The Crystallization of American Drug Law

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The necessity of strong drug laws, vigorously enforced, is no longer at issue. The mushrooming pharmacopeia of recent years has rendered every individual a potential victim of mistake or fakery.[1] Despite numerous amendments of the Federal Food, Drug, and Cosmetic Act (FDCA)[2] since its enactment in 1938, the specter of drug-related catastrophe has not been banished entirely. During the 1960's, for instance, hundreds of European infants suffering grotesque physical deformities were born to mothers using the tranquilizer Thalidomide during pregnancy.[3] Although Dr. Frances O. Kelsey of the Food and Drug Administration (FDA) courageously refused, under intense industry pressure, to permit general marketing of the tranquilizer in this country, its limited distribution for experimental purposes caused the birth of at least 10 "Thalidomide babies."[4] In another situation, the drug Flexin was associated in less than 3 years with 39 cases of hepatitis and 11 fatalities, of which 20 cases and six deaths were directly ascribed to the medication.[5]

Such incidents raise serious doubts about the adequacy of the current scheme of drug regulation and have prompted the introduction of far-reaching legislation, such as that introduced by Senator Gaylord Nelson.[6] Assuming the indispensable requirement of thorough enforcement, it appears that any effective system of drug regulation must meet five tests. Initially, it must assure that drugs are

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1. "Seven out of every ten prescriptions filled today could not have been filled in 1935." *Hearings on Administered Prices Before the Subcomm. on Antitrust and Monopoly of the Senate Comm. on the Judiciary*, 86th Cong., 2d Sess. 10,685 (1960) [hereinafter cited as *Price Hearings*].
2. Act of June 25, 1938, *as amended* 21 U.S.C. §§ 301 *et seq.* (1970).
3. NEWSWEEK, July 30, 1962, at 70.
4. J. TURNER, THE CHEMICAL FEAST 224 (1970).
5. *Hearings on Drug Safety Before the Subcomm. on Intergovernmental Relations of the House Comm. on Government Operations*, 88th Cong., 2d Sess., pt. 2, at 577 (1964).
6. Omnibus Drug Bill, S. 2812, 92d Cong., 1st Sess. (1971).

safe. This is absolutely essential, being in fact the primary justification for drug regulation and inherent in the reasons for using drugs. Next, the system must assure that drugs are efficacious—able to do what is claimed for them.[7] Failure to do so would permit a double fraud on the consumer. The purchaser would be defrauded both economically by receiving nothing of value for his money, and therapeutically because while using the worthless nostrum he would probably ignore available orthodox remedies. Thus, a worthless medication might be a positive danger to one who believed in and employed it.[8]

Third, in order to eliminate the *potential* for harm, the regulations must act before a drug reaches the market. In addition to the individual consumer's economic loss and therapeutic deprivation in using worthless medications, the public at large pays the price, through higher drug costs and taxes, every time a product has to be litigated off the market. In addition, the system must function quickly and simply, neither delaying unnecessarily the marketing of new drugs nor discouraging research. Delays dilute the value of medications by denying them to those who need them; impediments to research render society vulnerable to future attack by disease organisms which develop immunity to existing treatment. Finally, the regulations must encourage research. The overwhelming majority of medicines now available are the result of the efforts of private industry, spurred by the profit motive.[9] Having proven to be eminently successful, this method should not be materially changed without assurances that the replacement will be equally productive.[10]

This analysis will examine the American experience with the regulation of drugs in light of these five criteria. Having developed a thorough understanding of the strengths and weaknesses of the current structure and analyzed recent proposals for change, it will then be possible to assess the need for viable improvements or alternatives.

REGULATION IN THE PRE-KEFAUVER ERA (1902-1962)

The two major goals of drug regulation, efficacy and safety, did

7. *Hearings on H.R. 11581 and H.R. 11582 Before the House Comm. on Interstate and Foreign Commerce,* 87th Cong., 2d Sess. 80 (1962).

8. United States v. Kordel, 164 F.2d 913, 916 (7th Cir. 1947), *aff'd,* 335 U.S. 345 (1948).

9. "All but one antibiotic discovered since World War II and produced commercially in the U.S. came from American research. And . . . every one . . . resulted from efforts of private pharmaceutical manufacturers." *Price Hearings, supra* note 1, at 10,685.

10. Testimony presented at the Price Hearings indicated that the research accomplishments of American industry far outstripped those of Britain, that extensive state control had rendered the Austrian industry moribund, and that Soviet Russia had not produced a single significant new compound since the Revolution. *Id.* at 10,708.

not developed simultaneously. A sick person is usually unaware whether something he takes is damaging his liver, but he will certainly know whether it relieves his condition. In this sense, efforts have been made to insure efficacy since the first snake oil salesman was run out of town by a citizens' committee. Safety, however, is essentially a mid-20th century consideration because it is primarily a function of potency. A formulation must be of considerable power before an appreciable danger from toxicity or side effects arises, and the compounds in this class are, almost without exception, the products of the past 40 years.[11] It is entirely logical, therefore, that the first primitive attempts to regulate drugs were directed toward guaranteeing effective treatment and that safety did not enter the picture until efficacy had been partially attained.

