

Fifty Years of Drug Amendments Revisited: In Easy-to-Swallow Capsule Form

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I. INTRODUCTION

When the Federal Food, Drug, and Cosmetic Act (FDCA) was enacted in 1938, it was a scant twenty-two pages in length. The drug provisions of the statute totaled just about five pages. In the ensuing years, the body of the Act has been expanded by amendments to nearly 250 pages, of which approximately seventy apply directly to drugs. The rate of expansion of the length of this legislation has been largely the same as the rate of economic inflation over the same period of time. The reasons for the changes in the statute are more easily discerned.

At the time of its passage, the FDCA was not radically different from its predecessor 1906 Act with respect to the concepts of adulteration and misbranding. The scope of these concepts had been expanded, but the Act was still largely a policing statute. The FDCA did not distinguish meaningfully between whether a drug could be marketed over-the-counter (OTC) or only on prescription. It provided no statutory mechanism through which either the various manufacturing and processing entities in the pharmaceutical industry, or the products they marketed, could be readily identified. Neither the statute nor the FDA's regulations spoke explicitly of the standards to be followed in the manufacture of drugs.

The most significant innovation applicable to drugs in the 1938 Act was the new drug provisions, which, on a comparative basis, were far more limited than they are today. Perhaps the most important change in the Act as a whole was the factory inspection provision, which applied equally to all facilities in which products subject to the statute's reach could be found, whether those products were food, drugs, devices, or cosmetics.

II. INSULIN (1941) AND ANTIBIOTIC AMENDMENTS (1945, 1947, 1949)

By 1949, the drug provisions had been amended to subject insulin and the antibiotic penicillin — both critically important lifesaving drugs — to the requirement of preclearance by the FDA, as well as the requirement of batch certification. Batch certification of insulin-containing drugs was adopted to fill the gap caused by the expiration of the insulin patents that had been held by the University of Toronto. By licensing the patents to commercial entities, the University had been able to maintain strict control

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The current areas of regulatory focus with which most readers may be familiar are largely the result of amendments to the 1938 law. The review that follows discusses elements of the underlying political, economic, and public health reasons for several of the amendments dealing with drugs. As will be noted, this is the sole footnote in the article, and the author draws almost entirely upon his 40 years' experience during which he was witness to the enactment of many of the amendments.

over the quality of insulin batches. When the patents expired, the U.S. government stepped in by amending the FDCA to require batch-by-batch certification by the Food and Drug Administration (FDA).

A somewhat different reason existed for adoption of the batch certification requirement for penicillin (and subsequently other antibiotics), although the objective was the same — to maintain consistent quality. At that time, just prior to the conclusion of World War II, penicillin was of critical importance in the treatment of life-threatening infections but the means of producing penicillin were relatively crude. The batch certification approach was successful in ensuring sustained quality of product. As new antibiotics were developed, a total of five of them became legislatively subjected to the same requirements. This continued until enactment of the Drug Amendments of 1962, when batches of all antibiotic drugs for human use were required to be certified.

In the years that followed, the production of most antibiotics has become more standardized, and, as a result, the FDA in 1986 adopted regulations exempting most antibiotics from the batch certification requirements. Thus, a program that initially was adopted out of a practical need was administratively relaxed when the need was determined to exist no longer. At this time, the FDA is considering the elimination of batch certification for insulin-containing products, but the agency has taken no action in that direction to date.

III. DURHAM-HUMPHREY AMENDMENT (1951) AND THE PRESCRIPTION/OTC DISTINCTION

When enacted, the 1938 Act did not differentiate between OTC drugs and prescription drugs. Rather, the statute required that all drugs bear labeling containing “adequate directions for use.” Quite soon after the Act’s passage, however, the FDA asserted that there was a category of drugs for which adequate directions for use could not be written. This view derived from the agency’s belief that “adequate directions” referred to a layman’s ability to know when and how to use a drug. The agency believed that many drugs could not be safely and effectively used by laymen; rather, in the FDA’s view, the use of such drugs required the intervention of a person who held an appropriate license to practice the healing arts.

In furtherance of its view, in the early 1940s the FDA adopted regulations exempting from the statutory requirement for adequate directions for use drugs that were not considered safe for lay use. This exemption was conditioned on those drugs bearing labeling that limited them to dispensation on a physician’s prescription and to a chain of possession prior to being dispensed (e.g., from manufacturer, to distributor, to pharmacy, to patient) that was consistent with this labeling limitation. Under the FDA’s regulations, the line between prescription status (i.e., exempt from adequate directions) and nonprescription status (i.e., OTC) was drawn largely at the discretion of the drug’s manufacturer. At times, a drug from one manufacturing source would carry directions for use in its labeling and be sold OTC, while the same type of drug from another source would carry the prescription legend and be available only on order of a licensed practitioner. Congress sought to bring order to this chaotic and unwieldy situation, and in 1951 enacted the Durham-Humphrey Amendment. This law set out statutory criteria for distinguishing between the prescription and OTC status of drugs for human use.

The amendment established three separate categories for determining if a drug was a prescription drug: (1) if it were “habit forming” as specified in section 502(d) of the Act; (2) if “because of its toxicity or other potentiality for harmful effect or the method

of its use, or the collateral measures necessary to its use [it] is not safe for [lay] use”; and (3) if it were limited by a new drug application to use under the supervision of a licensed practitioner. All drugs that did not fall into one of the three enumerated categories were to be available OTC.

The Durham-Humphrey Amendment reduced the regulatory uncertainty that had existed under the FDA’s regulations for determining a drug’s dispensing status. Even under Durham-Humphrey, however, there were circumstances that still called for the exercise of manufacturers’ discretion when determining whether a product should be prescription or OTC — especially for drugs that were not either habit forming or the subject of new drug applications (NDAs). It was only as a consequence of the Drug Amendments of 1962, with the broadening of the “new drug” definition and the FDA’s efforts to reevaluate the legal status of pre-1962 drugs (including “old” and “new,” OTC and prescription), that the line between OTC and prescription status has become more discernible.

