




1999

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Recommended Citation

Steven C. Carlson, *COMMENTARY: The Case Against Market Exclusivity for Purified Enantiomers of Approved Drugs*, 1 *YALE J.L. & TECH* (1999).

Available at: <https://digitalcommons.law.yale.edu/yjolt/vol1/iss1/6>

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COMMENTARY: The Case Against Market Exclusivity for Purified Enantiomers of Approved Drugs

Steven C. Carlson*

I. INTRODUCTION

Advances in synthetic chemistry offer pharmaceutical manufacturers a novel means of extending their monopolies over proprietary drugs beyond the 20-year limit of the patent laws. Pharmaceutical companies now have the capability to produce superior drugs by purifying existing drugs into their isomer components. The Food and Drug Administration (FDA) is considering whether to grant new drug status to these purified compounds, and to afford them several years of market exclusivity.¹ This Comment argues that the FDA should not extend such market exclusivity to purified isomers of existing drugs.

THE SCIENCE

Many chemicals come in two forms called enantiomers. Enantiomers are mirror images of each other, differing structurally only in the spatial arrangement of atoms around a chiral (i.e., asymmetric) center. They are termed “right-handed” or “left-handed” based upon their geometry. When both forms of enantiomers are present in a drug, the drug is said to be racemic, or a racemate. Enantiomers have essentially identical physical properties except when acting in chiral environments. Technology has lacked the means until recent years to permit large-scale synthesis and/or purification of single enantiomers.

Enantiomers often act differently from one another in the chiral environment of the human body. Bodily proteins are typically right-handed, and often recognize right-handed drugs more readily than left-handed ones.² Thus, enantiomers of racemic drugs often exhibit different pharmacokinetic properties, with one being less therapeutic or more toxic as compared to the other.³ Enantiomeric drugs are especially valuable in those cases where the opposite enantiomer imparts toxicity upon the racemic parent.⁴

THE REGULATORY STRUCTURE

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¹ See Policy on Period of Marketing Exclusivity for Newly Approved Drug Products with Enantiomer Active Ingredients; Request for Comments, 62 Fed. Reg. 2167 (1997) [hereinafter Enantiomer RFC].

² See DONALD VOET & JUDITH G. VOET, *BIOCHEMISTRY* 64 (2d ed. 1995).

³ See Chirality Is the Science of One Hand Clapping, *GENESIS REPORT-RX*, June 1, 1997 [hereinafter *Science of Chirality*].

⁴ In the case of allergy drugs, for example, the brand-name drug Seldane, a racemate, was found to exhibit toxic side effects not associated with its subsequently developed enantiomer, Allegra. The FDA removed Seldane from the market upon the availability of Allegra. See Laura Johannes & Thomas M. Burton, *Son of Prozac: A New, Purer Version Of Top Antidepressant Is in Eli Lilly's Sights*, *WALL ST. J.*, Dec. 7, 1998, at A1.

It provides numerous incentives for the creation of novel pharmaceuticals. The FDA grants a five-year period of market exclusivity for new drugs,⁵ and a three-year period for new drugs that contain active ingredients of previously approved drugs.⁶ This grant of market exclusivity is independent of the incentives offered by the patent laws.

The FDA offers limited incentives for the production of enantiomer-based drugs, currently encouraging their production by offering them a relaxed new drug approval process. It does not require such drugs to be resubmitted to many of the tests that are mandatory for approval of the parent racemate.⁷ These reduced requirements permit approval of enantiomer-based drugs to occur in four-to-six years instead of the customary ten-to-fourteen years for pioneer drugs.⁸ The FDA, however, does not currently recognize enantiomer-based derivatives of existing drugs as “new drugs.” As such, it currently does not grant a period of market exclusivity to enantiomeric compounds once a parent drug has already garnered such protection.

Drug companies argue that the FDA should reverse this policy and should reward the development of enantiomeric drugs by granting producers limited market exclusivity.⁹ The FDA has opened a formal comment period to consider whether it should grant up to five years of market exclusivity to producers of enantiomers that are derived from already-approved compounds.¹⁰

THE ARGUMENT IN FAVOR OF EXCLUSIVITY

Manufacturers of brand name drugs are urging the FDA to offer a five-year grant of exclusivity for the development of enantiomers that are derived from already-approved drugs. These manufacturers correctly underscore the importance of developing chiral drugs. The two enantiomers of racemic drugs can exhibit radically different properties in the chiral environment of the human body. In many racemates, such as Seldane,¹¹ one enantiomer is therapeutic while the other is toxic. Production of enantiomers of existing drugs is a sensible way to utilize existing scientific and regulatory knowledge to boost the performance of today’s pharmaceuticals.