The first major statement on the problem of efficacy was made in 1902 in *American School of Magnetic Healing v. McAnnulty.*[12] For the present purposes, the significance of the case rests in the Court's discussion of proof of therapeutic claims and its conclusion that "there is no precise standard by which to measure the claims of [competing schools of medical thought], for people do recover who are treated according to the one or the other school."[13] In this rather forlorn statement, the Court signaled its difficulty with a question which has haunted the battle for a workable drug law: *relative* efficacy. The fear was that, should government be allowed to judge efficacy, the opportunity would exist to reject one drug or theory on the grounds that it had less to offer than another. Such an invasion of the doctor's prerogative to treat solely on the basis of his professional judgment has been consistently viewed with great apprehension by the medical profession.[14] The search for a standard by which efficacy might be judged was to have a significant impact on the language of all future drug legislation.

Congress first entered the field of drug regulation with the Federal Food and Drug Act of 1906.[15] The Act did not establish a requirement of either safety or efficacy as such, but demanded that a product have whatever qualities the manufacturer chose to ascribe to it. Section 8 applied the term "misbranded" to all drugs, "the pack-

11. As recently as 1935 the average doctor had no access to drugs powerful enough to be described as "life saving." *Id.* at 10,615.
12. 187 U.S. 94 (1902).
13. *Id.* at 106.
14. Such apprehension remains strong even today. A group of over 200 doctors recently presented a petition to the FDA, challenging the agency's right to advise doctors when they should or should not prescribe particular drugs. *See Doctors Question FDA Authority*, TRIAL, Jan.-Feb. 1972, at 63.
15. Act of June 30, 1906, ch. 3915, 34 Stat. 768.

age or label of which shall bear any statement, design, or device regarding such article, or the ingredients or substances contained therein which shall be false or misleading in any particular." The Act was first tested in 1911, in *United States v. Johnson.*[16] Despite a thunderous dissent by Justice Hughes, the Supreme Court virtually destroyed enforcement efforts by rigidly restricting the misbranding clause, which it found to be "aimed not at all possible false statements, but only such as determine the identity of the article."[17]

Shocked and angered by this judicial emasculation of the Act, Congress immediately amended the clause to include a drug as misbranded "[i]f its package or label shall bear or contain any statement, design, or device regarding the curative or therapeutic effect of such article or any of the ingredients or substances contained therein, which is false and fraudulent."[18] This addition, labeled the Sherley Amendment, permitted the government to move once more against false therapeutic claims, until 1916 when it was challenged in *Seven Cases of Eckman's Alternative v. United States*[19] on the perennial charge that the law had entered the sphere of speculation. Justice Hughes answered for a unanimous court: "Congress deliberately excluded the field where there are honest differences of opinion . . . . It was, plainly, to leave no doubt upon this point that the words 'false *and fraudulent*' were used."[20]

This was to remain the state of the law for 22 years. While the Sherley Amendment prevented the 1906 Act from being rendered impotent, not all "false or misleading" statements could be prosecuted because of the *Seven Cases* intent requirement.[21] Even as amended, the Act did not furnish the threshold requirements of an adequate regulatory system. There was neither a guarantee of minimal safety nor assurance of drug effectiveness. Further, all enforcement was after the fact—the most blatant of violators could not be barred from reaping wrongful profits until a misbranding prosecution could be initiated. With the enforcement of these weak provisions hinging upon the manufacturer's advertising skills, it became clear by the 1930's that the system had to be substantially amended or replaced.

16. 221 U.S. 488 (1911).
17. *Id.* at 497.
18. Act of August 23, 1912, ch. 352, 37 Stat. 416.
19. 239 U.S. 510 (1916).
20. *Id.* at 517.
21. This ready-made defense was limited slightly in Simpson v. United States, 241 F. 841 (6th Cir. 1917), which allowed conviction under the Sherley Amendment for label representations made in wanton disregard of truth or falsity.

Legislation for this purpose was introduced as early as 1933, but it received a hostile reception due to industry lobbying. In 1937 the drug sulfanilamide was distributed throughout the country in a solution of diethylene glycol, a poisonous agent used in antifreeze. One hundred and seven persons died, but the maximum penalty available against the manufacturer was a fine of $26,000 for multiple counts of misbranding. These facts aroused a powerful grass-roots demand for a better drug law and forced Congress in 1938 to enact legislation aimed at ensuring safety as well as efficacy in drugs.[22]

Senate Bill 5, which became the Food, Drug, and Cosmetic Act of 1938,[23] was the first truly systematic attempt to control drugs. It provided a procedure for pre-marketing clearance of all new drugs, and absolutely required disapproval whenever proper tests "show[ed] that such drug is unsafe for use . . . or do not show that such drug is safe" under the conditions prescribed, recommended, or suggested in its labeling.[24] The efficacy standards were redefined by making misrepresentation a form of misbranding. This avoided the probable unconstitutionality of a pure prohibition of doubtful therapeutic claims which had been implied in the *McAnnulty, Johnson,* and *Seven Cases* decisions.[25] Comments on the floor of the House pointed out that this change, combined with the abolition of the restrictive Sherley Amendment language, would permit prosecutions for misbranding without a showing of fraudulent intent.[26] A provision partially defining "false and misleading representations" as those "not supported by persons who . . . are qualified as experts on the subject to which such representation relates"[27] was deleted, however, because it was feared this would lead to confusing battles of experts in the courtroom.