The dividing line still is not as bright as it might be because the dispensing status of a drug under the second criterion of Durham-Humphrey, mentioned above, is largely dependent on two distinct factors — a drug’s composition (including its route of administration) and the uses for which it is intended. If the composition of a drug, irrespective of its intended use, is such that it presents risks that are beyond the ability of laymen to safely assume, then it will be regulated as a prescription drug. If a drug, by reason of its composition, presents no inherent risks to a layman but is intended for a medical condition that is beyond the layman’s capacity to recognize and treat, then it too will be a prescription drug. If a drug of that same composition, however, were to be labeled with directions for use that were within a layman’s ability to understand and use without risk, it would be an OTC drug.

This variable situation has been recognized by the FDA (albeit uncomfortably) and is an element of the agency’s ongoing OTC drug review, which seeks to establish monographs that cover acceptable active ingredients used in OTC drugs together with labeling conditions for the drug products in which those ingredients may be used. In various OTC monographs, the same active ingredients may be used in products having different use indications in their labeling. Some drugs’ indications are restricted by regulation to use in “professional labeling,” which the FDA says is not to be provided to the general public, but only to health professionals. Nevertheless, containers for those drug products could bear both professional and OTC indications if the drugs were distributed and labeled as prescription drugs.

IV. THE DRUG AMENDMENTS OF 1962

When assessed in the light of its thirty-three-year history, it is no overstatement to assert that implementation of the Drug Amendments of 1962 has been the greatest force in the federal regulation of pharmaceutical products since enactment of the 1906 Food and Drugs Act. The immediate impetus for the Amendments was the public revelation of the Thalidomide birth-defect tragedy. But for that event, legislation of a more modest scope would have been enacted.

The Amendments were in many ways an omnibus statute in that they not only modified existing provisions of the drug law but added new ones, the full impact of which was not appreciated for more than a decade after their enactment.

A. The Revised Definition of “New Drug”

The most notable provision of the 1962 Drug Amendments was the explicit broadening of the 1938 definition of “new drug” to add the requirement that before a new drug could enter the market it must be shown to be “effective” for its intended use — the use recommended in its FDA-authorized labeling. The original 1938 requirement was that a new drug must be shown to be safe for such use. While effectiveness had always been a consideration, even when the concept of safety was the only articulated statutory standard, the evaluation of safety itself was based on relative risk. For example, if a drug were indicated for use in a life-threatening or other serious condition but was not adequately effective, it could be deemed not to be safe. If a drug for an innocuous condition was itself innocuous, however, it reasonably could be considered safe even if it did not work. A benefit/risk calculation was applied in the assessment of drug safety.

Under the 1938 law, if a drug were generally recognized among qualified experts as safe for its intended use, it would not be subject to classification as a “new drug” and could be marketed without having to undergo any premarket review by the FDA. Under the 1962 revision of the definition of new drug, if a drug were generally recognized by experts as safe but not effective for its intended use, or if it were recognized as effective but not safe (i.e., its risks outweighed its benefits), it was classified as a “new drug” requiring premarket review and approval by the FDA.

As the 1962 new drug provisions were interpreted by the Supreme Court in 1973, for a drug not to come within the “new drug” definition, it was necessary that general recognition of its safety and effectiveness be based on the same quantity and quality of data as would be necessary to obtain FDA approval of a new drug application. Thus, according to the Court, there was no practical distinction, insofar as the quality and quantity of data on safety and effectiveness were concerned, between a product obtaining an approved NDA and a product being classified as a “not-new drug,” that is, a drug that was generally recognized among qualified experts as safe and effective for its intended uses.

Prior to the enactment of the Drug Amendments of 1962, administrative precedent had been firmly established that a drug that had been the subject of an NDA under the 1938 new drug definition could shed its new drug status with the passage of time and the acquisition of marketing experience. To use a short-hand expression, a “new drug” could become a “not-new drug” or an “old drug” — that is, a drug accepted by the FDA as being generally recognized as safe. Once a drug product had cast aside its “new drug” status under the 1938 definition, either by FDA pronouncement or as a result of the manufacturer’s own decision, other products of its genre from other sources could freely enter the marketplace with the same pattern of labeling, but without having to go through any FDA regulatory clearance procedure. (Such products came to be referred to as “me-too” drugs.) Until 1963, such a transformation was, for the most part, accepted by the FDA and could be rationalized under the then-existing statutory provisions. In 1964 the FDA began to construe the 1962 amendments such that the shift from “new drug” to “old drug” status was not only halted, but was reversed for many of those products that had made the transition from “new” to “old” prior to 1962.

The process by which FDA began to turn “old drugs” back into “new drugs” came about during the Drug Efficacy Study Implementation (DESI) review, an administratively created program that sought to apply the 1962 statutorily mandated assessment of effectiveness to all “new drugs” that had been cleared for marketing prior to 1962 on the criterion of safety alone. In the DESI review, the FDA assembled panels of experts to assess the effectiveness of all pre-1962 new drugs. This review took several years

and even today has not been completely accomplished. Those “once-new” drugs that ultimately were found effective in the DESI review were permitted to remain on the market under renewed new drug applications, and their me-too counterparts also were allowed to stay on, or enter, the market under so-called “abbreviated new drug applications” (ANDAs). The ANDA was an administrative mechanism created by the FDA to subject all me-too drugs to market clearance. It was a concept that might have been challenged as inconsistent with the statutory mandate, but it endured and, in 1984, was statutorily recognized. At that time, the ANDA was expanded substantially in scope, and it has since gained national importance politically, socially, and economically. Most of those pre-1962 new drugs and their me-too counterparts that were not found to be effective in the DESI review ultimately were forced from the market by the FDA, often after years of litigation.

