

# Pushing Drugs: Genomics and Genetics, the Pharmaceutical Industry, and the Law of Negligence

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*Chris Rock:* They got AIDS out there. You think they gonna cure AIDS? No. They can't even cure athlete's foot. They ain't gonna cure AIDS. They ain't never curing AIDS. Ain't no money in curing it. The money's in the medicine. That's how you get paid. Sick people. That's how you fuckin' get paid. Coming back and back . . . fucking cure AIDS. Ha! Curing AIDS! That's like Cadillac making a car that lasts for fifty years. They ain't gonna do that. Ain't no money in that. And you know they can do it. They got metal on the space shuttle that can go around the moon and withstand temperatures of up to fifteen thousand degrees. You mean to tell me you don't think they could make a Cadillac where the fucking bumper don't fall off. They can but they won't. So what they will do with AIDS — same thing they do with everything else — they will figure out a way for you to live with it. That's right. And they don't cure shit, they just patch it up. So what they will do, they will figure out a way for you to live with it.<sup>1</sup>

## I. INTRODUCTION

Like any good satirist, Chris Rock takes the ideas of planned obsolescence and disease control, rather than cure, to their extremes. But again, as with any good satire, Rock's riff has seeds of truth. In this paper, I cultivate two of these seeds: the idea that for a long time pharmaceutical companies have indeed relied for their profitability on drugs that control, not cure, medical conditions, and the notion that there is a rapidly decreasing difference between a pharmaceutical manufacturer and an automobile maker (or, for that matter, any other large producer of consumer goods). Unlike Rock, though, I think the

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1. CHRIS ROCK, *Insurance, Track 11, on BIGGER & BLACKER*, (Dreamworks Records 1999).

science, law, and business of pharmaceuticals will push drug manufacturers to develop and merchandise drugs that may cure, by influencing disease at the level of genetics. Whether this push will produce net social benefit depends upon how riskily pharmaceutical companies merchandise a coming generation of gene-tailored drug therapies.

This article presents a piece of a larger, ongoing project on the phenomenon of market-driven manufacturing (MDM) and how tort law should address it.<sup>2</sup> In contrast to the larger project, this article provides a relatively brief overview of the general phenomenon of MDM, but zeros in on how pharmaceutical manufacturers specifically practice MDM. MDM is a well-documented, much practiced activity,<sup>3</sup> although American courts do not recognize MDM as a discrete category of conduct.<sup>4</sup> The basic idea of MDM is that marketing considerations should continuously control every aspect and stage of a product's lifecycle.<sup>5</sup> When a company engages in MDM, it completely inverts the conception of product design, development, and dissemination that seems natural to those unfamiliar with modern producer practices. Somebody thinking rather loosely about products manufacturing might well think the process goes as follows. A person or group of people notice a need or desire other people seem to have and envi-

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2. See Heidi Li Feldman, *Market-Driven Manufacturing, and Its Challenges for Tort Law: Climates of Risk and the Law of Negligence* (forthcoming 2004).

3. Companies use MDM for all sorts of products. For example, in the early 1990s Lever Brothers Company decided to launch a new soap, notwithstanding already stiff competition in the market for bar soaps. ROBERT J. THOMAS, *NEW PRODUCT SUCCESS STORIES: LESSONS FROM LEADING INNOVATORS* 220, 221 (1995). Despite strong competition from rival products, Lever 2000 became the third largest selling bar soap only one year after its launch. *Id.* at 220. One business analyst attributes this success to the "strategy-driven marketing research and technical product development by [Lever]," the close working relationship between Lever and its advertising agency in the research and development stage of Lever 2000, and a "highly integrated marketing program." *Id.* at 226-27. According to Thomas, the positioning of Lever 2000 as "healthy skin care for the whole family" was delivered through a technically superior product design, the "2,000 body parts" advertising campaign, an effectively designed high tech package, a bar design that was soft and rounded to the touch, heavy sampling to induce trial, heavy couponing to offer value and build repeat purchase, and intensive distribution. The marketing program produced the desired consumer response and led to market success. *Id.* at 227.

4. MDM resembles other potentially tortious acts, in that it can be performed either negligently or non-negligently. We can compare MDM to driving. Driving is a collection of acts that, for tort purposes, are understood as integrated conduct (nobody files claims for negligent steering or negligent checking-the-rearview-mirror). It makes sense to understand driving at a certain level of generality, the level at which the integrated acts together potentially pose excessive risk. So, too, with MDM: its components, which can be conceptually distinguished from one another, should, from a tort perspective, be understood at a higher level of generality, as a non-coincidentally integrated set of acts with the potential to create inappropriate risk. Just as drivers can act negligently or non-negligently, so too can practitioners of MDM. In both cases, it depends on whether they act as a reasonable person of ordinary prudence and caution, with due regard for the safety of others, would act in similar circumstances.

5. As early as 1971, two authors coined the term "social marketing" and defined it as "the design, implementation and control of programs calculated to influence the acceptability of social ideas and involving considerations of product planning, pricing, communication, distribution, and marketing research." Shelby D. Hunt, *The Nature and Scope of Marketing*, in *PROMOTIONAL MANAGEMENT: ISSUES AND PERSPECTIVES* 2, 3 (Norman Govoni et al. eds., 1988) (quoting Philip Kotlar & Gerald Zaltman, *Social Marketing: An Approach to Planned Social Change*, 35 *J. MARKETING* 5 (1971)).

sion a product that would fulfill the need or gratify the desire. These people then invent that product and manufacture it. The inventors/manufacturers then turn to other people to get their product into a distribution chain — wholesaler to jobber to sales representatives to retailers, for example. The retailers sell the product to the ordinary consumer.

MDM essentially turns this simple picture upside down. A modern corporation often starts by fanning or instilling desires or needs in the general population, thereby stimulating or creating demand for a product the company has not yet fully envisioned.<sup>6</sup> Only after development of demand does the company invest in design, tailoring its product to the now-felt needs and desires that the company itself has promoted.<sup>7</sup>

In addition to developing demand before producing product, a company engaged in MDM does not hold itself at the distance from the ultimate consumer envisioned by the unreflective picture of manufacturing.<sup>8</sup> Modern companies often gain information about consumers and adapt consumers' needs and desires by working very closely with retailers — the people closest to those who will actually buy products. Furthermore, practitioners of MDM exercise careful control over wholesalers and retailers, trading availability of their product in exchange for information about end users and opportunities to promote directly to them. The unreflective take on manufacturing pictures it acontextually, most notably ignoring the way in which MDM includes influencing the political process and legal system,<sup>9</sup> at all levels, to make it easier to create and stimulate demand and to avoid consequences of creating risks leading to injury. Practitioners of MDM organize the process of MDM from the top down, often hiring full service public relations consultants to coordinate and integrate all aspects of MDM.<sup>10</sup>

This article explores the relationship between pharmaceutical MDM and the fledgling field of pharmacogenomics — the development of drugs based on the explosion of basic research into the human genome and human genetics in the past thirty years. This basic research is just that — basic — yet it is also regarded as the most fertile ground for developing drugs to cure or prevent ailments and condi-

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6. The need for MDM grew as American producers saturated the market with “obviously” desirable consumer goods. See WILLIAM LEACH, *LAND OF DESIRE: MERCHANTS, POWER, AND THE RISE OF A NEW AMERICAN CULTURE* xiii, 382-85 (1993).

7. See generally Neil H. Borden, *The Concept of the Marketing Mix*, in *PROMOTIONAL MANAGEMENT: ISSUES AND PERSPECTIVES*, *supra* note 5, at 16, 18.

8. See Thomas A. Petit & Martha R. McEnally, *Putting Strategy Into Promotion Mix Decisions*, in *PROMOTIONAL MANAGEMENT: ISSUES AND PERSPECTIVES*, *supra* note 5, at 24, 26.

9. Borden, *supra* note 7, at 20.

10. See Wilbur Schramm, *How Communication Works*, in *PROMOTIONAL MANAGEMENT: ISSUES AND PERSPECTIVES*, *supra* note 5, at 45, 55.

tions that have been controllable at best, and untreatable at worst. Pharmacogenomic drugs are alluring. They promise health benefits to everybody and renewed financial strength to the pharmaceutical sector.