While the safety provisions of the 1938 Act have never been challenged, the efficacy provisions were attacked in *United States v. 7 Jugs of Dr. Salsbury's Rakos.*[28] Noting that the *Seven Cases* decision had rejected the *McAnnulty* thesis of a complete lack of standards, the court held that "[w]hat Congress has done is to permit a

22. C. JACKSON, FOOD AND DRUG LEGISLATION IN THE NEW DEAL 151-68 (1970). This work deals primarily with political maneuvering; for a compilation of all official legislative materials on the efforts to revise the drug laws between 1933 and 1938, see C. DUNN, FEDERAL FOOD, DRUG, AND COSMETIC ACT (1938).
23. Act of June 25, 1938, ch. 675, 52 Stat. 1040.
24. 21 U.S.C. § 355(d) (1970).
25. H.R. REP. No. 2139, 75th Cong., 2d Sess. 7-8 (1938).
26. 83 CONG. REC. 7774 (1938).
27. C. DUNN, *supra* note 22, at 659-60.
28. 53 F. Supp. 746 (D. Minn. 1944).

claim of effectiveness to be found false or misleading where the question of effectiveness is demonstrable as a fact."[29] This meant that misbranding was a question of fact for the jury, to be proved by a preponderance of evidence, and that a court would be justified in overturning only those findings of ineffectiveness made "on the basis of evidence which indicated only a contrariety of opinion."[30] To have held otherwise would have permitted a defendant to fend off conviction with a mere scintilla of "expert" opinion, the situation Congress had been so careful to avoid.

Thus, after 40 years of legislative and judicial efforts, the consumer had a modicum of legal protection. New drugs had to be safe when used as directed in order to be marketed and all drugs had to be as effective as their labeling claimed. This left unsolved two major problems. First, no matter how blatantly false the therapeutic claims of a nondangerous drug, it theoretically could not be barred from the market in the first instance. Further, it was extremely difficult to regulate the efficacy of prescription drugs under the misbranding clause because only rarely does either physician or patient see the actual labeling on such drugs.

The FDA succeeded in at least partially solving the first deficiency through administrative procedures. For its own use in determining approval of a new drug, it formulated a guideline which tied efficacy to the pre-marketing requirement of safety. This guideline is a benefit-risk ratio, in which benefits from the drug must be greater than the attendant risks in order to justify the drug's introduction.[31] The benefit side of this ratio is a function of both the drug's effectiveness and the gravity of the illness the drug is designed to cure. A drug to cure cancer, for example, would be permitted introduction with higher risks than a drug designed only to alleviate influenza. Conversely, a drug possessing little effectiveness or of use only in treating minor ailments would have to be nearly risk-free in order to enter the market.[32]

Thus, minimal pre-marketing efficacy and safety requirements were linked together by administrative action. On the other hand, the complete solution to the efficacy problem and the control of pre-

29. *Id.* at 757.
30. *Id.* at 758.
31. *Hearings on Drug Safety Before the Subcomm. on Intergovernmental Relations of the House Comm. on Government Operations,* 88th Cong., pt. 7, at 150 (1964) [hereinafter cited as *Fountain Hearings*].
32. *Id.*

scription drugs was not to appear without further legislation. Such legislation did not become a reality, however, until almost a quarter of a century after the passage of the 1938 Act.

STANDARDS AFTER KEFAUVER (1962-72)

In 1959 Senator Estes Kefauver, as part of his hearings on Administered Prices, began receiving testimony on the prescription drug industry. By the time the final witness had been heard late the next year, considerable controversy had been generated by the disclosure of intra-industry collusion, grossly excessive profits, and hazards casually inflicted on an unsuspecting public.[33] As a result of these revelations, Kefauver introduced Senate Bill 1552.[34] The bill contained two types of changes: those designed to curb economic abuses, and those aimed at protecting public health.[35] The most innovative aspects of the public health element centered around the concept of efficacy. For the first time a finding of efficacy in use "under conditions prescribed, recommended, or suggested in the labeling"[36] would be required *before any* new drug would be permitted on the market. Moreover, the Secretary would be able to suspend any existing new drug application (NDA)[37]—and hence the sales of most drugs—if he found the drug to be inefficacious.[38] In addition, a statement of a drug's efficacy and dangerous properties would be required in all labeling and advertising.[39]

Additionally, there were imaginative assurances for safety in new drugs. All antibiotics were to be certified on a batch-by-batch basis,[40] allowing certainty as to the strength, purity, and effectiveness of these vital medications. Authority was granted to the Secretary of Health, Education, and Welfare (HEW) to establish official names

33. For a synopsis of the findings of the Administered Price Hearings, see S. REP. No. 448, 87th Cong., 1st Sess. (1961).

34. 107 CONG. REC. 5584 (1961). An identical measure, H.R. 6245, was introduced the same day in the House and assigned to the Judiciary Committee. *Id.* at 5691.

35. *Hearings on S. 1552 Before the Subcomm. on Antitrust and Monopoly of the Senate Comm. on the Judiciary*, 87th Cong., 1st Sess. (1961) [hereinafter cited as *Kefauver Hearings*]. The bill contained two economic provisions, both of which were eliminated before passage. First, it would have amended the Sherman Antitrust Act to abolish certain licensing practices. *Id.* at 20. Second, it proposed amending the patent laws to forbid the granting of a patent for any drug resulting from a molecular modification of a drug or the combination of two or more drugs unless the Secretary of Health, Education, and Welfare determined that the new drug had a "significantly greater . . . therapeutic effect" than the modified or combined drugs. *Id.* at 20-22.

36. *Id.* at 22-23.

37. NDA's are discussed extensively in the text accompanying notes 87-111 *infra*.

38. *Kefauver Hearings, supra* note 35, at 22-23.