Vestiges of the FDA’s DESI review of pre-1962 drugs exist to this day. The DESI review originally encompassed both prescription and OTC pre-1962 new drugs, but in the early 1970s the FDA embarked on an administratively-created program for the review of the safety and effectiveness of the active ingredients contained in all OTC drug products, as well as the appropriateness of the labeling of products containing them. That review, which continues today, utilizes FDA-framed and published monographs, originally adopted as notice-and-comment regulations that define the circumstances in which specified active ingredients and labeling representations are generally recognized as safe and effective. As long as a product meets the compositional and labeling requirements of an OTC monograph, it may be marketed without obtaining specific clearance from the FDA.

It is well over twenty years since the OTC monograph program was initiated. While challenges have been raised verbally to its legality since its inception, the program has not been challenged successfully in court. As time passes, the potential for a successful challenge continues to dim.

B. Current Good Manufacturing Practice

While revamping the new drug system was the subject most focused on at the time of the 1962 Drug Amendments’ enactment, it was only one of many notable innovations. In retrospect, the provision of the 1962 amendments that created the concept of “current good manufacturing practice” probably has been of much broader application and at least of equal impact.

Prior to 1962, the only statutory provisions relating to the compositional qualities of a drug dealt with whether it had been prepared under insanitary conditions, whether its container was composed of substances that might render the contents injurious to health, whether its qualities met compendial standards, or whether a substance had been mixed with it so as to reduce its quality or strength. There were no provisions that focused on whether the drug was consistently made in a manner that would provide substantial assurance that it would be what it was supposed to be. The latter focus was provided by Congress in the 1962 Drug Amendments, when it directed that a drug would be deemed adulterated if “the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to . . . current good manufacturing practice . . .” This provision was applicable not only to new drugs but to all drugs subject to the FDA’s authority. While the provision was framed in such a way as to be operational without the need for FDA regulations, the FDA subsequently adopted regulations addressing the principles and practices it believed were essential to

be observed in pharmaceutical manufacturing, storage, and handling to ensure product's quality and integrity. Industry has, on the whole, sought to conform to the agency's prescribed standards, which call for a continuing program of vigilance and control over all of the components and processes involved in the manufacture and handling of drug products from the time of receipt of raw materials through and beyond the shipment of finished product. These standards might be summarized in the catch-words "validation," "documentation," and "investigation," each of which is essential to corroborate the integrity of a drug and its processes.

C. Reportmaking and Recordkeeping Obligations

Perhaps one of the reasons the FDA chose to abandon the "no longer new drug" policy that it had accepted prior to the 1962 amendments was the realization that, if it had not done so, the agency would have lost a significant element of authority that had been included in those amendments; namely, requiring holders of approved applications to establish and maintain records, and to report data to the FDA relating to clinical experience with their drugs for the purpose of assessing whether problems might be occurring of a type, or at a frequency, not foreseen when the drug was approved. While it is now a moot point whether such reports and recordkeeping requirements could have been imposed prior to the 1962 amendments, suffice it to say that the FDA never sought to do so. In utilizing the explicit authority granted in 1962, the FDA has established a systematic program for maintaining awareness of both real and potential problems associated with approved new drugs. The agency has extended this program, to a limited degree, to prescription drugs that have not been required to be the subjects of NDAs.

D. Prescription Drug Advertisements

When the FDCA was enacted in 1938, Congress divided direct regulatory oversight for drug advertising and drug labeling between two separate federal agencies. The FDA was given authority over drug labeling, and the Federal Trade Commission (FTC) oversight of drug advertising. Labeling was defined in the FDCA as "written, printed or graphic matter (1) upon any article [of drug] or any of its containers or wrappers, or (2) accompanying such article." The scope of the word "accompanying" has been interpreted very broadly by the courts so as to include almost any "written, printed or graphic matter" that promotes the drug and is disseminated by a person involved in the drug's distribution.

The term "advertisement" is defined in the Federal Trade Commission Act only in the context of a "false advertisement," which is said to mean "an advertisement, other than labeling, which is misleading in a material respect." The reason underlying the bifurcation of regulatory authority over drug labeling and advertising was purely political, and might be likened to King Solomon actually cutting the infant in half. While the FTC's regulation of drug advertising was to the total exclusion of the FDA, the FTC's authority was less than complete. In the case of advertising addressed to members of the medical profession, the FTC could move only if the advertisement contained a *false* representation of a material fact. For drug advertising addressed to lay audiences, the FTC's authority was broader and applied to "an advertisement other than labeling, which is *misleading* in a material respect."

In the late 1950s, Congress raised concerns about advertising prescription drugs to health professionals in a manner that was considered misleading but which did not

appear to run afoul of the “false representation of a material fact” standard contained in the FTC Act. This concern was addressed in the Drug Amendments of 1962 by requiring certain information to be included “in all advertisements and other descriptive printed matter [pertaining to prescription drugs that were] issued or caused to be issued by the manufacturer, packer, or distributor” The information called for included providing the “established name” (as distinct from the trade name) of the prescription drug in the advertising (and labeling) as well as including in the advertisement “information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in [FDA] regulations” The failure to conform to the FDA’s prescription drug advertising regulations would cause the drug involved to be deemed misbranded.

A controversial element in the FDA’s regulatory policy on the dissemination by a drug manufacturer or distributor of information about its prescription drug products is the application of the First Amendment’s free speech clause. This issue arises where the information presented, although framed in a truthful and nonmisleading manner, goes beyond the FDA-approved uses of the drug involved. While a physician in the physician-patient relationship is free to use any drug in any way seen fit and without fear of FDA regulatory interference, the manufacturer and distributors of the drug may not, in the FDA’s view, recommend it for off-label use no matter how reasonable that use may be.

Direct authority over OTC drug advertising remains subject only to FTC authority, although the line separating written, printed, or graphic material as labeling, and distinct from advertising, is still somewhat illusory. Conceptually, the distinction seems arbitrary.