Manufacturers of brand name drugs assert that a period of market exclusivity is essential to create incentives to produce these drugs. They argue that firms must invest significant resources to identify those compounds that are most promising for enantiomeric development, and must dedicate further resources to shepherd the enantiomers through the FDA approval process. Firms will not be willing to make these investments, the argument goes, if they have no guarantee of exclusivity at the end of

⁵ See 21 U.S.C. § 355(c)(3)(D)(ii) (1994).

⁶ See 21 U.S.C. § 355(c)(3)(D)(iii) (1994).

⁷ See *Science of Chirality*, supra note 3 (quoting Dean Handley, Ph.D., Director of Scientific Affairs, Sepracor, Inc.) (“The FDA has basically said that if you have an established drug on the market and you want to make a racemic switch to a single enantiomer (one-isomer drug), we’ll help you out. You can avoid 2-year carcinogen immunogenicity studies, sigma I and 3 [sic] reproductive studies, immunogenicity studies, and huge Phase III studies.”).

⁸ See *id.*

⁹ See Bruce Downey, Chairman, President, and CEO, Barr Laboratories, Testimony Before House Commerce Committee, Apr. 23, 1997 [hereinafter Downey Statement] (refuting proposals of brand-name drug industry), available in 1997 WL 10570067.

¹⁰ See Enantiomer RFC, supra note 1.

¹¹ See Johannes & Burton, supra note 4.

the approval process. Otherwise, rival firms would identify the compounds that have already gained approval and “free-ride” off the investments made by the original sponsor through exploitation of the abbreviated new drug application process.

A SUPERFLUITY OF INCENTIVES

The current proposal is unnecessary because it is superfluous. The FDA already promotes creation of enantiomer-based drugs through a relaxed new drug approval process. As mentioned above, the FDA offers a dramatically shortened approval process for enantiomeric versions of approved drugs.

The promise of patent protection also creates vast incentives for the production of chiral drugs. The Patent and Trademark Office (PTO) has granted patents on a number of enantiomeric versions of already-approved compounds.¹² Enantiomers of existing drugs qualify for an additional twenty years of patent protection if it can be shown that the enantiomer exhibits unanticipated characteristics. By following a patent on a pioneer drug with a patent on that drug’s enantiomers, brand name drug manufacturers can secure up to a 40-year monopoly for their products. The Wall Street Journal recently reported on just this strategy behind the marketing of Prozac.¹³ While the patentability of these compounds raises troublesome policy issues, the willingness of the PTO to grant patent protection for purified enantiomers creates major incentives for their production.

Furthermore, basic marketing strategies create incentives for the development of chiral drugs. When firms have already established the brand name of a racemic parent, it makes good business sense to extend these brand names through the production of new, improved versions of these compounds. Firms can secure this marketing advantage cheaply by virtue of the scientific knowledge and regulatory experience gained through development of the racemic parents.

Finally, fear of tort liability also drives the production of enantiomeric drugs. Pharmaceutical firms are foregoing the development of racemates in favor of using enantiomers in order to avoid liability for unforeseen toxicity concerns.

Production of racemates has now become “a high risk route.”¹⁴ Through all the above incentives, manufacturers of brand name drugs have ample “carrot and stick” incentives that drive the development of chiral drugs. As a result of these incentives, chiral chemistry is booming. It has been estimated that 75% of the pharmaceuticals marketed in the United States by the year 2000 will be single-isomer compounds.¹⁵ Demand for chiral chemistry is at an all-time high, with emerging growth in the agrochemical and the optical materials markets as well.¹⁶ The costs of synthesizing, purifying, and analyzing chiral chemicals are down, rendering the argument that it is too expensive

¹² See Johannes & Burton, *supra* note 4.

¹³ See *id.*

¹⁴ Andy Richards & Ray McCague, *The Impact of Chiral Technology on the Pharmaceutical Industry*, CHEMISTRY & INDUSTRY, June 2, 1997, at 422.

¹⁵ See *id.*

¹⁶ See David Rotman & Alex Scott, *Mirroring Changes in Chiral Technology*, CHEMICAL WEEK, July 16, 1997, at 32.

to produce enantiomers “no longer valid.”¹⁷ The market shows that free-rider concerns are not discouraging pharmaceutical firms from developing enantiomeric versions of approved racemates.