39. *Id.*

40. *Id.* at 23.

for drugs,[41] which were to be a required part of all labeling and advertising.[42] This enabled physicians to know the exact contents of any drug despite a welter of varying brand names for the same substance. Finally, all manufacturers of prescription drugs would be required to be licensed.[43]

Hearings on the bill pointed out as a major weakness of the efficacy provisions that no guidelines were included as to the kind of proof of efficacy required.[44] This was remedied by an amended version of the bill that altered the new-drug provisions of the FDCA to require refusal or suspension of an NDA where the Secretary found "a lack of substantial evidence . . . supported by investigations of experts . . . that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."[45] The report accompanying the amended bill emphasized this *substantial evidence* test: "When a drug has been adequately tested by qualified experts and has been found to have the effect claimed for it, this claim should be permitted *even though there may be preponderant evidence to the contrary* based on equally reliable studies . . . ."[46]

The 1938 Act defined a "new drug" as one not generally recognized as safe.[47] The 1962 bill as passed into law added to this definition an efficacy requirement, so that any drug not generally recognized as being effective as well as safe would be a "new drug," no matter how long it had been marketed.[48] This meant that therapeutic claims would have to be proven in new NDA's, and all drugs would be subject to exclusion from the market if they failed to fulfill their claims. This is not to say, however, that as of the date of passage every drug approved for marketing between 1938 and 1962 which lacked substantial proof of efficacy suddenly disappeared. Nine years were to pass before the law of the statute book was applied in even a small way as the law of the marketplace.[49] After a minor burst of

41. *Id.* at 25-26.
42. *Id.* at 22-23. This was also aimed at breaking down the value of trade names, thereby forcing the manufacturers into price competition rather than promotional competition.
43. *Id.* at 23-25.
44. *See, e.g., Kefauver Hearings, supra* note 35, at 2,007.
45. S. REP. No. 1744, 87th Cong., 2d Sess. 5-6 (1962).
46. *Id.* at 16 (emphasis added).
47. 21 U.S.C. § 321(p)(1) (1970).
48. *Id.*
49. There were several reasons for this tremendous lag time. The first was the law itself which in section 107 established a complex timetable under which various classes of drugs were to come under the requirements of the amendments. The second factor contributing to delay was the sheer complexity of the amendments from a legal standpoint. Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Pro-*

initial enthusiasm by FDA in 1963,[50] work virtually ceased until the spring of 1966, when Dr. James Goddard assumed the office of Commissioner of Food and Drugs.

Goddard contracted to have the National Research Council of the National Academy of Sciences (NAS-NRC) evaluate the effectiveness of the pre-1962 drugs. Besides alleviating tremendous logistical difficulties, this procedure had the advantage of including impartial, non-governmental experts in the evaluation process, thereby theoretically rendering the results more acceptable to both the pharmaceutical industry and the medical profession.[51] The actual plan of operation was relatively simple and rapidly executed. NAS-NRC developed guidelines for the Drug Efficacy Study, and selected the experts who were to participate.[52] Meanwhile the FDA assembled the information on which the study was to be based. This was accomplished by means of an order requiring anyone holding an NDA approved between 1938 and 1962 who wished to retain the drug on the market to submit certain types of information to FDA, including a bibliography of publications relevant to the claims made for the drug and a copy of all labeling.[53]

Under the study guidelines, the panels were to base their evaluations on three factors: freely available scientific literature; the material made available by the manufacturer, FDA, or other sources; and

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visions of the 1962 Drug Amendments, 19 FOOD DRUG COSM. L.J. 110, 114-15 (1964). Finally, there was the irreducible bulk of the subject matter. For example, 83 NDA's were approved in 1966. *Hearings on Competitive Problems in the Drug Industry Before the Subcomm. on Monopoly of the Senate Select Comm. on Small Business*, 90th & 91st Cong. 757 (1967) [hereinafter cited as *Nelson Hearings*]. This figure seems insignificant until one realizes the amount of supporting material to be processed with each application. One NDA had 26 volumes at the time of approval and eventually accumulated a total of over 100, covering 137 separate studies. *Id.* at 2,809. The class of drugs to be reviewed, those marketed under NDA's between 1938 and 1962, consisted of approximately 7,000 preparations, of which about 4,000, involving some 300 different chemical entities, were still on the active market in 1966. DIVISION OF MEDICAL SCIENCES, NATIONAL RESEARCH COUNCIL, DRUG EFFICACY STUDY—FINAL REPORT TO THE COMM'R OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION 1 (1969) [hereinafter cited as DES REPORT]. The task of reviewing all of these drugs was far beyond the capabilities of the FDA staff, which could barely keep up with its routine workload.

50. This consisted of formulating a set of new regulations defining "newness" and amending the reasons for refusing approval of NDA's under the 1962 statutory changes which were promulgated in June 1963. 28 Fed. Reg. 6377 *et seq.* (1963). Much of the content of this definition had been found in the law before the 1962 amendments. Merritt Corp. v. Folsom, 165 F. Supp. 418, 421 (D.D.C. 1958).

51. *Nelson Hearings, supra* note 49, at 5178.