E. Factory Inspections

Authority for the FDA to make factory inspections has been part of the FDCA since its 1938 passage. The original inspection provision applied equally to all product categories subject to the FDCA. In 1952, the Supreme Court found the provision too vague, and therefore unconstitutional, because it made inspections dependent on consent, but made the refusal to give consent a crime.

In 1953, the inspection provisions of the Act were reframed to authorize factory inspections by the FDA at “reasonable times and within reasonable limits and in a reasonable manner” on presentation of appropriate credentials to the person in charge. The scope of inspection in the 1953 amendment was the same for all product categories subject to the Act, and extended to “all pertinent equipment, finished and unfinished materials, containers and labeling therein.”

In the 1962 Drug Amendments Congress substantially broadened the factory inspection provision as it applied to prescription drugs. While the inspection authority was extended to apply to all things (“including records, files, papers, processes, controls, and facilities”) bearing on whether prescription drugs may be in violation of the Act, specific limitations were provided that denied FDA inspection of “financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this Act), and research data (other than that relating to new drugs . . . subject to reporting and inspection under regulations lawfully issued)”

The scope of inspection remains unchanged since 1953 with respect to OTC drugs that are not new drugs. Nevertheless, for OTC drugs generally, FDA investigators frequently will request, and often be provided with, documents and materials beyond the

scope of the specified statutory inspection authority. For many manufacturers and distributors, discretion remains the better part of valor on this regulatory front.

F. *Registration of Drug Establishments (1962) and Drug Listing (1972)*

Until the 1962 Drug Amendments, there was no mechanism by which the FDA was able to easily ascertain the location of drug manufacturing and processing facilities in the United States. The FDA had to seek out such locations through utilization of whatever information source it might have.

The 1962 amendments imposed a requirement for annual registration of all drug manufacturing and processing facilities in the United States, with exceptions for pharmacies and practitioners licensed under local laws.

The registration requirement applies to all drug facilities, irrespective of whether their products come from, or enter into, interstate commerce. All registered facilities are subject to FDA inspection, the scope of which depends on the character of drugs involved (e.g., OTC or prescription; new or not-new). In fact, the law demands that the FDA inspect each such facility "at least once in the two-year period beginning with the date of [its] registration . . . and at least once in every successive two-year period thereafter." How successful the FDA has been in meeting this requirement is uncertain.

While registration of all drug establishments was a goal of the 1962 amendments, it was only in 1972 that the Drug Listing Act was passed requiring all drugs, including biologics, blood and blood derivatives, diagnostic products, veterinary drugs, and medicated feed premixes to be identified to, and listed with, the FDA by each registered drug establishment. Imported drugs and bulk drugs also were subjected to the listing requirement. Even though foreign drug establishments explicitly were permitted to register by the 1962 law, the FDA has yet to create a mechanism for such facilities to do so. The products of foreign establishments must be listed with the agency, however, as one of the conditions for eligibility to enter the United States.

V. ANIMAL DRUG AMENDMENTS (1968)

When enacted in 1938, the FDCA drew no distinction between drugs for human use and drugs for animal use, nor did the Act distinguish the requirements applicable to such drugs. In its regulations, the FDA had recognized that a drug might be labeled for use in animals and contain adequate directions for that use while, if offered for human use, it would have to carry the prescription legend required first by regulation and subsequently by the Durham-Humphrey Amendment. Thus, for example, sulfanilamide could be marketed OTC if it were offered for veterinary use, but not if it were offered for human use.

Relatively little confusion is known to have occurred relating to the dispensing status of veterinary and human drugs from the 1940s through the 1960s. In 1958, however, the Food Additives Amendment was enacted, through which substances that were not generally recognized as safe for food use were subjected to a requirement that they fall under a specific food additive regulation and be offered for use in accordance with the provisions of that regulation. The Food Additives Amendment applied both to foods for human use (including animal products) and foods for animal use. In the case of foods for animal use, it had become an established practice for veterinary drugs to be mixed into animal feed, either for growth promotion purposes or for disease avoidance

and cure. Because many animals and their by-products are used as food for humans, concern existed with respect to the presence of animal drug residues in food for human use.

From the time of the FDCA's passage in 1938, the original new drug provisions of the Act applied to drugs for veterinary use, as did the antibiotic batch certification requirements. These provisions interacted with the provisions of the Food Additives Amendment when it became part of the statutory structure in 1958. With enactment of the Drug Amendments of 1962, more stringent premarket clearance and licensing requirements were imposed on new drugs, both human and veterinary. Thus, by 1962 three separate clearance procedures (food additive, new drug, and antibiotics) were being imposed on animal drug and medicated feed manufacturers. Because products subject to the Food Additives Amendment were regulated under the food provisions of the Act, separately from drugs, animal drug and medicated feed manufacturers were subject to the less-than-congruent regulatory policies of two separate bureaus within the FDA. In an effort to simplify this regulatory quagmire, in 1968 Congress enacted the Animal Drug Amendments.

The Animal Drug Amendments essentially consolidated the separate regulatory programs previously applicable to animal drugs and medicated feeds. These amendments adopted a procedural mechanism significantly different from that used for the clearance of new drugs for human use, although both had the objectives of ensuring safety and effectiveness. The animal drug mechanism consists of publication of a regulation applicable to each new animal drug that is approved as safe and effective for its intended use. The regulation specifies the holder of the approval, the identity of the drug, the uses to which the drug may be put, whether the drug may be used in animal feeds, and for which types of animals it may be used. If the drug may be used in feed, there are distributional limitations placed on it, requiring that it may be mixed only by a holder of a license permitting such activity and that the medicated feed must be used in conformity with its labeling.

After more than twenty-five years of practical experience under the Animal Drug Amendments, the disparate elements applied to animal drugs in the 1960s have largely, but not completely, merged into an harmonious regulatory scheme.