At the same time, as with many drugs, this generation of pharmaceuticals will carry risks to health as well as benefits. When new drugs come out, it is often difficult to predict their actual effectiveness or to anticipate major detrimental side effects from taking them. Some of this uncertainty arises from the nature of science itself.<sup>11</sup> But much of it arises from the financial incentives for drug companies to hurry new drugs to market in a relatively weak administrative-regulatory environment. This riskiness has always been a by-product of drug development. MDM, however, exacerbates the risks to health posed by pharmaceuticals based on novel science because MDM operates to increase demand for risky products while simultaneously downplaying the dangers they pose. MDM also involves ensuring that the administrative regulation of pharmaceuticals remains lax. This creates an opportunity for a powerful industry that promises people one of the most basic human goods — health — to cultivate demand for, and then develop and promote, drugs that may well pose more danger than benefit.

Notwithstanding this state of affairs, tort law, our legal system's most fundamental, most traditional method for addressing such situations, does not currently provide recourse to those injured by pharmaceutical MDM. This is because current tort law does not, so to speak, "see" MDM in general, and certainly has not recognized it in the pharmaceutical context.<sup>12</sup> The problem is heightened because phar-

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11. See Heidi Li Feldman, *Science and Uncertainty in Mass Exposure Litigation*, 74 TEX. L. REV. 1 (1995).

12. In litigation against gun manufacturers, private plaintiffs have articulated something like a claim for negligent MDM. See *Hamilton v. Accutec*, 62 F. Supp. 2d 802, 817-46 (E.D.N.Y. 1999) (explaining in a post trial memorandum and order the details of the negligence theory under which the action proceeded and reporting damages awarded by trial); *Hamilton v. Accutec*, 935 F. Supp. 1307, 1332 (E.D.N.Y. 1996) (dismissing shooting victims' tort claims against gun manufacturers on theories of products liability and ultra-hazardous liability, but permitting cause of action to proceed on negligence theory alleging negligent marketing that fostered the trade in illegal sale of handguns); *Hamilton v. Beretta U.S.A. Corp.*, 750 N.E.2d 1055, 1059-66 (N.Y. 2001) (declaring, in response to a certified question, that, under New York state law, plaintiffs in *Hamilton v. Accutec* had failed to state a cause of action because defendant gun manufacturers do not owe any duty of care to shooting victims). On March 7, 2003, a trial court judge in San Diego dismissed a lawsuit brought by a dozen cities and counties. Alex Roth, *Bulk of Firearms Lawsuit Set Aside: California Cities Fail to Make Their Case*, SAN DIEGO UNION-TRIB., Mar. 8, 2003, at A1. Unlike the *Hamilton v. Accutec* litigation, however, this case was not brought on a negligence theory but under a theory of public nuisance, as has been attempted in other municipal suits against gunmakers. See *id.*; see also PETER HARRY BROWN & DANIEL G. ABEL, 20 OUTGUNNED: UP AGAINST THE NRA (2003). Some government litigation against pharmaceutical companies for economic loss seems to cast the companies' wrongdoing in terms of problematic MDM. See *infra* text accompanying notes 83-87. Regardless of the disposition of these claims involving economic harm, I maintain the need for a cause of action for negligent MDM resulting in physical injury.

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maceutical MDM involves biological knowledge alien to most laypeople, including courts.

Basic tort doctrine suggests that to recover for a negligently inflicted injury one brings a cause of action for negligence. In practice, however, there is no generic cause of action for negligence. When a plaintiff brings suit on a negligence theory, the plaintiff complains of *particular conduct* he alleges the defendant executed negligently. For example, in a suit arising from an automobile accident, the plaintiff pleads negligent driving, not simply negligence, as the conduct for which the defendant should be held liable. Likewise, if a surgeon leaves a sponge in a patient, she will be sued for medical malpractice rather than general negligence.

It is one thing to comprehend MDM as discrete conduct, but if one also appreciates that excessively risky MDM may in some cases result in injuries, then one can see the need for courts and legislatures to recognize a specific cause of action for negligent MDM. Courts and legislatures could even take a more particularistic approach. Suppose judges and legislators fear excessively risky MDM in some manufacturing sectors but not others: courts and legislatures could recognize causes of action for negligent MDM in selected sectors, e.g., permitting a cause of action for negligent pharmaceutical MDM or negligent handgun MDM. My point is not that courts and legislatures ought to be quite so incremental, but that this option is entirely consistent with the structure of tort doctrine.

Because this article focuses on the conduct of, financial challenges faced by, and business opportunities available to the American pharmaceutical industry, I start with an examination of this industry and the way in which the budding field of pharmacogenomics now creates both high upside and high downside risks for the industry and the consumers it serves. After surveying the business and scientific climate in which pharmaceutical companies now operate, I will explain pharmaceutical MDM, using an illustrative case study of Pfizer and its blockbuster drug Neurontin. Finally, having established that pharmaceutical MDM is a likely candidate for excessively risky MDM, I will spell out how a cause of action for negligent MDM by a pharmaceutical company might look, including the defenses a company might raise. Pharmaceutical MDM need not inevitably be excessively risky MDM, a point I will demonstrate by discussing ways to engage in MDM non-negligently.

This last item is crucial. Not all MDM of pharmaceuticals is negligent. I am not arguing against MDM for new drugs generally, or against MDM for new drugs based on genomics and genetics. To the extent that these drugs will enhance human health, they have the po-

tential to contribute to human flourishing, just as many older pharmaceuticals have. Historically, tort doctrine has recognized this high-benefit/high-risk aspect of medicinal drugs, and tort law has shielded drug companies from liability imposed on other sorts of products manufacturers.<sup>13</sup>

Increasingly, however, pharmaceutical companies are behaving like other makers of consumer goods, particularly powerful producers of highly profitable product lines. Like other such merchandisers, pharmaceutical companies now engage in practices such as direct marketing and advertising to consumers of drugs, and the constant introduction of newer, slightly modified versions of already existing drugs, in an effort to generate demand for products that may not be medically necessary. They deploy public relations campaigns meant to woo physicians into prescribing their products. They utilize the full range of legal mechanisms to protect their operations. The more drug companies act as run-of-the-mill merchandisers do, the less fair it is to allow these companies to exploit legal protections afforded them because they have traditionally been perceived to be unlike other merchandisers.

Both economic and legal factors have inspired pharmaceutical companies to behave like traditional makers of consumer goods. Patents on drugs vital to health have long expired; patents on drugs that definitely enhance health are about to expire; drugs the companies are ready to patent now are not in any way critical to health; and a new generation of medically significant drugs — the generation based on genomics — is not yet producing income for pharmaceutical companies.

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13. For example, the pharmaceutical industry's products were always exempted from strict products liability. A comment to Section 402A of the Second Restatement of Torts specified that the strict liability contemplated in the black letter of the Section did not apply to legal drugs.

*k. Unavoidably unsafe products.* There 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 drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. The 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.

RESTATEMENT (SECOND) OF TORTS § 402A cmt. k (1965).

We can anticipate that modern merchandising practices, in combination with advances in pharmacogenomics, will enable drug companies to bring the next generation of pharmaceuticals — drugs tailored to treat disease at the genetic level — out of the laboratory and into consumers' hands relatively quickly. The effectiveness of modern merchandising and the relative immaturity of the science behind this generation of drugs together give rise to a problem tort law both should and must address. When producers and consumers are both intent on availability and use of a comparatively poorly understood yet risky product, the odds of personal injury go up. How high they go depends in part on whether the common law of tort permits juries to decide whether a merchandiser has acted negligently in its development and promotion of a drug.

In essence, the current state of affairs in the pharmaceutical industry, and the absence of a cause of action for negligent MDM, encourages drug makers to perform natural experiments on human subjects (sell drugs to patients), subjects who have been primed to participate by the experimenters (using MDM), experimenters who stand to gain much financially simply by running the experiment (selling the drugs), knowing that, at least for now, tort law makes it difficult for anybody injured in the experiment to state a valid claim, let alone win damages.