52. DES REPORT, *supra* note 49, at 2. For the text of the Guidelines, see *id.* at 39-53.

53. 31 Fed. Reg. 9426 (1966). By the time the period for submissions ended, on June 1, 1967, material had been received on 2,824 drugs, constituting almost 4,000 different formulations because of multiple sizes and dosage forms. Of these, 85 percent were prescription medications. DES REPORT, *supra* note 49, at 5.

their own informed judgment.[54] Their judgments of individual claims made for each drug were to be in the form of one of four ratings: *A*—Effective; *B*—Probably Effective; *C*—Possibly Effective; *D*—Ineffective.[55] In order to accurately convey the feelings of the panels, however, two other ratings, "ineffective as a fixed combination," and "effective, but . . . ," were also developed. The former was used to deal with those drugs, particularly antibiotics, which were effective separately but failed to demonstrate any appreciable advantages when combined. The latter "came to be the preferred rating for drugs for which there was substantial evidence that they did what they were claimed to do but, nevertheless, were no longer approved forms of treatment . . . . This rating [was] used by some panels to draw attention to vaguely worded or misleading claims."[56]

The results of these evaluations can only be described as shocking. Although a "considerable number" of drugs proved to be effective for all claims made, fully 7 percent were *ineffective* for *all* cited claims, and the majority of the drugs were "assigned ratings that [were] quite variable. In some cases, they . . . covered the gamut of the accepted categorical ratings."[57] In other words, in the majority of cases, the drugs upon which doctors and patients had relied failed partially or completely to do what they were represented as doing.

Having received these reports and recommendations, it was up to FDA to implement them. To do this a detailed regime of intra-FDA review was formulated, and put into effect on January 23, 1968.[58]

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54. DES REPORT, *supra* note 49, at 42.

55. *Id.* at 42-43.

56. *Id.* at 7. This graduated scale of effectiveness ratings could be construed as diluting the letter of the amendments, which indicates that nothing less than "efficacy" will suffice. However, given the Act's own attempt to cushion the practical effects of suddenly injecting this new requirement—the elaborate schedule of effective dates for its various provisions—as well as the administrative difficulties inherent in such a task, it appears the procedures conformed to the spirit of the statutory requirements.

57. *Id.* at 12.

58. Bryan & Stern, *The Drug Efficacy Study, 1962-1970*, 4 FDA PAPERS 14, 15 (1970). The review program required the agency to affirm the panel finding as to each claim. If the drug was found to be effective, the agency had to decide whether manufacturers of "me-too" formulations (see text accompanying note 95 *infra*) would be required to file complete original NDA forms or would be permitted to employ an abbreviated form. This step was particularly important because "the implementation of the reports will affect not only those drugs referred . . . for review, but many other similar marketed products (an estimated five products for every one reviewed)." *Id.* at 16.

A *Federal Register* notice was then drafted stating the effectiveness classification and the time allotted for furnishing evidence to support less than totally effective claims under a rule promulgated at 35 Fed. Reg. 11,273 (1970); this scale allows 12 months for "probably effective" drugs, 6 months for "possibly effective," and 30 days for "ineffective." The notices often indicated that other medications containing the same or similar compounds would also be subject to the implementation proceeding. After publication, compliance actions and follow-up procedures such as evaluation of new data were carried out.

The FDA's implementation of the results of the Drug Efficacy Study was targeted for first-phase completion by June 30, 1971, and that deadline was met.[59] Because of the staggered intervals at which further data is required and the necessity for enforcement actions, however, it may be several years before all drugs which were found to be less than effective are brought up to standards or removed.

As the FDA began implementing the results of the Study, the agency found itself confronted with two interrelated problems. Any attempt to banish drugs from the market would have to be based on the statutory definition of substantial proof of efficacy, which is less than a paradigm of clarity. This in turn meant extremely protracted litigation, perhaps even requiring reconsideration in every enforcement proceeding of what constituted an adequate and well-controlled study.[60] In order to solve both these problems, in May 1970 the Commissioner promulgated regulations detailing the agency's criteria for adequate and well-controlled studies.[61]

The merits of these regulations were attacked in *Pharmaceutical Manufacturers Association v. Richardson*[62] where the primary argument against the regulations was that they defined well-controlled investigations "so narrowly and rigidly as to be incompatible with the statutory definitions"[63] laid down by the 1962 drug amendments. The court rejected this view, citing repeated congressional objections to excessive reliance upon testimonials and subjective, uncontrolled observations as evidence offered in support of claims. Rather, the May regulations were found to "describe broad scientific standards for measuring the adequacy of an investigation of effectiveness while leaving the details of the investigation and study to the evaluator.

59. Bryan & Stern, *supra* note 58, at 16. A complete listing of all the drugs evaluated in the study, their efficacy ratings and the FDA action taken is available at F.D. COSM. L. REP. ¶ 72,999 (1971).

60. *See* Bryan & Stern, *supra* note 58, at 17. The magnitude of the problems suggested by this possibility is evidenced by previous examples of full-scale FDA evidentiary hearings, which have run for months or even years. *See, e.g.*, Atlas Powder Co. v. Ewing, 201 F.2d 347, 351 (3d Cir. 1952), *cert. denied sub nom.* Glyco Products Co. v. Federal Sec. Adm'r, 345 U.S. 923 (1953).

61. These regulations had first been promulgated without notice in September 1969, 34 Fed. Reg. 14,598, and were immediately attacked by the industry in several proceedings which reached different results. *Compare* Pharmaceutical Manufacturers Ass'n v. Finch, 307 F. Supp. 858 (D. Del. 1970), *with* Upjohn Co. v. Finch, 422 F.2d 944 (6th Cir. 1970). The Commissioner decided to accept the invalidity of the September regulations, probably a wise move in light of the factual variances between *Pharmaceutical Manufacturers* and *Upjohn*. He re-promulgated the regulations virtually unchanged as a proposal on February 17, 1970, 35 Fed. Reg. 3073, and officially issued them on May 8, 35 Fed. Reg. 7250, thereby proceeding in complete compliance with the Administrative Procedure Act.