VI. THE ORPHAN DRUG AMENDMENTS (1983-1988)

The Orphan Drug Amendments (ODAs) (1983, 1984, 1985, and 1988) are some of the few provisions of the FDCA that offer the potential of financial reward as an incentive to drug development. Because many medical conditions occur relatively infrequently, an all-out effort to develop a treatment for them is often economically unfeasible. It was to encourage such development that the ODAs were enacted, and their application in the years since has demonstrated the value as well as the risks of such statutory encouragement.

Seeking a mechanism to encourage the development of drugs for the treatment of serious diseases that afflict small numbers of people (such as Huntington's Disease, Myoclonus, Arterial Lateral Sclerosis/ Lou Gehrig's Disease, Tourette Syndrome, and Muscular Dystrophy), Congress chose a course of providing grants-in-aid, tax credits, and a seven-year period of marketing exclusivity. When initially enacted in 1983, the ODA granted eligibility for such incentives to manufacturers of drugs for diseases that occur "so infrequently in the United States that there is no reasonable expectation that the cost of developing . . . a drug . . . will be recovered from sales in the United States of

such drug.” The first ODA also limited orphan drug eligibility to products for which patents “may not be issued.” Congress provided that the FDA was to determine orphan drug status of a particular drug for a particular disease. At that time, Congress did not enumerate the infrequency of disease occurrence that would be the basis of identifying an orphan drug.

In 1984, Congress decided that one numerical quantity to define the incidence of a rare disease would lead to more definite determinations of orphan drug eligibility, and chose the number 200,000. A year later, Congress also dropped the requirement for patent ineligibility as a criterion for orphan drug designation. In 1988, Congress concluded that “the request for designation by the FDA of a drug should be made prior to the time a new drug application is submitted.”

Since 1988, there have been no additional amendments to the Orphan Drug Act, and the criteria currently in effect for orphan drug designation are:

- A drug will be automatically eligible if incidence of the disease it will treat in the United States is 200,000 or less at the time of the request for designation (eligibility also exists if incidence is more than 200,000 if it is shown that there is no reasonable expectation of cost recovery);
- designation as an orphan drug must be requested prior to submission of a new drug application;
- any number of persons may obtain designation, but only the first to obtain new drug approval wins seven years of market exclusivity;
- exclusivity may be shared between persons, either by consent of the initial holder or by determination of the FDA that the initial holder cannot ensure the availability of sufficient quantities of the drug to meet the needs of persons with the designated disease;
- exclusivity continues for seven years from the date of approval even if the incidence of the disease increases beyond 200,000;
- tax credits for clinical testing of the designated drug for the designated disease are available to each person holding the designation, whether or not the person obtains orphan drug exclusivity; and
- the determination of whether a designated drug is the “same” for more than one person is to be made under the standards of the FDA’s orphan drug regulations and can be subject to judicial review.

Through fiscal year 1993, more than 550 orphan drug designations were granted and over 100 orphan drug approvals issued. While the “winner-take-all” philosophy of the ODA may be harrowing, the legislation’s impact has been substantial and has resulted in the development and approval of drugs that otherwise might not have been available.

VII. DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984

The structure and implementation of the new drug provisions of the 1938 Act required that each new drug applicant provide adequate clinical data to support approval. While the FDA permitted an applicant to utilize and rely upon safety (and efficacy) data generated by another person if that person gave consent, the FDA would not do so otherwise. The FDA looked upon those data as proprietary to the person generating

them.

After enactment of the 1962 Drug Amendments, the initiation of the Drug Efficacy Study Implementation (DESI) review (the effectiveness evaluation of pre-1962 new drugs), and the creation by the FDA of the abbreviated new drug application (ANDA) concept (which did not require independent clinical data), many generic drugs entered the marketplace with FDA approval. The agency, however, was staunch in not entertaining ANDAs for post-1962 new drugs. For such drugs, the FDA continued to consider the essential preclinical and clinical data to be proprietary.

Early in the 1980s, the FDA began to utilize a concept that became known as “paper NDAs.” This was a drug approval process in which published studies (clinical and/or preclinical), if adequate, could be used to support the safety and effectiveness of generic versions of post-1962 new drugs. Implementation of the paper NDA procedure was unwieldy, although it successfully passed muster in the courts.

In an attempt to resolve problems relating to the availability of ANDAs, Congress enacted the Drug Price Competition and Patent Term Restoration Act (popularly called the Hatch-Waxman Act) on September 24, 1984. This statute, which dramatically altered the drug approval scheme, represented a compromise between brand-name and generic drug interests. In the more than ten-year period intervening since its enactment, the statute has generated both success and tragedy, the tragedy aspect of which is discussed later in this article.

The Hatch-Waxman Act utilized three concepts, which are listed and then discussed below:

- Statutorily structured ANDAs, with potential for a six-month period of marketing exclusivity for the product covered by the first approved ANDA;
- potential for a period of “nonpatent” exclusivity for NDAs; and
- potential for patent extensions for drugs for which patents had issued before approval of their NDAs.

A. *Statutorily Structured ANDA*

The ANDA concept adopted by Congress closely resembled the structure that the FDA had developed for DESI-effective drugs. It eliminated the need for preclinical and clinical data, and permitted approval of an ANDA where certain specified elements were satisfied. The ANDA had to refer and cite to the listed drug on which it was patterned; it had to have the same active ingredient(s) and the same dosage form as the reference listed drug and be of the same strength; it had to be made in conformity with current good manufacturing practices; and it had to be shown to be bioequivalent to the listed drug. If the listed drug were the subject of a patent, the ANDA applicant had to provide certification as to the status of the patent. If the ANDA applicant was of the view that a patent that claimed to cover the listed drug was either invalid or not infringed by the ANDA, certification to that effect had to be provided as well as notification to the holder of the patent and the NDA. If a patent infringement action were brought against the ANDA applicant, the FDA could not grant an effective approval of the ANDA for thirty months, in the absence of a court order to the contrary. If the ANDA holder prevailed in or avoided a patent action, and it was the first ANDA to be approved for that drug, a six-month period of freedom from generic competition was the reward.