## II. A CASE STUDY OF PHARMACEUTICAL MDM

From the mid-twentieth century to the century's end, the pharmaceutical industry enjoyed two major rounds of success. The first included the development of antibiotics and vaccines; the second, the development of drugs to control, if not cure, chronic serious health problems such as depression, high cholesterol, and high blood pressure. By the beginning of the twenty-first century, however, drug companies were no longer reaping such large profits from these two waves of drug development. Both legal and market forces have led to the decline. On the legal side, patent protection for many twentieth century "wonder drugs" has expired.<sup>14</sup> On the market side, both pri-

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14. Drug companies fight extremely hard to preserve patent protection. See, e.g., Milt Freudenheim, *Ruling Backs Some Patents on a Leading Ulcer Drug*, N.Y. TIMES, Oct. 12, 2002, at C14 (reporting AstraZeneca's success in demonstrating patent infringement on Prilosec by three generic drug manufacturers; Prilosec is one of the world's best-selling prescription drugs). "This ruling vindicates our very strong belief in our intellectual property, [said a spokeswoman for AstraZeneca]." *Id.* Before the expiration of Prilosec's original patent (not the one at issue in the aforementioned lawsuit), Prilosec, or omeprazole, was literally the world's best-selling drug, reaping at least \$6 billion in worldwide sales. *Id.* Aside from seeking to extend and expand patent protection for Prilosec, AstraZeneca is "trying to persuade doctors to switch patients from Prilosec to a similar successor drug, Nexium." *Id.* This matters because in the ruling stating that some generics makers had infringed AstraZeneca's patents, the judge also ruled that one generic version of Prilosec does not infringe any patents, opening the door to production of a lower cost version of the drug. *Id.*

vate and public insurers have pressured physicians, pharmacies, and patients to use generics or less expensive versions of branded drugs, part of a larger effort to control health care costs overall.<sup>15</sup> Hospitals too are trying to escape traditional purchasing systems that are financed by pharmaceutical manufacturers.<sup>16</sup> They seek independent bargaining power to negotiate lower drug costs.<sup>17</sup>

So, the pharmaceutical industry has lost some luster, both in terms of the sector's stock performance and in terms of maintaining a reputation for producing "wonder drugs." Manufacturers have addressed the decline in profitability through a combination of tactics, which create a climate infused with risk of harm, one that will only be exacerbated when the first pharmacogenomic drugs hit the market. For example, drug companies routinely pay insurance plans to increase the use of their products: the drug company pays the insurance plan to add its drug to lists of recommended drugs that are distributed to physicians and pharmacies.<sup>18</sup> Drug companies also give physicians and pharmacies direct financial reward for switching a patient from a rival's product to their own.<sup>19</sup> While many companies use these and other components of MDM for their pharmaceuticals, one drug maker, Pfizer, has used MDM to become, according to the *Financial Times*, the "world's largest pharmaceutical group."<sup>20</sup> "Pfizer has become the first company to capture more than 10% of the worldwide prescription pharmaceutical market."<sup>21</sup> This success is not unrelated to Pfizer's much remarked upon MDM.

In 2002, Pfizer was named "Marketer of the Year," according to a pharmaceutical trade publication, with "the company . . . exceeding its nearest competitor's annual sales by \$2.4 billion based on sales of Pfizer drugs and jointly promoted products."<sup>22</sup> Pfizer is on the verge of getting bigger through a shareholder-approved acquisition of Pharmacia, in a deal worth \$57 billion.<sup>23</sup> As is, Pfizer leads the drug market in central nervous system therapies, merchandising drugs to treat ailments such as depression, epilepsy, insomnia, and migraine

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15. See, e.g., Ron Winslow et al., *States, Insurers Find Prescriptions for High Drug Costs*, WALL ST. J., Sept. 11, 2002, at A1.

16. Mary Williams Walsh, *More Hospitals Change the Way They Buy Drugs and Supplies*, N.Y. TIMES, Dec. 28, 2002, at C1.

17. *Id.*

18. Robert Pear, *Drug Makers Battle a U.S. Plan To Curb Rewards for Doctors*, N.Y. TIMES, Dec. 26, 2002, at A1.

19. *Id.*

20. Ellen Kelleher, *Pfizer Wins Drug Approval*, FIN. TIMES, Dec. 30, 2002, at 19.

21. Frank Scussa, *Unparalleled*, MED. AD. NEWS, Sept. 1, 2001, at 149.

22. Andrew Humphreys, *Marketer of the Year: Pfizer; Touched by Pfizer; This Company Turns Drugs Into Highly Successful Brands*, MED. AD. NEWS, Mar. 1, 2002, available at 2002 WL 11845459.

23. Kelleher, *supra* note 20, at 19.

headaches.<sup>24</sup> With the addition of Pharmacia's drug portfolio, Pfizer will become a significant supplier of "drugs for cancer, ophthalmology, and endocrine disorders."<sup>25</sup>

Originally developed by Warner-Lambert, Neurontin is presently the number one acute epilepsy drug on the market and an important revenue generator for Pfizer.<sup>26</sup> Pfizer acquired the drug when it took over Parke-Davis, which had previously acquired Warner-Lambert. "Used by [over] 7.7 million patients in 75 countries, [Neurontin] generated sales of \$1.75 billion in 2001."<sup>27</sup> To ensure the continued success of Neurontin, Pfizer has engaged in three major practices to promote its usage. Pfizer has creatively attempted to extend patent protection; promoted Neurontin through direct ads to consumers; and encouraged "off-label" use of the drug. Pfizer's efforts have paid off handsomely. In December 2002, "Pfizer, Inc., reported that third-quarter net income increased by 12% to \$2.452 billion."<sup>28</sup> When asked what makes Pfizer's marketing strategy so successful, Pat Kelly, Senior Vice President of Worldwide Marketing, responded that "we practice integrated marketing. We integrate all the channels of marketing that we use with a common message and common approach."<sup>29</sup>

Claiming an infringement on two Neurontin patents, Pfizer brought suit against Apotex Corporation in the United States District Court for the Northern District of Illinois. With little discussion, the court found no genuine issue of material fact in Pfizer's patent infringement claim, granting summary judgment in favor of the defendants.<sup>30</sup> Additionally, the Health and Benefit Trust Fund of the International Union of Operating Engineers, AFL-CIO,

has filed an anti-trust [case] in the U.S. District Court for the Southern District of New York claiming illegal overcharges made for Neurontin. . . . According to the complaint, Warner-Lambert and Pfizer have maintained false patent-infringement lawsuits against potential generic competitors for Neurontin . . . for the purpose of delaying and preventing generic competition.<sup>31</sup>

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24. *Id.*

25. *Id.*

26. *Pfizer Faces Legal Actions Over Top-Selling Products*, MED. AD. NEWS, June 1, 2002, at 14 [hereinafter *Pfizer Faces*].

27. *Id.*

28. *Pfizer, Inc.: Pharmaceutical Announces Strong Third-Quarter 2002 Results*, BIOTECH WK., Dec. 4, 2002, at 45. "Revenues of \$8.725 billion in the third quarter of 2002 were up 12%, compared with the third quarter of 2001, paced by human pharmaceutical revenues of \$7.058 billion in the quarter, which grew 13%." *Id.* Neurontin figured significantly in this jump. "Eleven products — Lipitor, Norvasc, Neurontin, Viagra, Zolof, Celebrex, Bextra, Geodon, Aricept, Zyrtec, and Diflucan — representing 82% of Pfizer's human pharmaceutical revenues grew a combined 17%." *Id.*

29. Andrew Humphreys, *Breaking the Marketing Mold*, MED. AD. NEWS, Mar. 1, 2001, at 1.

30. *Warner Lambert Co. v. Apotex Corp.*, No. 98-C-4293, 2001 WL 1104618 (N.D. Ill. 2001); *Warner-Lambert Co. v. Apotex Corp.*, No. 98-C-4293, 1999 WL 259946 (N.D. Ill. 1999).

31. *Pfizer Faces*, *supra* note 26, at 14.

The AFL-CIO case has been consolidated with seventeen other cases for pretrial proceedings.<sup>32</sup> Original patents for Neurontin expired in 1994 and 2000. “In April 2000 however, a U.S. patent was granted for stable pharmaceutical compositions of Neurontin containing low levels of lactam impurity.”<sup>33</sup> Five generic manufacturers have filed abbreviated new drug applications to market generic versions of Neurontin. Although Pfizer seems likely to continue to fight for extended patent protection,<sup>34</sup> “[s]ales of Neurontin are predicted to decrease almost \$300 million after the product is exposed to generics, which is expected to occur in 2003.”<sup>35</sup> Pfizer, however, has already secured patent protection until 2017 on one version of Neurontin.<sup>36</sup>

Pfizer has sought patent protection for Neurontin against the following regulatory environment. In 1984, Congress sought to balance interests in the pharmaceutical industry by passing the 1984 Hatch-Waxman Act.<sup>37</sup> It included “patent protection and research incentives for brand-name drug makers,” along with incentives to encourage companies to sell less expensive generic versions of name-brand drugs once the name-brand patents expire.<sup>38</sup> However, loopholes in the law have allowed companies to prolong the typical twenty-year patent and keep generic alternatives out of consumers’ reach.

