indicating all effects noted with the drug, either causally or peripherally related.<sup>218</sup>
- (6) New drugs, including new uses for old drugs, must be approved by the FDA through the aforementioned NDA process and regarded as safe and effective for its desired use.
- (7) Similar to the requirements under 21 C.F.R. § 314.50, a NDA for a new chemical entity will contain an application, a summary, a technical section, patient data and case reports, drug samples and proposed language for labeling.

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<sup>217</sup> See *supra* notes 126-209 and accompanying text (discussing the effects and policies underlying fen-phen dispensation).

<sup>218</sup> See generally 21 C.F.R. § 310.303(a) (1974).

(a) The application will contain the name and address of the applicant along with the drug product's name and proposed indications for use via prescription.

(b) The summary will contain a general synopsis of the data and information regarding the empirical findings of studies conducted on the new drug. To the extent possible, tabular and graphic forms are advantageous in gaining a more thorough understanding of the drug's action. The summary shall also include a thorough explanation of the marketing history of all drug products involved including reasons for removal for any reason relating to safety and efficacy. The summary shall conclude with two sections: (i) the potential clinical benefits of the drug product and (ii) the potential side effects of the drug product.

(c) The technical section will contain all of the data and empirical information in sufficient detail in order "to permit the agency to make a knowledgeable judgment about whether to approve the application."<sup>219</sup> This includes: the composition and specification of the new drug; a full description of the drug substance including its chemical make-up; a description of the manufacturing and packaging procedures; assessment of environmental impact; and a section describing the results of animal and in vitro studies with the drug.

(d) The patient component will contain the findings and analysis relating to the clinical pharmacology of the drug. In particular, each study will be addressed separately with an abstract, introduction, methods, results and discussion section. Each separate report will conclude with a section addressing the possible imperfections of the study (i.e. too small of a subject pool, no placebo effect, too many confounding variables, etc.). The entire section will conclude with a report entitled "Evidence That Establishes The Safety and Efficacy Of The New Drug and Noted Adverse Reactions That Accompany The Drug's Use."

(e) The applicant shall submit a sample of the drug product proposed for marketing and the drug substance components that comprise the final product.

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<sup>219</sup> 21 C.F.R. § 314.50(d) (1985).

(f) The proposed label shall contain the proposed regulatory specifications for the drug, directions for use and all side effects (both confirmed or even remotely related to the drug's use).

(8) The NDA will include all phases of animal and clinical testing, pre and post-marketing requirements and periodic reports noting adverse reactions.

(9) The doctor must submit credible evidence, based on robust data and extensive scientific inquiry, that the proposed off-label use, if approved, will benefit society for its intended purpose. Cosmetic enhancement is not an acceptable reason to seek a NDA.

(10) Absent a life-threatening situation, a prescription for the drug shall be conditioned upon: (1) approval of the NDA by the FDA and (2) a thorough physical exam. A life-threatening situation (such as an off-label use of a drug that will cure an inoperable brain tumor on a person with only a short time to live, treatment for a congenital heart disease, AIDS, or cancer) will relax this requirement insofar as the patient will be able to try the new drug upon FDA approval but need not undergo a physical exam.<sup>220</sup> If it is later proven that the condition was feigned in an effort to acquire the drug, both the patient and the physician will be held accountable.

### *B. Reasoning Behind the Proposal*

The Congressional intent behind the establishment of the FDA was to ensure safety.<sup>221</sup> In accordance with such intent, the plain meaning of the term "new drug" encompasses the very act of dispensing off-label uses of drugs. It is true that a new drug product requires a huge expense in terms of money, research and time. However, it is only logical to take steps in an effort to ensure as little risk as possible to the general public prior to the product's

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<sup>220</sup> A life-threatening situation is not amenable to the time constraints imposed by the scheduling of a physical examination. Nor would it be reasonable to have these victims succumb to further examination when they already have been deemed gravely ill. Dispensing of off-label drugs to this very narrow category may prove to be one's last resort to either prevent a further decline in health or possibly improve the current condition.

<sup>221</sup> O'REILLY, *supra* note 15, at 13-2.

marketing, as opposed to having innocent people suffer and the product later recalled amidst numerous litigation suits.<sup>222</sup>

Describing [b]road developments in social-intellectual history reminds us of the context within which the problem of medical mishaps has taken center stage. Modern industrial societies are committed, as never before, to adopting technological innovations wherever these serve the welfare of the individual members. In accepting this general policy, they inevitably expose these individuals to certain novel risks also. In earlier times, the consistent use of "routine and accepted" procedures in all sectors of life had given some people the assurance of knowing in advance both the limited benefits and the limited risks they could expect. Technological progress has raised the stakes on both sides. The availability of new methods holds out the reasonable prospect of major new benefits; but, at the same time, it creates the likelihood that unforeseen hazards will harm some fraction of those people who are on the receiving end of those innovations.<sup>223</sup>

Medicine has historically been distinguished from business and trade simply by appearing "above the market and pure commercialism."<sup>224</sup> We revere our physicians' skill and trust that they will

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<sup>222</sup> See *supra* notes 151-171 (discussing litigation arising from various adverse problems resulting from the use of fen-phen).