B. Nonpatent Exclusivity

NDA "nonpatent exclusivity" was provided under specified circumstances as a form of compensation to the holder of an approved new drug application. For NDAs that had been approved on or after January 1, 1982 and up to September 24, 1984 (and that contained no active ingredient that was in any other approved application), no ANDA for such a drug could be approved for a ten-year period from the NDA approval date. Two years of freedom from ANDA competition (that is, to September 24, 1986) were granted for all NDAs that had been approved between January 1, 1982 and September 24, 1984. (All pre-enactment grants of nonpatent exclusivity had expired by September 24, 1994.)

Five-year and three-year periods of nonpatent exclusivity continue to remain available under the statute. A five-year period from ANDA approval is granted to NDAs for new chemical entities, i.e., those containing no previously approved active ingredients. A three-year period is granted to NDAs and supplements for which new clinical studies are essential for approval.

C. Patent Extensions

Patent extensions were authorized by the Hatch-Waxman Act to holders of patents for approved NDAs, as a form of compensation for patent time that was lost prior to NDA approval. The duration of such extensions is derived from an intricate formula using a combination of the time periods covered by the investigational new drug (IND) and the NDA. The maximum period of patent extension provided is five years.

In the decade since its enactment, the Hatch-Waxman Act has radically altered the drug availability pattern in the United States. At one time, ANDAs were looked upon with disdain by the research-oriented, brand-name segment of the drug industry. Today, there is hardly a brand-name drug company that does not hold its own ANDAs.

VIII. GENERIC DRUG ENFORCEMENT ACT OF 1992

In 1988, as implementation of the Hatch-Waxman Act was approaching full momentum, a series of apparently unrelated but disturbingly similar events came to light. These events revealed the existence of corruption in the FDA and in segments of the generic drug industry. The events involved bribery and pay-offs that had taken place in the ANDA review and approval process. Several companies ultimately were implicated and convicted for submitting false data to the FDA, and many individuals in industry and the FDA were convicted for criminal offenses. Perhaps the most amazing facet of this tragic tale is that no users of the implicated drugs were known to be injured.

Reaction to the scandal was swift and dramatic. Aside from the fines and prison terms that ultimately were imposed, the "generic drug scandal" also resulted in enactment of the Generic Drug Enforcement Act of 1992 (GDEA).

The GDEA and its sanctions focused largely, but not exclusively, on the generic drug industry. The Act set out procedures intended to guard against recurrent corrupt events of the type that were known to have taken place, so as to protect the integrity of the drug approval process, particularly with respect to full and abbreviated NDAs. Applicants submitting either NDAs or ANDAs must certify that no one in any way connected with those applications has been debarred under the statute's provisions. Additionally, ANDA applicants have to submit with their applications a list of persons re-

sponsible for the development or submission of the ANDA who have been convicted of specified crimes within the previous five years. The GDEA, however, does not provide for criminal sanctions; rather, it focuses on excluding persons convicted of various criminal offenses from participation in the drug industry. Additionally, the GDEA provides new mechanisms for withdrawing and suspending approved ANDAs and for blocking approvals of pending applications.

A. Debarment: Mandatory and Permissive

The GDEA provides for two types of debarment: “mandatory” and “permissive.” Mandatory debarment is required to be imposed through appropriate administrative proceedings involving individuals convicted of a federal felony for conduct relating to the development or approval of any drug product or “otherwise relating to the regulation of any drug product under the” FDCA. Although they are required to be based on a prior conviction, mandatory debarments are not self-executing, but rather are dependent on specific findings of the requisite conviction(s). Because of the simplicity of this procedure and the self-evident nature of the required findings, however, any appeal to the courts of an administratively imposed mandatory debarment presumably would be limited to issues about the constitutionality of the statutory debarment provisions and their appropriate application to the debarred person’s conduct. Mandatory debarment will endure throughout a debarred individual’s lifetime.

Permissive debarment for a period of up to five years is authorized, but not required, to be imposed for certain federal misdemeanor convictions, state felony convictions, and for specified activities that need not be preceded by any conviction. Generally, the various grounds for imposing permissive debarment are aimed at punishing conduct that, while not rising to a level that would justify mandatory debarment, nevertheless poses a significant threat to the integrity of the drug approval process. Because such grounds are more fact-specific than the grounds for mandatory debarment, various factual findings must be made for permissive debarment that take into consideration the nature and seriousness of the person’s conduct. Unlike most of the FDA’s other administrative powers, the GDEA provides subpoena authority for the agency to investigate and conduct all debarment proceedings.

Debarment, both mandatory and permissive, can be imposed on individuals or persons other than individuals (i.e., corporations, partnerships, and associations). Both mandatory and permissive debarment of an individual precludes the debarred person from providing services in any capacity to a person (i.e., any entity) that has an approved or pending drug product application (ANDA or full NDA). Thus, a debarred individual is excluded from being employed by, or acting as an agent for, the vast majority of pharmaceutical manufacturers in the United States as well as foreign companies holding or seeking any application through the FDA. To put teeth into these provisions, the statute further provides that civil financial penalties can be imposed on both a debarred person who violates the conditions of debarment and a person who employs or retains a debarred individual.

For entities other than individuals, the scope of debarment is more limited; the debarred entity is excluded only from submitting, or assisting in the submission of, any ANDA to the FDA. This is no minor limitation, but it is not total exclusion from the industry. This debarment is for a period of not less than one year and not more than ten years, but a subsequent act that leads to a second debarment within ten years of the initial debarment will result in permanent debarment of the same scope as for individu-

als. Thus, the differences in mandatory debarment for individuals and for other entities are dramatic.