Companies can get an automatic 30-month extension [of a patent] simply by filing suit against a generic manufacturer asserting that the generic product will infringe secondary patents on packaging and other minor items.

In some cases, manufacturers have been able to get even longer extensions by filing multiple patent-infringement suits [and gaining sequential 30-day extensions].<sup>39</sup>

Following the lead of a Senate bill introduced the previous summer (a bill not acted upon by the House to date),<sup>40</sup> in the fall of 2002, President Bush proposed regulations to expedite approval of low-cost generic versions of prescription drugs.<sup>41</sup> According to President Bush’s proposed rule, “when a brand-name manufacturer believes that a generic product has infringed its patents, it can delay approval

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32. See *In Re Neurontin Antitrust Litig.*, 217 F. Supp. 2d 1380 (J.P.M.L. 2002) (finding that all seventeen cases alleged that Warner-Lambert and its parent, Pfizer, “violated anti-trust laws and excluded generic competition for [Neurontin] by bringing sham patent infringement actions against a number of generic drug manufacturers”).

33. *Pfizer*, MED. AD. NEWS, Sept. 1, 2002, at 150.

34. *Pfizer Faces*, *supra* note 26, at 14.

35. *Id.*

36. *Pfizer*, *supra* note 33, at 150.

37. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

38. Robert Pear, *Bush Seeks Faster Generic Drug Approval*, N.Y. TIMES, Oct. 22, 2002, at A24.

39. *Ending a Drug Patent Scam*, N.Y. TIMES, Oct. 22, 2002, at A30.

40. See Pear, *supra* note 38, at A24.

41. *Id.*

of a generic copy [only once] for 30 months, while a court tries to resolve the dispute.”<sup>42</sup> “In addition, the proposal would forbid brand-name companies from getting new patents for three kinds of reasons, including redesigned pill packages, that the FTC concluded were frivolous and used mainly to forestall competition.”<sup>43</sup> Critics fault Bush’s recommendations for failing to address “the agreements under which brand-name drug companies sometimes pay generic companies to keep low-cost generic versions off the market.”<sup>44</sup>

While the effort to plug the loopholes of Hatch-Waxman and place other constraints on brand-name drug manufacturers may limit the role of patent protection in MDM of pharmaceuticals, so far Pfizer has relatively successfully used the patent system to protect Neurontin. While Neurontin may face generic competitors in 2003, Pfizer’s efforts have prevented generic versions from reaching the market for three to nine years longer than contemplated under the original patents.<sup>45</sup>

Most people in the United States have noticed that drug companies advertise their products on television, radio, and in print media.<sup>46</sup> These ads encourage patients to ask their doctors if such-and-such a drug is right for them. Physicians report that patients do indeed ask for particular branded drugs, sometimes influenced more by the pitch than the product’s actual medical purpose.<sup>47</sup>

“Among all pharmaceutical companies, Pfizer ranked No. 2 in consumer expenditure through October 2001, at \$301.5 million, representing 12.6% of the industry’s \$2.4 billion consumer expenditure.”<sup>48</sup> “Pfizer markets eight prescription brands that generate more than \$1 billion in annual sales. [It] spends more than any other company on

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42. *Id.*

43. Amy Goldstein, *Bush Plan to Increase Generic Drugs Draws Flak*, WASH. POST, Oct. 22, 2002, at A6.

44. Pear, *supra* note 38, at A24.

45. According to one industry journal:

By listing patents with the Food and Drug Administration that do not claim the FDA approved form of the drug or its approved uses, . . . [Pfizer] has been able to delay generics competition for 18 months past the expiration of [Neurontin’s] basic patent. The potential lost savings to Americans by this delay has already amounted to approximately \$825 million.

Furthermore, by strategically timing the submission of patents to the FDA, [Pfizer] effectively converted the automatic 30-month stay of generic approvals into 54 months of additional market exclusivity.

Kathleen Jaeger, *Access to Affordable Generics Saves Billions of Dollars*, CHAIN DRUG REV., Aug. 5, 2002, at Rx28.

46. In a survey conducted by The Intermedia Advertising Group, the most-remembered television ads for prescription drugs during the 2001-02 television season were for the following drugs: Viagra, Flonase, Procrit, Vioxx, Lipitor, Zyrtec, Celebrex, Nexium, and Paxil. Viagra ads, the most remembered, were produced by Cline, Davis & Mann. Allison Fass, *Marketing Medicine*, N.Y. TIMES, July 22, 2002, at C8. Note that Cline, Davis & Mann is the same agency that markets Neurontin for Pfizer. See *infra* text accompanying note 53.

47. See, e.g., Erin N. Marcus, *When TV Commercials Play the Doctor*, N.Y. TIMES, Jan. 3, 2003, at A21 (discussing how prescription drug ads can create frivolous demands).

48. Humphreys, *supra* note 22.

product promotion, and outspends the closest company by about \$600 million in research and development.”<sup>49</sup> Apart from just toting up total numbers spent on product promotion and development, pharmaceutical industry publications report specific ways Pfizer leverages its global promotional apparatus to squeeze the most value from its products.<sup>50</sup> Its field and marketing personnel, spread throughout the world, number in excess of thirty thousand employees.<sup>51</sup> For direct-to-consumer advertising, Pfizer spent \$250 million in 2000; this was the third largest expenditure on this item in the pharmaceutical industry as a whole.<sup>52</sup>

Cline, Davis & Mann (CDM), one of the most admired full service agencies in the health care advertising industry, won the Neurontin account in 1996.<sup>53</sup> In 1987, CDM created a group, CDM Consumer, specifically charged with developing demand for the products developed by pharmaceutical companies. Over the years, CDM has managed many aspects of consumer-oriented MDM: it “has experience across a broad range of categories, including over-the-counter products, direct-to-consumer advertising of prescription products, . . . and prescription to over-the-counter switches” for specific drugs.<sup>54</sup> CDM provides these services via a concerted, trademarked, personnel-coordinated system called StrategySession. StrategySession deploys multi-disciplinary teams comprised of advertising specialists and representatives from the client’s organization.<sup>55</sup> This team format enables CDM to fully integrate the marketing of clients such as Pfizer — that is, to accomplish MDM.<sup>56</sup>

Although physicians have total regulatory freedom to supply any drug approved by the Food and Drug Administration (FDA) for any use, the FDA forbids drug companies from marketing a drug for indications other than those for which the drug has won FDA approval.<sup>57</sup> This ban applies to marketing to physicians as well as to consumers, although pharmaceutical companies may “share research and journal articles with doctors that discuss unapproved uses.”<sup>58</sup> When physi-

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49. Scussa, *supra* note 21, at 149.

50. *See, e.g., id.*; *see infra* text accompanying notes 70-79.

51. Scussa, *supra* note 21, at 149.

52. *Id.*

53. Frank Scussa, *Cline, Davis & Mann, Inc.*, MED. AD. NEWS, Apr. 1, 2002, at 46.

54. *Id.*

55. *Id.* These experts often comprise team members from agency account, creative, media and research groups.

56. *Id.*

57. Associated Press, *Group Sues Pharmacia Over Drug Promotion* (Dec. 24, 2002), available at [http://www.1800lawinfo.com/practice/news.htm?story\\_id=3986&topic=bextra](http://www.1800lawinfo.com/practice/news.htm?story_id=3986&topic=bextra).

