



# THE EFFECT OF FDA'S POLICIES ON THE DECREASING EFFECTIVENESS OF ANTIBIOTICS

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THE EFFECT OF FDA'S POLICIES ON THE DECREASING EFFECTIVENESS OF  
ANTIBIOTICS

A. INTRODUCTION

Over the last century, Americans have seen their life expectancies increase dramatically from an average age of 47.3 years to an age of 71.5 years for men and 78.3 years for women. Today's two leading causes of death are heart disease and cancer; whereas, in 1900, the leading causes of death were bacterial diseases such as pneumonia, influenza, tuberculosis and diarrhea.<sup>1</sup> What is it that has brought about such tremendous changes in the lives of Americans? Antimicrobial drugs have played a significant role. The discovery of antibiotics in the World War II era and afterwards meant that most bacterial infections could be controlled and cured. In the ensuing decades, other antimicrobial agents were also developed to combat certain viral, parasitic and fungal infections. The existing complement of antimicrobials has made society quickly forget that microbial infection can be lethal.

This changed when a deadly new disease appeared in the 1980s -

- Acquired Immunodeficiency Syndrome (AIDS) - which now threatens to kill an increasing number of Americans each year. AIDS is caused by the human immunodeficiency virus (HIV). This virus destroys the human host's immune system, thereby making the human

<sup>1</sup> Peter Barton Hutt & Richard A. Merrill, Food and Drug Law 867 (2d ed. 1991).

susceptible to cancer and severe bacterial infections. Although

scientists are frantically trying to develop a cure and physicians are desperately trying to treat AIDS patients with the drugs presently available, AIDS relentlessly continues to kill. The uncontrollable onslaught of this infectious disease should cause concern not only about the virulence of HIV, but also about our continued ability to combat infectious disease in general.

The threat of AIDS parallels the bigger threat of uncontrollable bacterial disease. The many bacterial diseases which in this century became treatable by antibiotics are once again becoming as uncontrollable and dangerous as AIDS. The cause

— microbial drug resistance. Soon after the discovery of antibiotics, physicians and scientists noticed that bacteria could develop resistance to an antibiotic by changing their biochemical composition. Likewise is the case with viruses. Antiviral drugs face an even greater problem of drug resistance because viruses tend to mutate very quickly and efficiently. In addition to these findings, scientists have shown that drug resistance can pass from one microbe to another when the biochemical components which cause drug resistance in one microbe are transferred to the other microbe. Furthermore, scientists and physicians now see that bacteria can gain resistance to multiple drugs.<sup>2</sup>

These days, our society is having trouble treating diseases which used to be routinely treated with antibiotics. Multi-drug

<sup>2</sup> To understand how antibiotic resistance works, see S.B. Levy, *The Antibiotic Paradox* 67-103 (1992).

resistant tuberculosis has become a serious problem in the United States, particularly in big cities such as New York City.<sup>3</sup> Another excellent example of multiple drug resistance can be found among Staphylococcus bacteria which cause potentially lethal infections such, as Toxic Shock Syndrome. In 1952, Staphylococcus infections were almost 100 percent curable by penicillin, whereas, now fewer than 10 percent of such infections can be cured by penicillin.<sup>4</sup> Presently, only vancomycin remains as a reliable antibiotic to combat these infections.<sup>5</sup> However, vancomycin too threatens to lose its effectiveness against Staphylococcus given findings of vancomycin resistance in other types of bacteria.<sup>7</sup>

Physicians now have to use higher dosages and different antibiotics to rid a patient of an infection. Furthermore, there are more patients who now become afflicted with bacterial diseases that cannot be combatted by any known antibiotic and so the patient dies of the infection. The famous Muppets puppeteer, Jim Henson, suffered such a fate when he became infected with Streptococcus

~ Jim Henson died of pneumonia – a rare cause of death among otherwise healthy individuals in this day and age. Henson

~ Id. at 97-98. See also Neglected Infrastructure Means Uphill Battle Against TB Epidemic, Health Care Policy Report, Dec. 6, 1993, at 39.

Laurie Garrett, The Coming Plague 411 (1994).

~ Id. at 412.

M.L. Cohen, Epidemiology of Drug Resistance: Implications for a Post-Antimicrobial Era, 257 Science 1050 at 1051 (1992).

Levy, supra note 2 at 134.

was attacked by a particularly virulent bacterial strain that became uncontrollable.

Drug resistance has become a problem in the United States and in the world. Antibiotics imposed a Darwinian force of natural selection on the microbial population and so it was inevitable that some resistant microbial strains would emerge. However, this natural emergence of resistant strains would never have occurred as quickly were it not for the tremendous amount of antibiotic use over the last fifty years. A serious public health problem has resulted from the continuous overuse of antibiotics and the slow development of new antibiotics to replace old ones that have lost their therapeutic value.