62. 318 F. Supp. 301 (D. Del. 1970).

63. *Id.* at 306.

These criteria appear wholly reasonable and certainly are within the Commissioner's power to issue . . . ."[64]

With the addition of a pre-marketing efficacy requirement covering all drugs, the present regulatory structure, at least on its face, satisfies the first three criteria suggested earlier: it covers safety as well as efficacy, and functions before the drug reaches the market.[65] This does not ensure that the individual consumer will be protected in every case, however. Concomitant with the responsibility for immediate consumer protection is the danger that over-zealous regulation by the FDA may prevent new, sorely-needed drugs from reaching the consumer. This balancing of interests has been viewed by some as an unresolvable conflict between the requirements of present and future health.[66] Present health is best served by restricting marketing to safe, effective drugs, while future health is dependent upon new and more effective drugs gaining introduction. To require absolute safety of our present drugs would entail a regulatory system so rigorous that the advent of a new drug on the market would be an extremely rare event, thereby endangering the health of the nation over the long run. In an imperfect world, the balancing approach seems the only workable one.

PROPOSED CHANGES—REGULATORY PHILOSOPHY

While the fundamental approach to ensuring drug safety has seen little alteration since the development of the benefit-risk ratio shortly after passage of the 1938 Act, the attempt to guarantee efficacy has had to undergo considerable change in order to achieve the same level of task fulfillment. Both concepts appear now to have reached a peak of development and crystallized into a complete scheme of drug regulation. Nonetheless, there are numerous proposals for modifying the present system.

Several of these are embodied in the recently introduced Nelson bill which, among other things, would require that in order to be approved a new drug must demonstrate "safety or effectiveness . . . significantly greater than the safety or effectiveness of any other drug . . . which [has] received application approval . . . used for the same purpose or purposes as the new drug."[67] This proviso is a

64. *Id.* at 311.
65. The other criteria, and the success of the system in meeting them, are discussed in text accompanying notes 71-111, *infra.*
66. Note, *The Drug Amendments of 1962*, 28 N.Y.U.L. REV. 1082 (1963).
67. S. 2812, 92d Cong., 1st Sess. § 103(e) (1971).

clear attempt to introduce the bête noire of relative efficacy into American drug law. Senator Nelson's rationale for this radical move is that it "would encourage the channeling of the drug industry's research into more productive and useful areas,"[68] rather than merely duplicating already marketed drugs. While it is possible that it would have this effect, the question remains whether such a contingent advantage is worth the cost.

The medical profession views with grave mistrust any attempt to encroach on one of its oldest perquisites, the right and responsibility of the physician to treat and prescribe without interference. Its unfavorable reaction to present regulations[69] is a strong indication of the probable reaction of the profession to a situation in which doctors would be stripped of their ability to decide which drug would be most beneficial in a given case. There is also the practical difficulty of defining precisely what is meant by the term "greater effectiveness." In testifying on Senate Bill 1552, then Secretary of HEW Abraham Ribicoff posed the following riddle:

> An antihistamine, for example, used to relieve hay fever, may give good results in 80 percent of the patients treated. Another new antihistamine may be effective in 75 percent of the patients, but this 75 percent may include many individuals who get no benefit from the first drug. Would the new drug be patentable [or approvable]? The fact that it treats successfully some patients not relieved by the first drug might indicate that it would; but does it have a 'significantly greater therapeutic effect?'[70]

Finally, it must be recalled that the Nelson plan speaks not only of relative efficacy but of relative safety as well, thereby immeasurably complicating the problems of administration. Projecting the Ribicoff riddle, there arises the situation where an FDA official will have to decide which of two drugs to allow on the market for use against a particular ailment, one more "relatively" effective, but the other more "relatively" safe. These types of decisions can properly be made only by a competent physician with the facts of an individual case. The idea of attempting to determine *in vacuo* which single drug "most" safely and "most" effectively fights a disease which may mani-

68. 117 CONG. REC. 17,601 (daily ed. Nov. 4, 1971).
69. *See* text accompanying note 14 *supra.*
70. *Kefauver Hearings, supra* note 35, at 2597. This riddle also points up the fallacy in attempting to judge safety or efficacy in terms of a fixed standard, such as a percentage of cases. In a large and heterogeneous population under attack by constantly evolving disease organisms, it does little good to tell a sufferer that he is part of the 5 percent, for example, that the "standard" drug doesn't help. The physician should have as many safe drugs at his disposal as possible because in essence every case is different.

fest itself at random throughout a multifarious population of over 200 million persons appears on the perimeter of rationality.

At the other end of the spectrum of proposals, economist Milton Friedman would seem to favor a complete deregulation of the drug industry. He argues that FDA makes two types of errors: approving dangerous drugs and failing to approve drugs with good effects. Because only the first type is readily detectable, FDA personnel "have an enormous incentive . . . to make too many errors of the second kind . . . ."[71] Therefore, the industry should be left to its own unhindered devices, and everyone will be better off because of the myriad of important new drugs which will be developed. While the simplicity of such an approach may be appealing, it fails to recognize that the primary reason FDA's errors in granting approval come so sharply before the public eye is that they are the tragic exceptions to the usual rule of successful regulation. Deregulation would, to name but one example, have allowed Thalidamide unfettered access to the American marketplace. This single drug could have destroyed a generation, and it is but a drop in the mounting tide of new chemical compounds.