The foregoing is a general discussion of the statutory grounds and bases on which the FDA may impose mandatory or permissive debarment on individuals and other entities. The statutory provisions pertaining to mandatory debarment of individuals clearly reflect congressional intent to exclude from the drug industry persons who have been convicted of criminal offenses. While it may not be difficult for the agency to impose mandatory debarment, permissive debarment depends on agency fact-finding that ranges from difficult to impossible to establish, particularly when the individuals in question have not been convicted of a criminal offense. The FDA's expenditures in time and resources to achieve permissive debarment likely will be so substantial as to make that concept useful chiefly for its *in terrorem* effect on potential miscreants.

Through June 1995 (the three-year period after enactment of the GDEA), a total of thirty-six mandatory debarments of individuals had been imposed (four involving former FDA officials). During that same period, however, there have been no "other entity" debarments, nor has there been a single permissive debarment of an individual.

B. *Civil Penalties*

Under the heading of civil penalties, the GDEA sets forth criteria for imposing monetary liability for conduct by individuals and "other entities" under a variety of circumstances. Several of these courses of conduct are, independent of the GDEA, also grounds for judicial criminal prosecution of the entities involved; others are not, such as the knowing employment of a debarred person by an entity that has an approved or pending drug application, or a debarred individual providing services "in any capacity" to a person with an approved or pending application. For each violation, the monetary liability under the GDEA can be as much as \$250,000 for an individual and \$1,000,000 for any other person. These civil penalties can be sought through either an administrative proceeding initiated by the agency or through a judicial civil action initiated by the Attorney General. In addition, there are awards of up to \$250,000 available to individual informants who provide information leading to the imposition of a monetary penalty against another person.

C. *Limitations on Liability*

While the GDEA provides that the passage of time (up to ten years) will bar the imposition of most debarments and civil penalties, an approved ANDA may be administratively withdrawn, without time limitations, where bribery, payment of an illegal gratuity, fraud, or a material false statement was involved, or where the applicant repeatedly has demonstrated the inability to produce the drug in accordance with application standards and the drug has been adulterated or misbranded on attempted entry or actual introduction into interstate commerce.

This article section has violated the article's title in that it is not "in easy-to-swallow capsule form;" rather, it constitutes an uncomfortable bolus dose. Its complexity arises from the congressional wrath after the generic drug scandal, which produced unique legislation in this area. The degree to which the GDEA will impact the conduct of those potentially subject to its provisions will be assessable only in the years ahead.

In both the 1906 Food and Drugs Act and the 1938 FDCA, Congress limited the adulteration and misbranding provisions to the distribution of products in interstate commerce. These provisions comprised the prime mechanism by which goods could be deemed violative and subject to seizure, and the persons responsible could be held subject to liability.

While Congress did not intentionally encourage the shipping abroad of goods that would be considered adulterated or misbranded under the FDCA if distributed domestically, Congress at least implicitly deferred to the sovereignty of foreign nations and cast on them responsibility for determining the suitability of drugs entering their jurisdiction. In both the 1906 and 1938 Acts, Congress permitted the exportation of drugs that would be considered adulterated or misbranded if offered in domestic interstate commerce, so long as those goods did not violate the law of the country to which they were being exported, met the specifications of the foreign purchaser, and were described on their shipping containers to be for export only.

A violation of the new drug provisions of the FDCA was not classified as either an adulteration or misbranding. Rather, such violations were of their own kind — called “new drug” violations. As a consequence, when the FDA turned to the subject of the export of unapproved new drugs, it concluded that the export provisions of the Act applied only to adulterations and misbrandings and, if a drug were an unapproved new drug, it was not eligible for export.

The FDA’s imposition of ineligibility on unapproved new drugs for export was both applauded and condemned. The applause came from those who believed that it would be immoral for the United States to permit the export of drugs that could not be marketed domestically. The condemnation came from those who were of the view that limitations on unapproved new drugs were contrary to the international law principle that sovereign nations are entitled to make their own determinations as to what they will or will not accept within their borders.

The FDA held steadfast to its restrictive position over the years. As a partial consequence, many American manufacturers opened facilities abroad at which they manufactured and sold drug products that met the standards of the nation in which they were made, but had not acquired approved new drug status in the United States. American companies thus legitimately were able to market abroad drugs made in their foreign facilities that could not be marketed in the United States until an NDA had been approved. The fact that certain drugs were available abroad, but not at home, raised the issue of the so-called “drug lag” under which the United States was claimed to have fallen behind other nations in the availability of new drug products. The situation also was pointed to as contributing to the general economic detriment of the country through reductions in both employment and new pharmaceutical products.

In 1986, Congress enacted the Drug Export Amendment Act. That statute opened the export door part-way by authorizing distribution of unapproved drugs from the United States to specified countries under specified circumstances.

Twenty-one countries were identified by name in the Act as potentially eligible to receive unapproved drugs from the United States. These countries had regulatory programs that supposedly were capable of evaluating drug products and that already had approved the particular drug sought to be exported from the United States. The drug intended to be exported had to have the same active ingredient as an unapproved new drug that was covered by an investigational exemption in the United States, and for which approval was being pursued actively by the person holding the exemption. A number of other conditions and commitments were required to be made by the exporter,

including obtaining approval of an export application from the FDA and limiting distribution of the drug only to the specified eligible countries.

In the nine years since enactment of the Drug Export Amendments, a substantial number of export applications have been acted upon favorably. A question continues as to whether the limitations of the statute are necessary and/or beneficial for either the United States or for the foreign nations to which the drugs are exported.

X. PRESCRIPTION DRUG MARKETING ACT OF 1987

The Prescription Drug Marketing Act of 1987 (PDMA) was enacted to curb perceived abuses in the prescription drug distribution scheme. These perceived abuses were thought to occur in at least four distinct areas.