This paper will evaluate the effect that the Food and Drug Administration (FDA) has had on the drug resistance problem and will consider how the FDA could tailor its regulatory policies to better safeguard the effectiveness of the American antibiotic supply. The discussion will be divided in two parts. First, we will look at the consequences of FDA's approach to controlling the dissemination of antibiotics. Secondly, we will examine the effect that FDA policies have had on the development of new antibiotics. In both parts, we will consider how the FDA's present approach may be improved upon.

#### B. FDA'S ROLE IN THE DISSEMINATION OF ANTIBIOTICS

As mentioned earlier, overuse of antibiotics has led to a more

accelerated decline in antibiotic effectiveness. Antibiotics have

been overused in both human and animal treatment. Physicians and veterinarians both have prescribed antibiotics too often when an antibiotic was not needed. Furthermore, humans have misused antibiotics by not completing a prescribed course of antibiotics, or by leaving the antibiotic around and by using the leftover antibiotics for a later ailment. Antibiotics have also been overused in subtherapeutic doses in animal feed.

As an agency concerned with the health and safety of Americans, it is well within the Food and Drug Administration's jurisdiction to control this widespread use of antibiotics. In this part, we will consider how the FDA has exercised control over the use of antibiotics. An evaluation of FDA's approach will be undertaken as well.

1. Introduction to the FDA regulation of drugs

The Food and Drug Administration seeks to protect the health of Americans against impure and unsafe foods, drugs, cosmetics and other similar hazards. This important mission is carried out by some 7400 employees using systems of premarket approval followed by enforcement activities.<sup>7</sup> Our particular concern centers around FDA's activities in the area of drugs. The FDA regulates not only the development of new drugs and their introduction into the marketplace, but also the sale and marketing of drugs once they are in the marketplace. Both human and animal drugs are subject to

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Hutt & Merrill, su~ra note 1 at 16.

regulation by the FDA.

The FDA has several tools in its hands to control the use of antibiotics in both humans and animals. For example, the FDA determines how drugs should be labeled and what kind of advertising can accompany the sale of drugs. The FDA also controls the dissemination of drugs. In fact, product labeling is what led to such controlled dissemination.

In a 1938 regulation which was promulgated shortly after the coming into force of the Food, Drug, and Cosmetic Act (the Act),<sup>9</sup> the FDA decided that those drugs which were labeled as to be used only by or on the prescription of a physician, dentist or veterinarian could only be sold to a consumer upon obtaining a prescription from a physician.<sup>10</sup> Hence, the distinction between prescription and over-the-counter drugs was developed.<sup>11</sup> In 1951, the regulation was changed so that the FDA instead of the manufacturer determined what drugs were to carry prescription status. From that time on, the FDA would give prescription status to a drug if

its toxicity or other potentiality for harmful effect ... ha[d] been determined by the Federal Security Administrator, on the basis of opinions generally held among experts ... to be safe and efficacious for use only after professional diagnosis.<sup>12</sup>

<sup>9</sup> 21 U.S.C. §321 *et seq.*

<sup>10</sup> 70 Fed. Reg. 3168 (December 28, 1938).

<sup>11</sup> Peter Temin, The Origin of Compulsory Drug Prescriptions 22

J. L. & Econ. 91 (1979). <sup>12</sup> *Id.*

This distinction between prescription and over-the-counter drugs, which was first developed through regulation and was not set out in the Act itself until later,<sup>13</sup> has had a massive effect on the availability of drugs, including antibiotics.

Just as the FDA has limited the sphere of dissemination for human drugs, the FDA also has the power to control the dissemination of animal drugs used for therapeutic purposes and as growth promoters in animal feed. This power comes from a broad reading of the concept of safety as it is used in §512 of the Act. We will examine FDA regulation of animal drugs more closely a little later.

2. Controlling the dissemination of antibiotics

Apart from maintaining prescription status for antibiotics, the FDA may have little authority under the present Act to impose greater controls on the dissemination of antibiotics. Past case law suggests that, generally, the FDA cannot interfere with a physician's prescribing of drugs, nor can the FDA restrict the distribution of drugs.

The FDA's limitations in trying to interfere with a physician's prescribing practices can be seen in the context of physicians prescribing approved drugs for unapproved uses. In United States v. Evers, the FDA unsuccessfully challenged Dr.

<sup>13</sup> Section 503(b) of the Food, Drug and Cosmetic Act is the provision that established the notion of prescription drugs.