58. *Id.*

cians prescribe a medication for a condition other than the one(s) recognized by the FDA, the practice is known as off-label usage.<sup>59</sup>

Originally, Neurontin was FDA-approved only for epilepsy.<sup>60</sup> In 2002, Pfizer gained approval for Neurontin as a treatment for managing pain associated with shingles, the only additional FDA-approved use for the drug.<sup>61</sup> Currently, the Boston United States Attorney's Office, "47 states[,] and the District of Columbia are investigating" potentially illegal promotion of off-label usage of Neurontin during the period Warner-Lambert merchandised the drug.<sup>62</sup> Discovery has uncovered memoranda from 1995 and 1996 documenting the decision by Warner-Lambert's "new product committee" not to conduct large clinical trials required for FDA approval of Neurontin for treatment of migraines and social phobia.<sup>63</sup> The committee decided instead to perform small studies and place the results in medical journals.<sup>64</sup> A 1995 company memorandum stated "that 25 percent of Neurontin prescriptions were" for off-label usage.<sup>65</sup> In 2001, the majority of all Neurontin prescriptions written in the United States — roughly three-quarters of them — were for off-label uses.<sup>66</sup> Sales figures for Neurontin in 2001 were \$1.75 billion.<sup>67</sup> In 2002, it appears that approximately eighty percent of Neurontin prescriptions were written for conditions other than epilepsy, the FDA-approved indication;<sup>68</sup> and early estimates show that Neurontin has reached two billion dollars in sales in 2002.<sup>69</sup>

The memoranda documenting the activities of Warner-Lambert executives were released by the attorney for a private plaintiff, Dr. David Franklin, M.D. — a former Parke-Davis "medical liaison"<sup>70</sup> — now suing Pfizer.<sup>71</sup> According to press reports, Franklin, "alleges he was forced to participate in a national marketing campaign in which

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59. Off-label usage is both common and, in some cases, controversial. For example, Pharmacia, the company about to merge with Pfizer, has recently been sued by a California senior citizens group alleging "that Pharmacia hired Scirex, a clinical testing firm owned in part by Omnicom, a large advertising conglomerate, to study Bextra for use in cases of acute pain caused by impacted molars." *Id.* The FDA has approved Bextra for chronic pain associated with a variety of conditions, but not pain caused by dental problems. *Id.* In fact, the FDA had specifically refused Pharmacia's request for Bextra for acute pain due to impacted molars. *Id.*

60. Melody Petersen, *Memos Cast Shadow on Drug's Promotion*, N.Y. TIMES, Dec. 20, 2002, at C2.

61. *Id.*

62. *Group Sues Pharmacia Over Drug Promotion*, *supra* note 57.

63. Petersen, *supra* note 60, at C2.

64. *Id.*

65. *Id.*

66. Liz Kowalcyk, *Pfizer Drug Strategy Probed States Question Marketing Tactics for Neurontin*, BOSTON GLOBE, Oct. 18, 2002, at D2.

67. *Id.*

68. Petersen, *supra* note 60, at C2.

69. *Id.*

70. *United States ex rel. Franklin v. Parke-Davis*, 147 F. Supp. 2d 39, 44 (D. Mass. 2001).

71. David Armstrong & Charles Forelle, *Health & Technology: Drug Officials May Have Broken Rules on Neurontin*, WALL ST. J., Dec. 20, 2002, at B4.

he and others made exaggerated or false claims about the safety and efficacy of the drug.”<sup>72</sup> Franklin also claims that “illegal promotion of the drug defrauded the federal government out of hundreds of millions of dollars in Medicaid payments.”<sup>73</sup>

Other documents uncovered in Franklin’s suit and reported in the press further detail Warner-Lambert’s MDM strategy: allegedly, the company provided ghost-written journal articles for physicians to publish under their own names and rewarded the largest potential prescribers with all-expense paid weekend trips to a Florida beach resort (in addition to expenses, each physician allegedly received a \$250 honorarium).<sup>74</sup>

Franklin claims that he recorded a manager telling company medical liaisons, “When we get out there, we want to kick some ass. We want to sell Neurontin on pain. All right?”<sup>75</sup> According to media reports, the unsealed documents in the litigation also reveal how “Parke-Davis [now Pfizer] hired Medical Education Systems [(MES)] of Philadelphia to draft 12 articles and opinion letters on antiepileptic drug therapy.”<sup>76</sup> Parke-Davis’ agreement with MES “gave Parke-Davis the right to select the authors of the articles, receive prepublication copies of the articles and suggest changes to them.”<sup>77</sup> According to the company memos, as described in the media,

MES compiled a list of topics, such as the use of antiepileptics for pain and psychiatric illness, and proposed physicians to act as authors. The company paid the doctors \$1,000 each to review and revise drafts written by MES and lend their names to the articles . . . . In an Oct. 29, 1997, memo, MES told Parke-Davis that it still was trying to track down Dr. John Pellock of the Medical College of Virginia for an article about pediatric seizure disorders: “Author interested; still playing phone tag. MES HAS DRAFT COMPLETED, WE JUST NEED AN AUTHOR.”<sup>78</sup>

It was also reported that Dr. Franklin revealed he was “told to cold-call doctors and sell them on the off-label benefits of Neurontin while at Warner-Lambert.”<sup>79</sup>

In addition to the civil actions against Pfizer, the federal Justice Department is investigating whether Pfizer made illegal payments to Medicaid providers, including an enquiry into the “prescribing prac-

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72. *Id.*

73. *Id.*

74. Liz Kowalczyk, *Drug Company Push on Doctors Disclosed*, BOSTON GLOBE, May 19, 2002, at A1 (noting further that the Neurontin marketing team wrote that doctors who attended the conference “were delivered a hard-hitting message about the drug”).

75. *Id.*

76. *Id.*

77. Armstrong & Forelle, *supra* note 71, at B4.

78. Kowalczyk, *supra* note 74, at A1.

79. Jon Chesto, *Suit Questions Off-label Sales of Neurontin*, BOSTON HERALD, May 18, 2002, at 20.

tices of individual doctors for dates before and after their exposure to specific marketing practices. . . . In Massachusetts, Medicaid spending on . . . Neurontin grew from \$1.1 million in 1996 to \$14.1 million in 2000, the height of the marketing campaign.”<sup>80</sup> “Newly unsealed court documents reveal that some physicians, in exchange for money, have allowed pharmaceutical sales representatives into their examining rooms to meet with patients, review medical charts and recommend what medicines to prescribe.”<sup>81</sup> This “shadowing program” enables Pfizer to promote both approved and off-label uses.<sup>82</sup> The program “involved an estimated 75 to 100 doctors in several Northeast states . . . . Each doctor was paid \$350 or more for each day they let sales representatives watch as they examined patients, according to court documents.”<sup>83</sup>

Despite this flurry of inquiry, Pfizer remains alert to opportunities to market Neurontin and its other drugs. Pfizer has moved into health-care practice management<sup>84</sup> — presumably seeking the benefit of vertically integrating the distribution of their drug products through managed care providers controlled by Pfizer. To increase the appeal of Pfizer’s drugs directly to doctors, Pfizer, working with IBM and Microsoft, plans to “provide physicians with an integrated suite of Web-enabled software and devices to minimize paperwork” involved in prescription and insurance practices.<sup>85</sup>

Nevertheless, political, economic, and legal pressures make protection of existing drugs something of a rearguard action. The pharmaceutical industry as a whole is looking to a new wave of drugs, based on pharmacogenomics, to protect the long-term profitability of the sector. Presumably, Pfizer, which tops the industry by an extra \$600 million per year spent on research and development, is also hoping to develop gene-tailored therapies, drugs meant to cure and prevent disease by intervening at the genetic level of the human organism.<sup>86</sup> Researchers and manufacturers alike see such drugs (genuceuticals) as the wave of medicine’s future.

### III. TOWARD PHARMACOGENOMICS: MAPPING THE HUMAN GENOME

Two major organizations have mapped the human genome. One is a publicly financed international consortium called The Human

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80. Kowalczyk, *supra* note 74, at D2.

81. Melody Petersen, *Suit Says Company Promoted Drug in Exam Rooms*, N.Y. TIMES, May 15, 2002, at C1.

82. *Id.*

83. *Id.*

84. Scussa, *supra* note 21, at 152.

85. *Id.*

86. *Id.* at 149.

Genome Project (HGP);<sup>87</sup> the other a private corporation called Celera.<sup>88</sup> The relationship between these two groups, their efforts to map the genome, and the public policy issues raised by their competition to complete a useable map, all bear upon the drug companies' prospects of cashing in on human genomics.

The Human Genome Project began before Celera's efforts. The organizers of HGP did not anticipate competition from the private sector, primarily because the technology and knowledge required to map the human genome seemed sufficiently costly to develop and obtain that it seemed unlikely any private actor could compete with the highly sophisticated international consortium's efforts. This hypothesis turned out to be wrong. A combination of excellent fund-raising and good science enabled Celera to become a serious candidate for mapping the human genome before HGP.