One area of perceived abuse involved the re-entry into the United States of prescription drugs that previously had been legally exported from the United States by American manufacturers (a process known as the "gray market"). Circumstances often permitted such drugs to be re-offered by their overseas recipients for U.S. distribution at lower prices than the manufacturer charged to its domestic customers in the United States. Concern was expressed by American manufacturers of these "re-entered" drugs that the drugs' integrity might have been compromised during transshipments from abroad and that they might constitute a threat to the health of those to whom they would be administered. Additionally, concern was expressed that the drugs' re-entry in the United States enhanced the ability of counterfeiters to copy the genuine articles.

Congress, being persuaded as to the merits of the perceived health and safety risks involving "American goods returned," enacted legislation that prohibits the importation into the United States of a "drug subject to § 503(b) [of the FDCA] which is manufactured in a State and exported unless the drug is imported by the person who manufactured the drug."

The PDMA sought to correct a second perceived abuse in the drug distributional system that involved manufacturers distributing samples of their drugs with the intent that the samples would not be sold but would promote only the sale of commercial packages of the drug. Concern in this area arose from the fact that drug samples distributed by a company might, contrary to the manufacturer's intent, be sold by persons employed to distribute the samples or by the persons to whom the samples were distributed. Congressional findings indicated that such practices had gone on "for decades and has resulted in the sales to consumers of misbranded, expired, and adulterated pharmaceuticals . . ." To curb this practice, Congress imposed strict limitations on the sale, purchase, or trade of any drug sample, and provided severe criminal and civil penalties for violations. These sanctions apply not only to the act of improperly disposing of the samples, but also to the sale, purchase, or trade of coupons through the use of which a drug may be obtained at no cost or at a reduced cost.

A third area of concern addressed by the PDMA pertains to the mode of distribution of drug samples. To curb the sale and diversion of drug samples, Congress devised an elaborate scheme of required documentation and accountability. Distribution of drug samples is limited under the Act to practitioners licensed to prescribe such drugs, and can occur only in response to a written request by such practitioners for themselves or for health care entities. The practitioner must provide a receipt containing specified information for such samples. If a drug distributor wants to provide drug samples by means other than the mail or common carrier (e.g., by company representatives), an even more complex scheme of control is imposed by the PDMA.

The fourth concern addressed by Congress in enacting the PDMA pertained to what was called the “diversion market.” Curbs were placed on the activities of certain wholesale distributors, as well as the bulk resale of below-wholesale-priced prescription drugs by health care entities. In the case of health-care entities, the statute essentially restricts the disposition of drugs to certain affiliated entities; a wholesaler who has not been authorized as a distributor of a drug by its manufacturer must provide to “each wholesale distributor” a record listing each previous sale of that drug.

In the nearly eight years since its passage, there is no clear assessment of what has been remedied, accomplished, or crippled by the PDMA. It is a cumbersome statute both for industry and health-care professionals to comply with and for the FDA to enforce.

XI. PRESCRIPTION DRUG USER FEE ACT (1992)

From 1938, when the new drug provisions of the FDCA were initially adopted, through September 1992, the cost of the FDA’s review of NDAs was borne entirely by U.S. taxpayers. During much of this time, there was dissatisfaction on the part of applicants with the slowness of the agency’s review, particularly because the statute required that the process be completed within 180 days and it never was. To alleviate the situation, the Prescription Drug User Fee Act of 1992 (PDUFA) was enacted.

PDUFA imposes charges upon persons who submit:

- full NDAs and supplements for which clinical data are required;
- certain section 505(b)(2) applications;
- antibiotic applications to which no existing certification monograph applies; or
- applications for licensure of a biological product.

PDUFA contains its own definitions for terms such as “human drug application,” “prescription drug product,” and “final dosage form.” Each term has a more restrictive statutory meaning than might be assumed from the individual words that comprise the phrases. PDUFA imposes a schedule of fees based on the nature of the application submitted. The fee structure commenced in 1993 with a fee of \$100,000 for a full new drug application, and is to advance to \$233,000 in 1997. In addition, there are annual fees levied for the facilities in which approved new drugs are manufactured (starting with \$60,000 in 1993 to \$138,000 in 1997) and fees for each approved prescription drug product that is the subject of a full NDA (ranging from \$6000 in 1993 to \$14,000 in 1997). The prescription drug product fees need not be paid if an ANDA or a section 505(b)(2) NDA is approved for that product. There also are provisions for waiver or reduction of fees for reasons specified in the law.

The impetus for PDUFA was to pass on to the applicant at least part of the cost of the FDA’s review of an application, on the theory that the applicant would benefit commercially if the drug were to be approved and marketed. Another goal of PDUFA was to provide additional funds, incentive, and encouragement so that the FDA would review applications more expeditiously.

The funds derived from the various user fees are intended to be dedicated to the drug review process for hiring additional review personnel at the FDA. Congress included in PDUFA a sunset clause of October 1, 1997, which will result in termination of the law at that time unless it is renewed, with or without modification.

XII. CONCLUSION

This article has discussed various substantive amendments to the drug provisions of the FDCA that currently are in effect. Each of these amendments was enacted for the purpose of improving the performance of the law in a manner considered appropriate by its enactors. In some instances, a particular statute has broadened drug approval opportunities and has altered significantly the historical structure operative at the time of its passage. Whether such impact has been positive or negative varies with the views of those who have been benefited or burdened by the amendments.

A noteworthy observation is that the FDCA has, over the years, been revised and updated to address new issues that have arisen. The statute has functioned and been administered in a way that is in keeping with the basic structure of our government; at times, the statute also has been misused and abused by some persons within and outside the governmental bureaucracy. As a creature of man, the FDCA cannot be expected to be any better or worse than man's weaknesses and strengths.

It must be acknowledged that this article's discussion of the amendments is neither exhaustive nor definitive. The author has sought to paint an accurate picture, but there remain subtleties and intricacies that can be grasped only by an in-depth familiarity with the language of the statutory provisions, with the FDA's regulations and policies, and with the judicial interpretations that have been handed down through the years.