643 F.2d 1043 (1981).

Evers' unapproved use of Calcium EDTA, an approved drug. Randall

J. found that the prescribing habits of Dr. Evers did not violate the provisions of the Food, Drug, and Cosmetic Act. Given that the FDA was unable to stop this physician's prescribing practice, it is unlikely that the FDA would be able to control a physician's prescribing of antibiotics for an unnecessary illness.

In all probability, the FDA would be equally unsuccessful in restricting the distribution of antibiotics to certain locations. In American Pharmaceutical Association v. Weinbercrer<sup>5</sup>, the Court held that the FDA exceeded its authority when it restricted the distribution of methadone to (a) approved maintenance treatment programs, (b) approved hospital pharmacies, and (c) in cases where hospital pharmacies were unavailable in a particular area, to selected community pharmacies. The Court decided that limited distribution of such a drug could be determined solely by the Justice Department.

Due to the prevalent use of antibiotics in genuine cases of microbial infection, it is questionable whether imposing further controls on physician prescribing or on drug distribution would even be a good idea. Such measures may severely sacrifice the short-term needs of a sick patient suffering from a microbial infection for the longer term public health concerns. On balance, it seems that proper physician training combined with continued prescription status of antibiotic drugs is the best regulatory strategy which is available to the FDA to control antibiotic

377 F.Supp. 824 (1974).

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dissemination.

Despite the seemingly obvious need to maintain control over antimicrobial drug use so as to prevent further decline in the effectiveness of the antimicrobial drug supply, the FDA has become increasingly keen about the idea of switching certain drugs, including antimicrobial drugs, from prescription (Rx) status to over-the-counter (OTC) status. In fact, antibiotic first aid creams already have OTC status. Recently, there has been consideration about whether to switch Zovirax (or acyclovir) from prescription status to OTC status. Zovirax is an antiviral drug that is used in the treatment of genital herpes. In deciding whether to switch the status of Zovirax, drug resistance is the

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main concern. Topical erythromycin for acne treatment has also been considered as an appropriate candidate for a Rx-OTC switch.

Prescription drugs can be switched to over-the-counter status in three ways. First, the holder of a new drug application (NDA) can submit a supplemental application requesting such a switch in status. Second, the manufacturer of the drug or any other person can petition for such a switch pursuant to 21 C.F.R. par. 310.200. Thirdly, a switch can be made following an internal FDA review of

Updates, FDA Rules on OTC Antibiotics, FDA Consumer, March 1988, at 2.

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Zovirax OTC Switch Advisory Committee Review Expected in Late 1994 or Early 1995, FDC Reports, The Pink Sheet, July 4, 1994, T&G-1-T&G-2.

'7                   Topical Erythromycin. Retin-A for Acne Are Logical Rx to OTC Switch Candidates. Derma FDC Reports, The Pink Sheet, Sept. 1, 1992, at 11-12.

the matter. These internal reviews are carried out using the OTC Drug Review process. Normally, the FDA considers the following factors in deciding whether or not to authorize a switch: (1) the toxicity of the drug; (2) the potentiality for harmful effect; (3) the method of use or collateral measures necessary to use; and (4) broad issues of social policy.

There are two main arguments that are made for the need to switch the status of antimicrobial drugs. First, such a switch would make the cost of treating an infection much lower. The consumer requiring a drug would not have to pay a dispensing fee or the fee of a visit to a doctor. Insurance companies would be happy indeed with the lower costs associated with such a system. Secondly, in the cases of drugs such as Zovirax which treat illnesses that are often embarrassing, the patient would be able to obtain treatment without having to undergo the humiliation of discussing the matter at the doctor's office.

However, given the drug resistance problem, these arguments for switching the status of certain antimicrobial drugs are not sufficiently convincing. In all likelihood, self-medicating patients would end up misusing and overusing the drugs even more than they are doing today. This is certainly the trend in those countries where antibiotics can be obtained without a prescription.<sup>20</sup> Over-the-counter availability of antimicrobial

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See P.B. Hutt, A Legal Framework for Future Decisions on Transferring Drugs from Prescription to Non  
37 Food Drug Cosm. L.J. 427 (1982).

20 Levy, supra note 2 at 107—14, 231—34.

drugs would lead to an even more rapid decline in the potency of our antimicrobial drug supply. The consequences could be disastrous. The cost savings in switching the status of antimicrobial drugs to over-the-counter status would be eliminated if those drugs lost their effectiveness in combatting disease. Treating infections caused by resistant strains is already incredibly expensive. The whole problem of drug resistance has

added \$100 to \$200 million a year to the United States' health care

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costs. Therefore, for public policy reasons, prescription status must be maintained for antimicrobial drugs.