While the competition between the two entities almost certainly accelerated the pace of scientific progress — as is typical in scientific enterprise more generally — the competition forced both parties to address significant and difficult choices, including whether and when to cooperate with each other, whether to attempt to patent any or all of the human genome, and whether to fight the patentability of the genome by anybody. HGP's mission had never been for-profit, but because Celera seemed prone to trying to patent the genome and findings related to it, those heading HGP also considered seeking patents. By doing so, they could then license the use of their findings and technology more extensively and at far less (perhaps zero) cost than a private company like Celera would be expected to, if Celera were willing to license its findings at all. Alternatively, either HGP or Celera might fight any patent application proffered by the other on the grounds that the proposed patent, say of a particular gene sequence, was not in fact a patentable entity. While in the short term that would mean that the winner of such a case would also lose the right to seek that sort of patent, in the long term the loss might be worth it, if the winner thought its venture would achieve a clearly patentable entity first — especially if the patent application in dispute revealed information that would be useful to further research. Basically, HGP and Celera were playing a many-layered game of chicken.

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87. The publicly financed international consortium consisted of eight laboratories. These included the Whitehead Institute in Cambridge, Massachusetts, the Washington University School of Medicine in St. Louis, Missouri, and Baylor College of Medicine in Houston, Texas. *Feds Pay to Push Genome Project*, WIRED NEWS, Mar. 17, 1999, at <http://www.wired.com/news/technology/0,1282,18520,00.html>. International HGP funding partners include the United Kingdom, France, Germany, Japan, and China. NICHOLAS WADE, *LIFE SCRIPT: HOW THE HUMAN GENOME DISCOVERIES WILL TRANSFORM MEDICINE AND ENHANCE YOUR HEALTH* 24 (2001).

88. For further information, see Celera's homepage at <http://www.celera.com>.

Happily, from a public policy perspective, neither HGP nor Celera sought patents on their most basic research findings. I say happily because the public availability of these findings makes it easier for those who want to use basic scientific findings in genomics and genetics to produce practical goods — especially beneficial pharmaceuticals — and to do so without having to incur potentially crippling up-front costs to gain access to these findings. From an ethical perspective, too, it seems inappropriate to attempt to patent a map of the human genome. I will not pursue the argument here, but I would claim it ethically wrong to privatize the basic information about what human beings so fundamentally share — a species-wide genetic heritage.

#### IV. GENOMICS MEETS GENETICS AND YIELDS PHARMACOGENOMICS

“A 1998 study of hospitalized patients published in the *Journal of the American Medical Association* reported that in 1994, adverse drug reactions accounted for more than 2.2 million serious cases and over 100,000 deaths, making adverse drug reactions (ADRs) one of the leading causes of hospitalization and death in the United States.”<sup>89</sup> One reason for the high rate of such adverse reaction is that, traditionally, drug companies have not been able to tailor drugs to differences in physiology due to genetic variation in individuals.

To produce drugs that treat disease at the genetic level requires two types of basic science. One is *genomics*, the acquisition and study of information encoded in the human genome.<sup>90</sup> Because the human genome has only recently been mapped to a meaningful degree (previous maps are drafts), and because the technology necessary to interpret the maps is very young,<sup>91</sup> genomics remains in its infancy. The other basic science necessary is *genetics*, understood most generally as the study of heredity, and, more specifically, as the study of the inheritance of particular traits.<sup>92</sup> Armed with information about an individual’s genome, which she shares with other members of her species, and information about the arrangement and expression of her particular genes, biomedical researchers have begun a new science — pharmacogenomics.<sup>93</sup>

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89. NAT’L CTR. FOR BIOTECHNOLOGY INFO., *JUST THE FACTS: A BASIC INTRODUCTION TO THE SCIENCE UNDERLYING NCBI RESOURCES, ONE SIZE DOES NOT FIT ALL: THE PROMISE OF PHARMACOGENOMICS*, at <http://www.ncbi.nlm.nih.gov/About/primer/pharm.html> (last revised Feb. 13, 2003) [hereinafter *JUST THE FACTS*].

90. MARK H. RICHMOND, *HUMAN GENOMICS: PROSPECTS FOR HEALTH CARE AND PUBLIC POLICY* 6 (1999).

91. This technology is known as bioinformatics and is the science of developing computer technology to analyze genomes.

92. RICHMOND, *supra* note 90, at 6.

93. “Pharmacogenomics is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a

One potential promise of genomics is the development of techniques that would enable physicians, working with geneticists, to pinpoint how a person will respond to a drug (this includes both positive and negative reactions). Without knowing all of the genes involved in drug response, scientists have found it difficult to develop genetic tests that could predict a person's response to a particular drug. Presumptively, a fuller understanding of the genome will alleviate this difficulty.<sup>94</sup> But a significant obstacle to gene-tailored pharmaceuticals is that drug reaction is a multigenic trait, the sort of genetic trait whose nature is most difficult to ascertain.<sup>95</sup> Furthermore, the best gene-tailored pharmaceuticals should take account not only of genomics but also genetics, specific information about gene expression in particular individuals. To appreciate the challenges faced by current pharmacogenomics, it helps to have some additional understanding of the basic science of genomics and genetics.

Each organism on earth has a genome, shared by organisms of that type. A genome "contains all of the biological information needed to build and maintain a living example of that organism."<sup>96</sup> Genomes specify the uniqueness of organisms through the biological information encoded in the deoxyribonucleic acid (DNA) that is the stuff of the genome. In turn, some of this DNA is "divided into discrete units called genes."<sup>97</sup> "Genes code for proteins that attach to the genome at the appropriate positions and switch on a series of reactions called gene expression."<sup>98</sup>

Protein coding genes matter because they instruct cells to perform functions that result in variation in organisms. Human protein coding genes, for example, instruct the human organism's skin cells to make human skin, human stomach cells to make human stomach, and so forth.<sup>99</sup> The coding regions of the human genome constitute less than five percent of the total genome.<sup>100</sup> With a map of the human

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patient will have a good response to a drug, a bad response to a drug, or no response at all."  
JUST THE FACTS, *supra* note 89.

94. RICHMOND, *supra* note 90, at 18.

95. JUST THE FACTS, *supra* note 89.

96. NAT'L CTR. FOR BIOTECHNOLOGY INFO., A BASIC INTRODUCTION TO THE SCIENCE UNDERLYING NCBI RESOURCES, WHAT IS A GENOME?, at [http://www.ncbi.nlm.nih.gov/About/primer/genetics\\_genome.html](http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html) (last revised Feb. 20, 2003) [hereinafter WHAT IS A GENOME?].

97. *Id.*

98. *Id.*

99. PETER LITTLE, GENETIC DESTINIES 13 (2002).

100. Scientists estimate the number of genes in a genome by looking for certain tell-tale signs of genes in a DNA sequence. These include: open reading frames, stretches of DNA, usually greater than 100 bases, that are not interrupted by a stop codon such as TAA, TAG or TGA; start codons such as ATG; specific sequences found at splice junctions, a location in the DNA sequence where RNA removes the noncoding areas to form a continuous gene transcript for translation into a protein; and gene regulatory sequences. This process is dependent on computer programs that search for these patterns in various sequence databases and then make predictions about the existence of a gene.

genome — and bioinformatic tools with which to navigate it — scientists can begin to correlate genes with traits, including diseases or predispositions to disease.

Even with good navigational tools, correlating genes with traits is extremely difficult. Very few human traits, including diseases or susceptibility to them, correlate to a single gene.<sup>101</sup> Instead, traits result from a complex interaction between genes that code for different proteins, as well as extra-genetic environmental factors.

Furthermore, individual members of the human species vary in their traits, ranging from recognizable differences in hair and eye color to less apparent ones such as blood type. When two individuals display different phenotypes (or expressions) of the same trait — e.g., eye or hair color — they have two different alleles for the same gene. This means that the gene's sequence is slightly different in the two individuals, and the gene is polymorphic. So, while people generally have the same genes, the genes do not have exactly the same DNA sequence.<sup>102</sup> Thus, we end up with genetic variation among members of a single species.

In contrast to genomics, which explores genetic information at the level of the species (and large populations within a species), the science of genetics explores genetic variation among individual members of a species.<sup>103</sup> One cause of genetic variation at this level is mutation, a change in the DNA sequence of a gene. Biomedical geneticists pay particular attention to mutations because a mutation can cause disease or predispose an organism to disease.<sup>104</sup> “When the information coded for by a gene changes, the resulting protein may not function properly or may not even be made at all. In either case, the

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WHAT IS A GENOME?, *supra* note 96.

101. Multigenic traits result from the expression of several different genes.

This is[, for example,] true for human eye color, in which at least three different genes are responsible for determining eye color. A brown/blue gene and a central brown gene are both found on chromosome 15, whereas a green/blue gene is found on chromosome 19. The interaction between these genes is not well understood. It is speculated that there may be other genes that control other factors, such as the amount of pigment deposited in the iris. This multigenic system explains why two blue-eyed individuals can have a brown-eyed child.