HARM TO THE CONSUMER

Consumers will be harmed if the FDA decides to grant market exclusivity for enantiomers of approved drugs. First, the decision might actually stifle the development of improved drugs by creating perverse incentives for manufacturers to postpone the sale of chiral drugs. Under the proposal, manufacturers will be able to strategically market their drugs such that they qualify, first, for a five-year period of exclusivity under the racemate, followed by an additional period under the enantiomer. These additional years of exclusivity will be especially valuable due to the fact that the later years of exclusivity are generally more lucrative once brand name and reputation have been established during the earlier years of protection. Under the proposal, it will be to the advantage of pharmaceutical firms to withhold improved products in order to win consecutive periods of exclusivity under their racemates and enantiomers.

Second, if the Administration approves the proposed policy, it will trigger a rise in the cost of drugs. Competition from generics currently helps to control the price of drugs. But even without the benefit of the privileges of exclusivity discussed here, brand-name drugs have been successful in dominating the market.¹⁸ Drug prices are higher than ever,¹⁹ with manufacturers of brand-name drugs using a host of marketing and regulatory tactics to forestall entry by generics.²⁰ Producers of brand-name drugs have already used enantiomers to force generics from the markets for anti-depressant and allergy drugs.²¹ If the Administration agrees to grant market exclusivity to enantiomers of approved compounds, then generic versions of the racemates will face even greater obstacles in gaining market share, leading to higher prices for drugs.

While all consumers will be affected by the increased expense of drugs, the elderly will be particularly hard-hit.²² Medicare does not cover the cost of prescription drugs, and roughly 19 million elderly Americans have little or no drug coverage.²³ Since the majority of elderly people have two or more chronic diseases, dependence on prescription drugs is high.²⁴ But the high costs of drugs force many to skip medications in order to stretch their supplies, or to forego them

¹⁷ See Richards & McCague, *supra* note 15.

¹⁸ See Thomas M. Burton, *Bested Interests: Why Generic Drugs Often Can't Compete Against Brand Names*, WALL ST. J., Nov. 18, 1998, at A1.

¹⁹ See *id.*

²⁰ See *id.*

²¹ See Johannes & Burton, *supra* note 4 (reporting on the grant of patent protection for the enantiomer for Prozac to extend its period of exclusivity, and on the banning of generic versions of racemate for Seldane to the benefit of its brand name enantiomer).

²² See Lucette Lagnado, *The Uncovered: Drug Costs Can Leave Elderly a Grim Choice: "Pills or Other Needs,"* WALL ST. J., Nov. 17, 1998, at A1.

²³ See *id.* (citing Congressional Budget Office).

²⁴ See *id.*

altogether.²⁵ The rising cost of prescription drugs is a serious problem, and the FDA must shape its policies with an eye to the economic effects that they will have.

LEGAL OBSTACLES

Policy issues aside, the FDA lacks the legal authority to grant this five-year period of exclusivity. Federal statutes limit the ability of the FDA to grant periods of market exclusivity to only those cases involving new drugs.²⁶ When the FDA has already approved the sale of a racemic compound, it strains logic to suggest that an enantiomer already marketed within the racemate is a new compound when sold alone.

Even if brand name drug manufacturers are persuasive in asserting that enantiomers of approved drugs are new drugs in their own right, federal law limits the period of exclusivity that the Administration can offer. A five-year period of exclusivity is only available for those new drugs that do not contain ingredients of previously approved drugs.²⁷ When a sponsored drug does contain ingredients of existing compounds, a three-year period of exclusivity is all that federal law permits.²⁸ Enantiomers of approved compounds do contain ingredients of approved drugs--namely, themselves. Thus, federal law limits the period of exclusivity that the FDA can offer to three years--a period unworthy of the social and economic costs of the proposal.

CONCLUSION

The FDA proposal makes bad policy. Granting market exclusivity to purified enantiomers of approved drugs will increase the price of drugs and harm consumers. This detriment cannot be justified through the promise of superior drugs and scientific advancement. As evidenced by the current boom in the chiral chemistry industry, significant incentives for the production of enantiomers are already provided through the FDA and other institutions. An estimated three-quarters of all new drugs will be chiral within the next few years. These advances have been made without the artificial stimulus of nonpatent market exclusivity. FDA reform is not necessary to promote chiral chemistry.

²⁵ See *id.*

²⁶ See 21 U.S.C. § 355(c)(3)(D) (1994).

²⁷ See 21 U.S.C. § 355(c)(3)(D)(ii) (1994).

²⁸ See 21 U.S.C. § 355(c)(3)(D)(iii) (1994).