2. Controlling the use of antibiotics using balanced advertising and complete labeling of antibiotics

There is no doubt that by maintaining prescription status for antibiotics, the FDA has limited their use. However, the system is not foolproof. Overuse is still a problem in this country. Physicians, who of all people should be aware of the drug resistance problem, often overprescribe antibiotics. This occurs for several reasons. First, physicians are often severely

pressured by their patients to prescribe an antibiotic for any

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ailment. Second, physicians prescribe broad spectrum antibiotics

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Ann Gibbon, Exploring New Strategies to Fight Drug-Resistant Microbes, 257 Science 1036 at 1036 (1992). Furthermore, treating one patient who has contracted multi-drug resistant tuberculosis can cost more than \$100,000. California County Officials Resort To Health Care Policy Report, Nov. 28, 1994, at 47.

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Levy, supra note 2 at 105-107, 210-11.

when a narrow spectrum antibiotic would do.<sup>23</sup>

Thirdly, physicians may prescribe too large or too small a dose of antibiotic to cure the infection in question.<sup>24</sup> Finally, the physician may get confused about which antibiotic to prescribe due to all the products on the market.<sup>25</sup> Patients also tend to misuse antibiotics by self-medicating with old antibiotics that remained in the medicine cabinet from a previous illness.<sup>27</sup> If physicians continue to be too lenient in their prescribing habits and patients continue to misuse drugs, using prescription drug status as a means of controlling antibiotic dissemination will be insufficient as a tool to offset a drug resistance crisis.

One way to induce proper behavior in both physicians and patients is through education. Because pharmaceutical companies know the most about the antibiotics they sell, physicians tend to

rely heavily on the information provided by these companies about

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their products. Many authors have commented that the information provided by pharmaceutical companies is incomplete and misleading and that this often results in improper antibiotic use.<sup>27</sup> Most

<sup>23</sup> Gibbon, supra note 21 at 1038.

<sup>24</sup> Levy, supra note 2 at 227-28, 234—36.

<sup>25</sup> Stephen Ackerman, Today's New Breed of Antibiotics, FDA Consumer, Dec/Jan. 1988, at 22.

<sup>26</sup> Levy, supra note 2 at 211-14.

<sup>27</sup> Garrett, supra note 4 at 681 n. 125.

<sup>26</sup> Stephen Ackerman, Today's New Breed of Antibiotics, FDA Consumer, Dec/Jan. 1988, at 22; Jeffrey A. Fisher, The Plague Makers 139-50, 159 (1994); Stuart B. Levy, The Antibiotic Paradox 237 (1992).

patients have obtained little or no education regarding the proper use of antibiotics and so this population still tends to think, albeit inaccurately, that an antibiotic is a miracle drug that is needed for everything, including all colds.<sup>27</sup>

The FDA seeks to educate the public, including physicians, by imposing advertising and labeling requirements on pharmaceutical companies. These requirements are different for physicians and for patients. Prescription drug advertising to professionals is governed by a federal regulation that dictates that advertising must not be false, lacking in fair balance or otherwise misleading.<sup>30</sup> Similar requirements are imposed on direct-to-consumer advertising of prescription drugs. The FDA has also established physician labeling regulations specifying the format and content of a professional package insert for all human prescription drugs.<sup>31</sup> As for patients, drug labeling is specified in §502 of the Act. However, prescription drugs are exempted from some aspects of these requirements in §503(2). A prescription drug label must only contain the following:

[T]he name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber, and, if stated in the prescription, the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription.<sup>32</sup>

Levy, *supra* note 2 at 208-14.

3021 C.F.R. §202.1(6)—(7).

21 C.F.R. 201.56 and 201.57.

<sup>32</sup> *Id.*

These provisions are supposed to ensure that the information being provided by pharmaceutical companies is balanced and accurate.

Despite these rules, both physicians and patients remain uninformed about proper antibiotic use. The FDA should review the current labeling and advertising requirements for antibiotics. Imposing more stringent labeling and advertising requirements on antibiotics regarding their proper use and their side effects would be one way to encourage proper use of antibiotics. Both physicians and patients must obtain more information about how their activities exacerbate the increasing drug resistance problem. This kind of information should be provided to the physician in the physician package insert and to the patient in the form of a patient package insert. Physicians must be given more information about the appropriateness of certain antibiotics to treat certain illnesses. Patients, on the other hand, must be told not to reuse old antibiotics nor to use antibiotics unless a bacterial infection is plaguing them.