*Id.*; see also LITTLE, *supra* note 99, at 45 (“In practice, there are relatively few features of human beings that are defined by a single-gene difference.”).

102. LITTLE, *supra* note 99, at 13.

103. Subspecialties of genetics include molecular genetics, which explore genetic variation at the biochemical level, examining the molecular structure of the genes embedded in DNA, and cytogenetics, which examines “the relationship between human cells . . . and heredity.” NAT'L CTR. FOR BIOTECHNOLOGY INFO., A BASIC INTRODUCTION TO THE SCIENCE UNDERLYING NCBI RESOURCES, MOLECULAR GENETICS: PIECING IT TOGETHER, at [http://www.ncbi.nlm.nih.gov/About/primer/genetics\\_molecular.html](http://www.ncbi.nlm.nih.gov/About/primer/genetics_molecular.html) (last revised Feb. 20, 2003) [hereinafter MOLECULAR GENETICS].

104. RICHMOND, *supra* note 90, at 12.

cells containing that genetic change may no longer perform as expected.”<sup>105</sup>

To understand the relationship between genes, heredity, and disease in humans requires an in-depth understanding of individual people’s karyotypes, a size-order alignment of chromosome pairs in a chart. To the extent geneticists can read a good chart in detail, they can connect chromosomes (which carry genes) to particular symptoms and traits. Obtaining a reasonably useful chromosomal chart has taken almost fifty years; and we still lack a fully useful chart for purposes of understanding how chromosomes, genes, and mutation work together to produce the traits expressed in individual human beings.<sup>106</sup>

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105. MOLECULAR GENETICS, *supra* note 103. For example, mutations in the gene that codes for the cholesterol receptor protein that are associated with a disease called Familial Hypercholesterolemia. The cells of an individual with this disease end up having reduced receptor function and cannot remove a sufficient amount of low density lipoprotein (LDL), or bad cholesterol, from their bloodstream. A person may then develop dangerously high levels of cholesterol, putting them at increased risk for both heart attack and stroke.

*Id.*

106. Early efforts to align the chromosome pairs were rudimentary. By 1959, about all that could be discerned was an extra or missing chromosome. Throughout the 1960s, pioneering cytogeneticists amassed techniques for capturing chromosomes at their most visible state. For most of a cell’s existence, the chromosomal material is unwound and unable to absorb dyes. It is only during cell division that the chromosomes condense and become detectable. Researchers learned that treating cells with a hypotonic solution would cause them to swell, spreading apart the tangle of chromosomes. Another chemical agent, colchicine, was found to stop cell division when the chromosomes were at their most striking state. A third chemical, phytohemagglutinin, was found to entice lymphocytes, the blood cells most accessible for chromosomal study, to divide.

*Id.*

Even with these tools, scientists still found it difficult to distinguish chromosome pairs. [R]esearchers had to rely on such large-scale and subjective clues as chromosome size and position of the centromere, a characteristically located constriction in each chromosome. Even staining the chromosomes distinguished unequivocally only four of the 23 chromosome pairs. These pairs were then grouped crudely by size, and only large sections of extra or missing chromosomal material could be discerned. By the 1970s, combining stains with digestive enzymes yielded far more subtle shading patterns, revealing the distinctive characteristic of each chromosome. Several different treatments were also developed that allowed researchers to further define the patterns of each chromosome. Now, tiny inversions — reversals in the banding pattern — duplications, deficiencies, and translocations — chromosomes that swap parts — could be detected. But building a karyotype required many hours of skilled work. The karyotyping procedure involved obtaining blood or some other appropriate tissue, separating out dividing cells, growing them in culture, fixing them, and then dropping them onto a microscope slide. Then, using a light microscope, a researcher had to find a cell in which all of the untangled chromosomes were present and a photograph was taken. A print was then developed, and the individual chromosomes were cut out and arranged in pairs by size order into a chart, referred to as the karyotype. It is literally a scissors-and-tape operation and . . . many cytogenetics laboratories still depend chiefly on this method of chromosome analysis. But now an automatic chromosome analyzer — a system that includes a camera, a computer, and a microscope — may radically speed and improve the accuracy of the chromosome views.

*Id.*

People continue to fashion new techniques for chromosomal analysis. One apparently promising approach is fluorescence in situ hybridization (FISH).

[FISH] uses fluorescent molecules, called dyes, to “paint” genes on a chromosome. This technique is particularly useful for gene mapping and for detecting various chromosomal abnormalities. In this procedure, short sequences of DNA complementary to

While both genomics and genetics have advanced, we do not have from either science complete and fully comprehensible maps of human beings, at either the species level or the individual level. The human genome is not entirely mapped and much of it is poorly understood; obtaining and interpreting karyotypes remains difficult. In fact, the same consortium behind the original Human Genome Project has just embarked on a \$100 million project to produce a new kind of genomic map, one intended to “hasten discovery of the variant genes thought to underlie common human diseases like diabetes, asthma and cancer.”<sup>107</sup>

This is not to deny biomedical advances based on genomics. Prior to the development of the latest maps of the human genome, most sequencing and analysis technologies — the methods for developing chromosomal maps — were developed from studies of nonhuman genomes, notably those of the bacterium *Escherichia coli*, the yeast *Saccharomyces cerevisiae*, the fruit fly *Drosophila melanogaster*, the roundworm *Caenorhabditis elegans*, and the laboratory mouse *Mus musculus*.<sup>108</sup> A large amount of genetic information has already been derived from these organisms, providing valuable data for the analysis of normal human gene regulation, genetic diseases, and evolutionary processes. For example, researchers have already identified single genes associated with a number of diseases, such as cystic fibrosis.<sup>109</sup> As research progresses, investigators hope to uncover the mechanisms for diseases caused by several genes, or by single genes interacting with environmental factors.<sup>110</sup> Genetic susceptibilities have been implicated in many major disabling and fatal diseases, including heart disease, Alzheimer’s, epilepsy, stroke, diabetes, and sev-

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the sequence of interest, called probes, are hybridized to the sample DNA. Because the probes are labeled with fluorescent tags, a researcher can see the exact location of the DNA sequence of interest on a chromosome. An additional advantage of FISH is that it can be performed on nondividing cells, making it much more versatile than traditional karyotyping.

Scientists can actually create three types of FISH probes, each of which has a different application. Locus-specific probes hybridize to a particular region of a chromosome and are useful for detecting the location of a gene on a chromosome. Alphoid, or centromeric repeat probes, are generated from repetitive sequences found at the centromeres of chromosomes. Because each chromosome can be painted a different color, researchers use these probes to determine whether an individual has the correct number of chromosomes. Whole chromosome probes are actually collections of smaller probes, called libraries, that each hybridize to a different sequence along the same chromosome. Using these libraries, researchers can paint an entire chromosome with various colors, generating what is called a spectral karyotype. These types of probes are useful for examining both large- and small-scale chromosomal abnormalities.

*Id.*

107. Nicholas Wade, *Gene-Mappers Take New Aim at Diseases*, N.Y. TIMES, Oct. 30, 2002, at A23.

108. WADE, *supra* note 87, at 27. James D. Watson, one of the co-discoverers of the structure of DNA, encouraged the HGP to map these genomes. *Id.*

109. RICHMOND, *supra* note 90, at 7.

110. *Id.* at 6-10.

eral kinds of cancer.<sup>111</sup> The identification of these genes and their proteins could pave the way to more effective therapies and preventive measures.<sup>112</sup> This is certainly the hope of pharmaceutical manufacturers hoping to capitalize on the advances in basic research in both genomics and genetics. Yet scientists still cannot reliably determine the genetic causes of most diseases, since most diseases are multigenic.<sup>113</sup> Genuceuticals for most diseases remain elusive.