<sup>223</sup> Mark Seigler & Mark Sheldon, *Paying the Price of Medical Progress: Causation, Responsibility, and Liability for Bad Outcomes after Innovative Medical Care*, in *MEDICAL INNOVATION AND BAD OUTCOMES: LEGAL, SOCIAL, AND ETHICAL RESPONSES* 8 (Mark Siegler, et al. eds., 1987). The compelling question is, "whether the progressive nature of American medicine and our society should modify our philosophical and legal attitudes toward medical maloccurrences and their compensation." *Id.*

<sup>224</sup> PAUL STARR, *THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE: THE RISE OF A SOVEREIGN PROFESSION AND THE MAKING OF A VAST INDUSTRY* 23 (1982).

Doctors' increasing authority had the twin effects of stimulating and restricting the market. On the one hand, their growing cultural authority helped draw the care of the sick out of the family and lay community into the sphere of professional service. On the other, it also brought political support for the imposition of limits, like restrictive



make decisions that are in accordance with our best interests. With this, we surrender our private judgment for that of another. Laws prohibiting laymen from obtaining certain classes of drugs absent a prescription only serves to increase our dependence on physicians.

"Printer's ink, when it spells out a doctor's promise to cure, is one of the subtlest and most dangerous of poisons."<sup>225</sup> This in no way implies that the sick are the best judge of their own needs. Undoubtedly, scientific knowledge holds a privileged status in our society. However, a problem arises when individuals who possess such knowledge play on the infirmities of their patients.

Doctors are aware of their overweight patient's vulnerability. However, whether a conscious decision or not, doctors are capitalizing on such a characteristic by dispensing drugs for unapproved purposes. Just as we should not put candy in front of a diabetic or liquor in front of a recovering alcoholic, we should not tempt the obese population with an unapproved drug combination that will inevitably lead people down the road of despair.

## CONCLUSION

How often I have wished that I had a willowy body and sculpted features like a movie star. I wished I were not just normal, but thin. Despite idolizing thinner and thinner women, Americans are growing fatter. A third of American

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licensing laws, on the uncontrolled supply of medical services. By augmenting demand and controlling supply, greater professional authority helped physicians secure higher returns for their work.

*Id.* at 24.

<sup>225</sup> STARR, *supra* note 224, at 131. Paul Starr addresses and analyzes what it is that doctors sell as a commodity . . . is it drugs, advice, time or availability? It becomes rather suspect when a profession can so easily turn its authority into economic gain. In particular:

Any physician who advertises a positive cure for any disease, who issues nostrum testimonials, who sells his services to a secret remedy, or who diagnoses and treats by mail patients he has never seen, is a quack. . . . Shut your eyes to the medical columns of the newspapers, and you will save yourself many forebodings and symptoms.

STARR, *supra* note 224, at 131.

adults are now overweight, and many will swallow any cure that comes along. But there's a price in swallowing potentially fatal diet pills.<sup>226</sup>

As we come full circle we once again encounter the question: who will regulate doctors when they are free to prescribe approved drugs for any and all uses they desire? A patient's willingness to try almost anything that a doctor prescribes mandates strict regulation of what can be dispensed. Therefore, it is clear that off-label uses of drugs create a new pharmacologic product that requires FDA approval. The fen-phen disaster should educate the federal health officials to step in sooner in an effort to "prevent [a] tragedy."<sup>227</sup>

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<sup>226</sup> Gail Boyer Hayes, *Paying a High Price For the Promise of Thinness*, WASH. POST, Sept. 16, 1997, at Z15. Nearly one-half of the people that develop pulmonary hypertension die within three to five years, and the remaining individuals are cursed with long-term heart problems. *Id.* Hayes is left questioning, "[W]hy didn't her doctors or federal health officials step in sooner to help prevent this tragedy?" *Id.* "The Food and Drug Administration, with authority to regulate the drug industry, doesn't oversee these experiments, as one might expect." See Richard Whitt, *Clinical Trial & Errors Uncontrolled Experiments Millions of Americans Submit Themselves as Human Guinea Pigs in the Race To Try Out New Drugs*, ATLANTA J.-THE ATLANTA CONST., Nov. 16, 1997, at D01. "Squeezed between the vise-like jaws of public demand for fast approval of the latest wonder drugs and congressional pressure to reduce red tape, the FDA's review process is cursory at best and little more than a rubber stamp at worst." *Id.*

<sup>227</sup> Hayes, *supra* note 226, at Z15. See *Deadly Rx//Experience With Diet Drug Shows Consumers and FDA Must Be Wary*, HARRISBURG PATRIOT (Harrisburg, Pa.), Nov. 19, 1997, at A10.

In short, fen-phen ranks as a major public health fiasco, one that has quickly emerged as a full-employment project for trial lawyers. But the broader questions are: How did this dangerous drug-combination manage to elude the system of checks that every legally sold drug must travel through before it can be sold on the market? Are there other potentially harmful drug combinations that lie in wait for unsuspecting consumers? . . . For its part, the FDA needs to resist political pressures to lower its standards to get drugs to the market faster, especially when . . . plenty of grounds for being cautious and demanding more test trials [exist].

*Id.*