4. Use of Antibiotics in Animal Feed

The same concerns as the ones raised above arise when considering the therapeutic use of antibiotics in animals. In the case of animals, the FDA has taken specific steps to limit the use of prescription drugs such as antibiotics. In a 1988 regulation, the FDA created the distinction between prescription and over-the-counter animal drugs.<sup>33</sup> These regulations have been upheld in the

Hutt & Merrill, supra note 1 at 655.

courts as being a valid interpretation of the statutory requirement in 21 C.F.R. 314.502(f)(1) for adequate directions for use.<sup>31</sup> Under those regulations, it is also generally unlawful for a veterinarian to prescribe a drug for an unapproved use. In extreme cases, extra-label use may be allowed. This additional limitation on the therapeutic use of antibiotics in animals is a wise decision of the FDA since it helps control the drug resistance problem.

However, the bigger concern with respect to antibiotic use in animals is the widespread subtherapeutic use of putting antibiotics in animal feed. Farm animals receive nearly half of all the antibiotics produced in the United States. In 1972, an FDA Task Force on the Use of Antibiotics in Animal Feeds came to the conclusion that antibiotic use in animal feed had to be limited to control the numbers of drug resistant micro-organisms. Upon the Task Force's recommendation, a new provision was inserted in the FDA Regulations which limits subtherapeutic use of antibiotics to those antibiotics which are not used in human treatment.<sup>32</sup> The regulation was particularly aimed at the use of penicillin and tetracycline in animal feed. This action produced a tremendous outcry from the industry and, to this day, the regulation is not enforced and antibiotics in animal feed continue to be used.

The following events led to this situation. Following FDA's

<sup>31</sup> *United States v. Colahan*, 635 F.2d 564 (6th Cir. 1980).

Food and Drug Administration, Compliance Policy Guide 7125.06 (Nov. 1, 1986).

<sup>32</sup> See 21 C.F.R. §558.15.

announcement of its proposed regulations, the House Appropriations Committee instructed FDA to delay regulatory action against the use of antibiotics in animal feed pending a study of the matter by the National Academy of Sciences (NAS). The NAS concluded that further studies had to be done to resolve the issue.<sup>36</sup> The House Appropriations Committee then instructed the FDA to conduct these further studies. Meanwhile, in February 1983, the FDA agreed to continue approving new uses and new combinations of antibiotics pending the outcome of the studies.<sup>39</sup> In 1989, the NAS completed the additional studies and reported that it was unable to find direct scientific proof of a link between human illness and subtherapeutic use of antimicrobials in animal feed. The NAS again recommended further studies which could be undertaken to establish such direct scientific proof.<sup>40</sup>

Experts are frustrated that the debate surrounding antibiotics in animal feed has continued for fifteen years and yet has yielded

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few results. Despite the absence of direct proof that antibiotics in animal feed exacerbate the drug resistance problem,

Hutt & Merrill, *supra* note 1 at 652—53.

<sup>36</sup> National Academy of Sciences, *The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feed* (1980).

48 Fed. Reg. 4490 and 4554 (February 1, 1983).

<sup>40</sup> Institute of Medicine of the National Academy of Sciences, *Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracycline in Animal Feed* (1988).

<sup>41</sup>

Karen Wright, *The Policy Response: In Limbo*, 249 *Science* 24 at 24 (1990).

many experts continue to claim that there is a definite link.<sup>2</sup> According to Levy, a leading expert in the antibiotic drug resistance field, the extensive use of antibiotics in animal feed has imposed a tremendous selective pressure on resistant organisms to breed in the intestinal tracts of animals. These resistant organisms get passed on to humans in several ways. First, farmers come in contact with these resistant organisms directly. Secondly, consumers come in contact with these organisms through animal meat. Thirdly, if fecal material of such animals is used as a fertilizer to grow vegetables, these organisms can be harbored in the plants we eat. These various modes of transmission have been illustrated through scientific studies.

In the case of regulating the use of antimicrobials in animal feed, the FDA is faced with the classic dilemma of how to regulate in the face of uncertainty. The FDA should restrict the use of antibiotics in animal feed despite absolute certainty. The opinion of leading experts should be heeded, especially when society is facing such a serious public health concern, namely, the decreasing effectiveness of antibiotics to treat infection. From a costbenefit point of view, the amount that society stands to lose if antibiotics lose their effectiveness greatly exceeds the gains of an increased growth rate in animals. This is particularly true given that: (1) more and more antibiotic must be given to promote growth and (2) even with these higher doses, the growth promotion

<sup>42</sup> See, for example, Levy, supra note 2 at 137-156.

Id.

effect is not nearly as great as it was twenty years ago.