The Nelson proposal would complicate drug regulation to a degree difficult to imagine while the Friedman approach is simply blind to the needs of consumers. Neither view has produced a really viable alternative to the present system, let alone demonstrated the need for replacing it. At most, they have raised questions about the practical functioning of a theoretically satisfactory regulatory scheme, and this entails some analysis of the mechanics of regulation.

DRUG REGULATION PROCEDURES

The size of the drug industry and the self-enriching, cumulative nature of scientific research requires the FDA to possess some orderly method of regulating the testing, evaluation, and ultimately the marketing of new drugs. As with other regulatory agencies, the FDA has undergone numerous changes of emphasis and method in order to cope with problems which increase in complexity at a rate matching or exceeding those of society in general. The present methods of enforcing drug laws should be scrutinized for three characteristics. Initially, the FDA procedures must ensure that the theoretical protection offered through premarketing testing for efficacy and safety becomes reality. Moreover, the system should reach this goal while

71. Friedman, *A Libertarian Speaks*, TRIAL, Jan.-Feb. 1972, at 22, 23.

adhering to the two remaining standards previously mentioned: first, that the system neither unnecessarily delay nor present unneeded obstacles to research; and, second, that the system result in a minimal distortion of the free enterprise system.

Drug regulation is divided into two categories. Supervision of experimental drugs is presently accomplished through the procedures for Investigational New Drugs (IND's) and drugs ready for marketing are regulated by the NDA procedures. While the previous discussion has touched briefly on NDA's, the present inquiry into FDA's entire testing and evaluation methodology necessitates a close examination of both procedures in order to determine their value in protecting consumers.

Investigational New Drugs

Because the IND procedures regulate research and development, they reflect more accurately than do other types of drug controls the basic confrontation between the innovators and the regulators concerned with averting medical catastrophies precipitated by hasty, ill-planned research. Section 505(i) of the FDCA, a special provision used solely for research or experimentation, allows sponsors of investigational drugs to apply for an exemption from usual regulatory strictures determining the safety and effectiveness of a drug for NDA purposes.[72] The IND process is a phase through which a drug passes on its way to effective NDA status. This phase has been defined as the "time from the first testing of a new drug on humans to the approval of a new drug application."[73]

An important distinction between present NDA and IND processes is that an IND's effectiveness is not contingent upon affirmative action by FDA. Sponsors submitting IND's must wait only 30 days after the FDA receives notice.[74] If the FDA does not order a restriction on clinical testing within this period the sponsor may automatically begin testing the drug on human subjects. This procedure has created a furor in the press recently, primarily over the use of investigational drugs later found to be carcinogenic.[75] Despite the ap-

72. 21 U.S.C. § 355(i) (1970) provides in part:
> The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this Section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs.

See text accompanying note 88 *infra* for a discussion of the NDA regulatory provisos.

73. Note, *supra* note 66, at 1097.

74. 21 U.S.C. § 355(i) (1970).

75. *See* Washington Post, Oct. 24, 1971, § C, at 1, col. 1. This automatic process is analogous to the automatic acceptance procedure used by the FDA prior to 1962

parent dangers involved, the distinction should be recognized as a valid one because, in minimizing cumbersome administrative procedures for IND's, research is made easier and thereby encouraged. Moreover, although testing may begin 30 days subsequent to filing if the FDA does not restrict, the IND continues to be subject to recall by the FDA.[76] This means that if a manufacturer attempts to take advantage of the FDA's administrative sluggishness under the 30-day rule, he must still run the risk of having his exemption summarily terminated. It is true that human testing could transpire during the period following the 30-day requisite and prior to the FDA's processing of the IND, but this possibility must be tempered by the feasible reluctance of a manufacturer to commence expensive testing before receiving an approval on his IND.

The initial notice of a claimed investigational exemption for a new drug[77] must contain all administrative details regarding the drug including its name, composition, method of preparation, and proposed labeling.[78] In addition, the applicant must give assurance of having performed sufficient preclinical testing to justify the clinical testing on human subjects.[79] Preclinical tests must include toxicity tests on animals,[80] which permits easy quantification of results and thus presents an efficient evaluative device for the FDA.[81] It must be noted, however, that toxicity results do not always remain constant between animals and their human counterparts.[82] Information gleaned from use of the drug in foreign markets indicates safety with much greater reliability than animal testing, and must be included in exemption requests whenever available.[83]

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for NDA's. In that system NDA's became effective automatically if the FDA failed to act on them within 60 days. The 1962 amendments changed this procedure to allow 180 days, or extended times if agreed to by the drug company and the FDA, which had the effect of requiring an affirmative act by FDA before an NDA can be effectuated. 21 U.S.C. § 355(c) (1970).

76. 21 C.F.R. § 130.3(d) (1971).

77. 21 C.F.R. § 130.3 (1971).

78. *Id.*

79. 21 U.S.C. § 355(i)(1) (1970).

80. *Id.*

81. It would seem that easily quantified records would be more difficult to falsify, but this is not always true. In the case of Toole v. Richardson-Merrell, Inc., 251 Cal. App. 2d 689, 60 Cal. Rptr. 398 (1967), the sponsor simply failed to report contra-indications, thereby allowing the drug MER/29 to pass through the NDA process.