## V. TORTS WAITING TO HAPPEN

Pharmaceutical companies are already positioned to gain a wide variety of information about the people who have consumed drugs prescribed by their physicians.<sup>114</sup> Ironically, some of the impetus for drug manufacturers to keep track of at least the identities of the end users came from the famous tort litigation, *Sindell v. Abbott Laboratories*,<sup>115</sup> involving the drug diethylstilbestrol (DES).<sup>116</sup> In *Sindell*, the California Supreme Court allowed each defendant's liability to be a rebuttable presumption: if a given defendant could prove that it was *not* the cause of a particular plaintiff's injuries, it would not be held liable.<sup>117</sup> Furthermore, the court held the defendants severally liable; if one defendant was insolvent, the other named defendants would not be liable for the insolvent defendant's portion.<sup>118</sup> So, *Sindell* permitted a defendant to avoid paying any damages to a particular plaintiff, if it could prove it was not the company that had supplied DES to her mother, or to exonerate itself from paying some damages if it could show that the DES ingested by a plaintiff's mother was made by a now insolvent defendant. Presumably, one effect of the imposition of Cali-

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111. *Id.* at 10.

112. *Id.* at 12.

113. The leaders of the consortium want to proceed with a new map due to difficulties in current methods of identifying the genetic bases of multigenic diseases. Wade, *supra* note 107, at A23.

114. RICHMOND, *supra* note 90, at 60.

115. 607 P.2d 924 (Cal. 1980).

116. In *Sindell*, the daughters of women who had taken DES sued all the major makers of the drug even though practically no injured plaintiff could identify which specific manufacturer had made the DES pills taken by her mother. Identification was impeded by the indistinguishability of the pills themselves and the lack of records kept by either pharmacies or drug companies as to which company's DES was prescribed to any particular patient. By the time the plaintiffs' injuries manifested, it was virtually impossible for them to identify the *specific* manufacturer of the drug taken by their respective mothers, but it was scientifically beyond question that DES caused serious medical injury to the plaintiffs. *See id.* at 925-27. The California Supreme Court adopted a theory of recovery called market-share liability, which permitted DES daughters to sue DES manufacturers and recover on a modified theory of joint and several liability. *Sindell* required the plaintiffs to name as defendants those manufacturers who were responsible for a substantial percentage of the DES market. *See id.* at 937. In addition, the court allowed each defendant's liability to be a rebuttable presumption: if a given defendant could prove that it was *not* the cause of a particular plaintiff's injuries, it would not be held liable. *See id.* For example, if evidence showed that the pills ingested by a given plaintiff's mother were pink, and a defendant's pills were white, the defendant could escape liability.

117. *See id.* at 937-38.

118. *See id.* at 938.

ifornia-style market share liability has been to spur pharmaceutical companies to keep better records of the end-users of their products; also presumably, this has meant negotiating feedback from pharmacies who seek supply from drug companies. As pharmaceutical companies gain genomic and genetic knowledge, they will be able to use this information to target people whose need for one drug suggests that they may have a predisposition for another health problem. This opens the field for highly personalized MDM of genuceuticals.

It also creates the opportunity for the following sort of scenario, just one possible way MDM of genuceuticals can create a new or heightened climate of risk leading to physical injury. For the sake of argument, let us assume the following hypothetical situation. Suppose Neurontin turns out to have a hitherto unknown latent dangerous effect: it causes a genetic mutation in the sons of fathers or mothers who have ingested Neurontin. This mutation predisposes the male offspring of Neurontin-takers to a virulent form of testicular cancer. Having contracted this form of cancer, Emerson Whittaker (a fictional plaintiff) brings suit against Pfizer for negligent MDM of Neurontin. Whittaker's father Guillermo took Neurontin for ten years, up to, and including, the time Emerson was conceived. Because Guillermo suffered from a neurological condition discovered to be genetically correlated with migraine, and because Pfizer had access to Guillermo's pharmacy records, Pfizer sent Guillermo glossy mailers about Neurontin, showing people who obviously were not suffering from migraine. Guillermo mentioned the mailer to his physician, Antonia Burrus, who had in fact been planning to suggest Neurontin to him for his migraine condition, in any event. Dr. Burrus was under contract to medical care organizations (MCO) controlled by Pfizer. In fact, she was among those identified by Pfizer as likely prescribers of Neurontin for migraine, and she attended various Pfizer-sponsored conferences at beachside resorts and received several honoraria for attending.

Emerson does not have a cause of action for malpractice against his father's physician because the practice of prescribing Neurontin for migraine was extremely widespread at the time Guillermo took the drug.<sup>119</sup> To recover for his injuries, Emerson must win a case against Pfizer. To prevail in a suit against Pfizer, Emerson must establish that Pfizer breached its duty<sup>120</sup> to behave as a reasonable person

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119. The standard of care for physicians is set by custom and is the standard of medical care provided by fellow physicians in like circumstances.

120. See RESTATEMENT (THIRD) OF TORTS: LIABILITY FOR PHYSICAL HARM § 6 cmt. b (Tentative Draft No. 2, 2002).

of ordinary prudence who acts with due care for the safety of others.<sup>121</sup>

Emerson could point to the MDM of Neurontin to establish breach. He would argue that alternative, safer treatments for migraine existed, but that Pfizer had created a demand for Neurontin for this indication and then met this demand. But note that Pfizer could defend itself. It may be that Pfizer could show that no alternative treatment had a better track record than Neurontin; Emerson, however, could well respond that MDM, particularly Pfizer's repeated efforts to gain extended patent protection for Neurontin, created an unreasonable barrier to entry for companies that might have invested in treatments for migraine.

Pfizer would be much better positioned to defend itself against Emerson's claim of breach if it had not engaged in such heavy duty MDM for Neurontin. Not every drug is pushed as hard as Neurontin. Additionally, Pfizer could have engaged in measures to offset the arguably excessive risk created by its MDM of Neurontin. For example, Pfizer itself could have worked to develop alternative treatments for migraine.

My point here is not to construct every possible support for or defense to a claim of negligent MDM. Nor is my goal to explore all the elements of a negligence action alleging tortious MDM of Neurontin. This brief hypothetical simply illustrates how a drug company can engage in MDM as a person of ordinary caution and prudence, with due regard for the safety of others, or it can fail to do so. If cogent legal arguments can be brought to bear on this issue, then a cause of action for negligent pharmaceutical MDM poses no special difficulties for courts to administer.

## VI. CONCLUSION

The symposium for which this article was written has as its theme "genetics and ethics in the courtroom." My paper challenges the American judiciary to accept the ethical responsibility of developing a cause of action that addresses risk created by advances in the sciences of genetics and genomics as these advances are put to use by pharmaceutical manufacturers. Without such a cause of action, conduct likely to create significant risk of personal injury will go legally unchecked. This raises immediate issues of corrective justice. But permitting or denying such a cause of action has deeper ethical dimensions. Permitting negligence actions against pharmaceutical manufacturers when they engage in conduct that, at least arguably, unduly increases the

121. *See id.* § 6(b) ("[A]n actor whose failure to exercise reasonable care is a factual cause of physical harm is subject to liability for any such harm within the scope of liability.").

climate of risk says something about how these manufacturers should act when merchandising their wares. How persons (natural or fictional) should act, whether they should be accountable for their actions, and if so, to whom, and in what manner — these are quintessential ethical concerns.

With the completion of the government-sponsored Human Genome Project and the corporation Celera's private effort to map the human genome, much of the basic research is in place for the development of a new generation of pharmaceuticals. Scientists anticipate that increased knowledge of genomics in general, together with increases in specific information about an individual person's genetic make-up, will enable the invention of drugs that either act at the molecular genetic level directly, or which specifically target genetically identifiable diseases and address them via biochemical mechanisms tailored to that level. Were such drugs available, safe, and effective, so much the better. While we can definitely expect their availability, we have much less reason to expect them to be safe and effective, especially in the first generation of gene-specific pharmaceuticals. Furthermore, not only should we expect that pharmaceutical companies will make available gene-specific drugs that pose undue risk, we should anticipate that pharmaceutical companies will engage in massive, systematic efforts to coordinate the design, manufacturing, marketing, and distribution of these drugs to end users — patients. Thus, the stage is set for a new round of pharmaceutically induced injuries.

Due to political and economic realities, the FDA and other administrative bodies are unlikely safeguards against this round of mass injury. The tort system will be called upon to play its traditional role in correcting wrongful injuries caused by pharmaceutical manufacturers, with the side effect of deterring continuing causation of excessively risky drug development and distribution. Yet the tort system is not ready to handle the types and volume of injuries that can be expected from the market-driven manufacturing of gene-specific pharmaceuticals. To get ready, jurists and commentators need to understand and appreciate the scientific and financial forces behind the potentially tortious behavior of pharmaceutical companies; modern methods of development and distribution of drugs; the gaps in current tort law that reduce its effectiveness in the face of these facts; and the ethical and legal issues at stake.