The FDA must impose more stringent controls on the use of antibiotics in animal feed. A straight ban on antibiotic use in animal feed may be too drastic a measure since such a measure might have serious effects on the quality and quantity of the food we eat. However, strict use of antibiotics in animal feed is essential to preserve the effectiveness of presently available antibiotics. Ultimately, determining the extent to which antibiotic use should be controlled involves the broad question of how best to ensure the health and safety of the American public. On the one hand, the food supply must be safe and nourishing. On the other hand, the drug supply must be safe and effective. The solution must balance these two concerns. The FDA should at least ban the use in animal feed of those antibiotics that are used in human therapy. This would prevent animals from passing on organisms to humans that are resistant to human antibiotics. It would also reduce the selective pressure being imposed on dangerous human pathogens.

C. FDA'S ROLE IN THE DEVELOPMENT OF NEW ANTIBIOTICS

The FDA must adopt a two-part strategy to ensure that the American population has an effective drug supply which can control

Id. at 142.

This policy has been adopted in Canada, England and other European countries. Levy, supra note 2 at 142.

the onset of infectious diseases.

In part B of this paper, we

considered what the FDA was doing and what it could do in addition to safeguard the effectiveness of the antibiotics presently available. Several strategies were identified, including, controlling and restricting the use of antibiotics, and educating the public about proper antibiotic use. However, because drug resistant organisms already exist in great numbers and because they will continue to develop through the process of natural selection, the FDA must promote a second strategy to combat drug resistance. The FDA must strongly encourage the development of new antibiotics. Promoting such development requires an FDA new drug approval system that is relatively efficient and that does not discourage manufacturers from developing new antibiotics.

1. The FDA approval system for new drugs and antibiotics

Although a read through § 505 and 507 of the Food, Drug, and Cosmetic Act of 1962 suggests that the FDA deals with new antibiotics differently from other new drugs, subsequent regulations effectively have removed the distinction. For example, antibiotics are now subject to the same investigational new drug

(IND) and new drug application (NDA) requirements as other new

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drugs. Furthermore, due to the high level of manufacturer compliance with antibiotic standards, FDA has exempted all classes

of antibiotics from batch certification as required by § 507 of the 21 C.F.R. Parts 312-314.

Act.<sup>7</sup> With these changes, antibiotics are now regulated in virtually the same manner as other new drugs.

In order to market a new antibiotic, a manufacturer must first obtain FDA approval of an NDA. The FDA evaluates the NDA on the basis of safety and effectiveness standards. Before submitting the NDA, the manufacturer must have conducted preclinical animal studies and clinical human studies to determine whether the new drug is safe and effective. The clinical research stage involves three phases and requires the filing of an IND application before the clinical research commences. Generally, under the IND, only those patients involved in the study have access to the drug. All the data gained from this preclinical and clinical testing must be included in the NDA which is submitted to the FDA for review and approval. The time elapsed between preclinical testing and final approval by the FDA of an NDA can be anywhere between 7 and 13 years. As can be seen, the FDA maintains the quality of the American drug supply but, as a result, the process of bringing new drugs into the market is incredibly expensive and time consuming. The requirements for the NDA are onerous and detailed. Each NDA consists of about 2 to 15 volumes of summary material accompanied by about 10 to 100 volumes (occasionally up to 400 volumes 100,000

<sup>7</sup> See 47 Fed. Reg. 19954 (May 7, 1982), 47 Fed. Reg. 39155 (September 7, 1982), codified in 21 C.F.R. § 433.1.

<sup>48</sup> Hutt & Merrill, supra note 1 at 514.

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to 200,000 pages) of raw data.<sup>49</sup>

The FDA has accorded expedited consideration to some new drug applications. This has usually been done for important new medicines. The FDA has taken efforts to accelerate the approval of important new drugs in two ways. First, the FDA has established a triage system whereby the important new drugs get priority in being reviewed.<sup>50</sup> Secondly, in the cases of important new drugs, biological products and antibiotics developed for life-threatening and severely debilitating diseases, the FDA has issued a new rule to streamline the NDA process.<sup>51</sup> The entire expedited approach set out in the rule was based on the procedure used to approve a new AIDS drug called Zidovudine (also known as AZT). The whole approval process for Zidovudine ended up being only two years as opposed to eight years.

Under the new rule, the FDA notes that it will increase its consultations with the drug manufacturer throughout the NDA approval process. The FDA also agrees to reduce, in some cases, the number of clinical trials that have to be done to get approval. Finally, the FDA notes that it may make approval conditional on an

The Food and Drug Administration's Process for Approving New Drugs, Report of the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology, 96th Cong., 2nd Sess. (1980).

Food and Drug Administration, Staff Manual Guide BD4820.3., as reproduced in Hutt & Merrill, supra note 1 at 529.

<sup>51</sup> Investigational new drug, antibiotic, and biological drug product regulations: procedures for drugs intended to treat lifethreatening and severely debilitating illnesses, 53 Fed. Reg. 41516 (1988).

agreement with the manufacturer to conduct further post-marketing studies regarding the safety and efficacy of the drug. Requiring additional post-marketing studies to expedite drug approval is not a novel idea. It was required by the FDA prior to the issuance of this regulation in the case of Levodopa, a new drug that was developed for the treatment of Parkinson's Disease.<sup>52</sup>

The FDA also allows investigational new drugs to be used in the treatment of life-threatening conditions even when the sick individual is not involved in a clinical study. Prior to the development of AIDS, emergency INDs and compassionate INDs were granted for this purpose on a case-by-case basis. With the onset of AIDS, treatment INDs were created so that a larger population could be treated by an unapproved new drug undergoing approval. These INDs are called Treatment INDs and may be granted under the following conditions:

- (i) the drug may be effective for its intended use in its intended patient population;
- (ii) the drug would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury;
- (iii) the sale does not constitute commercial marketing of a new drug for which a marketing application has not been approved;
- (iv) the drug is not being commercially promoted or advertised; and

<sup>52</sup> Nancy Mattison & Barbara W. Richard, Postapproval Research Requested by the FDA at the Time of NCE Approval 1970-1984, 21 Drug Information Journal 309 (1987).

Hutt & Merrill, supra note 1 at 553—54.

(v) the sponsor of the drug is actively pursuing marketing approval with due diligence).<sup>54</sup>

The FDA has agreed to allow companies to charge for drugs used by patients pursuant to the treatment IND in order to recoup their costs but has prohibited commercial marketing of the drug.<sup>55</sup> Although these treatment INDs are mostly for the benefit of patients, the system can also be beneficial for the drug manufacturers. The wider use of the drug can quickly reveal significant benefits and risks which dictate whether a continued investment in the development of the drug is warranted.

2. Tailoring FDA policy to accommodate current trends in antibiotic development

Until the 1980s, pharmaceutical companies were actively developing new antibiotics and so antibiotics always stayed a step ahead in the race against the microbes. However, in the 1980s, further development became uneconomical and numerous drug companies abandoned research into new antibiotics. Only nine new antibiotics were approved in 1992 and 1993 by the FDA.<sup>57</sup> Despite the increasingly serious problem of drug resistance, pharmaceutical

Investigational New Drug, Antibiotic, and Biological Drug Product Regulations: Treatment Use and Sale, 52 Fed. Reg. 19466 (1987).

~ Id.

~ Gibbon, supra note 21 at 1036.

~ Elizabeth Culotta, Funding Crunch Hobbles Antibiotic Resistance Research, 264 Science 362 at 363 (1994).

companies have remained relatively inactive in the area of antibiotic research.

A further problem with the few antibiotics introduced in 1992 and 1993 is that none of these antibiotics introduced any new operating mechanism for combatting infection.<sup>57</sup> Similarity in operating mechanism is, in fact, a weakness of all the antibiotics in existence. Although there are 160 antibiotics on the market, there are only 15 variations in the mechanisms used.<sup>58</sup> This lack of variability in the mechanism of antibiotics makes our drug supply even more weak in the face of attack from drug-resistant microorganisms.

The few large pharmaceutical companies that have continued antibiotic research have simply tried to manipulate those antibiotic compounds that have already been developed.<sup>60</sup> This is problematic since some scientists believe that companies have gone as far as they can with this strategy. The companies that are engaging in the most innovative research are the small biotechnology companies. These companies are exploring entirely new ways of attacking microbes. Some of these biotechnology companies are even trying to develop vaccines to stave off the most drug-resistant bacteria such as Staphylococcus aureus. Vaccines

Id.

Gene Bylinsky, The New Fight Against Killer Microbes, Fortune, Sept. 5, 1994, 74 at 76.

Id.

John Travis, Reviving the Antibiotic Miracle?, 264 Science 360 (1994).

are seen by experts as being one of the best way of conquering microbes because they prevent infection. By using the body's immune system to prevent disease, vaccines don't have resistance problems **62**

Although it is encouraging that small companies are engaging in antibiotic research, the concern is that they will not be successful in ultimately marketing a new antibiotic because of the tremendous costs involved. The estimated cost of bringing a new antibiotic agent to the market is \$300 million dollars.<sup>13</sup> When examining costs, the length of the approval process must also be considered. Not only may a small company have a hard time waiting ten years to obtain a marketable product, but so will society who will be faced with an increasing drug resistance problem. These concerns suggest that rather than safeguarding the health of Americans, the FDA may in fact hinder it by discouraging the development of new antibiotics. A streamlined NDA approval system is needed in this area. This approval system must be shortened without unduly sacrificing the FDA's policy that only new drugs that are safe and effective can be marketed.

The regulation that allows for expedited approval of lifesaving new antibiotics is obviously a step in the right direction.

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For more information about the research presently being undertaken by these biotechnology companies: (1) Gene Bylinsky, The New Fight Against Killer Microbes, *Fortune*, Sept. 5, 1994, at 74; (2) Joan OC. Hamilton, Who Will Stop the Mutant Microbes?, *Business Week*, Aug. 1, 1994, at 52; and John Rennie, No Snake Oil Here, *Scientific American*, March 1993, at 136.

13 Barbara E. Murray, Can Antibiotic Resistance Be Controlled?, 330 *N.E.J.M.* 1229 at 1230 (1994).

However, the problem is determining what antibiotics would actually be classified as being for the treatment of life-threatening and debilitating diseases. The requirement could be interpreted very broadly and very narrowly. If the applicability of the regulation were interpreted very narrowly, then presumably only a certain number of antibiotics might be considered eligible for expedited approval. Perhaps only those new antibiotics that could fight multiple drug-resistant strains would be included. The problem is that many microbial infections are life-threatening or severely debilitating if the individual fails to receive effective antimicrobial treatment. Furthermore, new antibiotics that could be useful against single drug-resistant microbes could be equally important to patients who are allergic to the alternative existing antibiotics.

At least two steps should be taken by the FDA in the area of new drug approvals. First, the scope of the new expedited approval process should be clearly ascertained as regards antibiotics. It has been suggested that the FDA has promised to expedite promising antibiotics through this process. If this means that all antibiotics will be given priority in consideration then no separate expedited approval process needs to be set up under the Food, Drug, and Cosmetic Act. Secondly, the FDA should consider establishing an expedited licensing process for new vaccines that may be introduced to combat infectious diseases in the future. Although this expedited licensing process would be undertaken under

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See Bylinsky and Hamilton, su~ra note 62.

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the Biologics Act, its elements could be very similar to the elements seen in the expedited approval process set up under the

Food, Drug and Cosmetic Act. By ensuring that both new antibiotics and vaccines are being approved quickly, the FDA could be instrumental in avoiding an acute drug resistance crisis.

#### D. CONCLUSION

There is reason to be concerned about the rising number of drug resistant microbes and the decreasing number of effective antibiotics. It is hard to imagine that a post-antibiotic era could come in which society would revert back to what it was before penicillin was discovered in the 1930s. Because it is within the FDA's jurisdiction to control the American drug supply, it is important to analyze what the FDA is doing to alleviate an antibiotic drug crisis and what it could do in addition. A study of the FDA's activities suggests that there is room for improvement in the FDA's approach.

42 U.S.C. §262. For historic reasons, biological products, including vaccines, are regulated under the Biologics Act instead of the Food, Drug, and Cosmetic Act. Different requirements are imposed on biologic producers as opposed to new drug and antibiotic producers before marketing can occur. Unlike producers of new drugs and antibiotics, producers of biologics must obtain separate licenses both for the manufacturing plant and for each individual product to be manufactured at the plant. Normally, the FDA requires clinical testing of a biologic being produced at a new location before it will license production of the biologic there. See Hutt & Merrill, su~ra note 1 at 664-65. Despite these differences, both antibiotics and vaccines have to undergo lengthy and costly pre-marketing reviews. Therefore, expedited approval is warranted in both cases.

The FDA must have a two-part strategy for dealing with the drug resistance problem. First, the FDA must safeguard the effectiveness of the antibiotics presently on the market. This means that the FDA should: (1) avoid switching antibiotics from prescription to non-prescription status; (2) better educate both physicians and patients about the proper use of antibiotics by imposing more stringent labeling requirements; and (3) ban the use of human antibiotics in animal feed. Secondly, the FDA must encourage rather than hinder the rapid development of new antibiotics and vaccines. Antibiotic and vaccine development could be greatly assisted by expediting the approval of these compounds.

Although the FDA could safeguard the effectiveness of the American drug supply by adopting all of these policies, it must be realized that drug resistance is a global problem. Other countries of the world are also facing drug resistance problems that are reaching crisis levels in developing countries. Ultimately, combatting drug resistance must be done on a worldwide scale. Nevertheless, the FDA must begin addressing the problem at least from the American perspective.

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For more information about the global drug resistance problem, see Levy, supra note 2 at 223-53, and Garrett, supra note 4.