82. Moreover, animal testing will be meaningless unless undertaken with attention to the conditions under which humans will receive the drug, including consideration of the "expected duration of administration of the drug to humans and the age and physical status of the patient, as, for example, whether they are infants, pregnant women, or premenopausal women." Note, *supra* note 66, at 1097 n.108. For these reasons, toxicity may not become immediately evident through animal testing, resulting in human usage until toxic results compel discontinuance of clinical testing. The Washington Post recently described a portion of the problem. *The Guinea Pigs,* Washington Post, Oct. 24, 1971, § C at 1, col. 1.

83. 21 C.F.R. § 130.3 (1971). Another item to be included in the exemption

An investigational exemption may be terminated without a hearing,[84] but the FDA must notify the sponsor of violations which might force termination. If these violations are not corrected immediately, the exemption will be terminated.[85] Moreover, this termination is not subject to judicial review, which is appropriate only upon rejection, suspension, or withdrawal of approval of an NDA.[86] Hence, the FDA retains the authority during the investigational process to promptly eliminate an exemption should the course of the research indicate that further research and development pose an unacceptable risk.

As a clinical testing device, the IND process is necessary to free research and development. While the system eliminates the lengthy and burdensome procedure of establishing safety and efficacy through pure research, public safety is maintained by requiring the consent of the individual test subjects.[87] The summary termination of exemptions may cause some delay in research, but those delays are minimal when compared to the time saved by the process generally and are a small price to pay for maintaining the system's integrity. Hence, it appears that present IND procedures are a viable and necessary part of drug regulation.

New Drug Applications

Section 505(a) of the FDCA[88] provides that no "new drugs" may be introduced into interstate commerce unless an approved NDA, one meeting the new efficacy requirement, is on file for that drug.[89]

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request is a statement by the investigator that he will either personally administer or closely supervise the administration of the investigational drug. 21 U.S.C. § 355(i)(2) (1970). Close supervision includes informing human subjects that the administered drug is being used for investigational purposes. The investigator may disregard the consent requirement, however, when in his judgment consent is infeasible or detrimental to the patient.

A further item to be included is the assurance that the sponsor will establish and maintain an adequate record-keeping and reporting system, designed to apprise FDA of all relevant facts in its evaluation of the drug. 21 U.S.C. § 355(i)(3) (1970).

84. An administrative hearing is provided to clinical investigators who face ineligibility to use investigational drugs because of submission of false information or failure to comply with usage requirements. 21 C.F.R. § 130.3(d) (1971).

85. 21 C.F.R. § 130.3(d) (1971).

86. 334 F.2d 844, 845-46 (6th Cir. 1964).

87. *But see* note 83 *supra.*

88. 21 U.S.C. §§ 301-392 (1970).

89. *See* Rutherford v. American Medical Ass'n, 379 F.2d 641, 644 (7th Cir. 1967): "[T]he new drug provisions of the Act, which prohibit introduction of new drugs without approval, apply without reservation to all new drugs." The term "drug" has been the subject of dispute, primarily with regard to the categorization of items as drugs or devices. This distinction is of import to manufacturers because devices are subject to less stringent controls than drugs.

Devices are regulated by section 501 of the FDCA and do not require applications for entry into the market. In AMP, Inc. v. Gardner, 275 F. Supp. 410 (S.D.N.Y.

What constitutes a "new" drug became a matter of great contention following passage of the 1962 amendments. The crux of the dispute was the interpretation of section 107(c), which governs what drugs are subject to the new efficacy requirement.[90] Basically, the amendment categorizes as "new" those drugs which are either not generally recognized as safe and effective for their intended uses[91] or although recognized through investigation as safe and effective, have not been in use to a material extent or for a material length of time.[92]

This simple division provided only a general guideline to the FDA when the agency began to enforce the efficacy requirements.

1967), for example, a new hemostat and suture to be used in tying blood vessels during surgery were encased in a syringe. Proceeding on the ground that the essential element of a product was determinative, the court concluded that encasing the hemostat and suture in a syringe would not override the fundamental nature of the product as a drug.

90. Act of October 10, 1962, Pub. L. No. 87-781, 76 Stat. 780. This uncodified section provides in part:

> (c)(1) As used in this subsection, the term 'enactment date' means the date of enactment of this Act; and the term 'basic Act' means the Federal Food, Drug, and Cosmetic Act.
>
> . . . .
>
> (3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date . . .
>
> (A) the amendments made by this Act . . . insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended . . . apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and
>
> (B) [Effective NDA's shall not be subject to suspension for lack of efficacy] until whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act . . . withdrawing or suspending approval of such application [for other reasons].
>
> (4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application . . . the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

91. 21 U.S.C. § 321(p)(1) (1970).

92. *Id.* § 321(p)(2) (1970). Historically, general recognition of safety or efficacy has been proved through expert testimony, as in Meritt Corporation v. Folsom, 165 F. Supp. 418 (D.D.C. 1958). There the court held that a conflict in testimony among experts on the question of general recognition of safety and efficacy was itself demonstrative that general recognition did not exist. *Accord,* Tyler Pharmacal Distrib., Inc. v. HEW, 408 F.2d 95, 99 (7th Cir. 1969); United States v. Allan Drug Corp., 357 F.2d 713 (10th Cir. 1966); United States v. Article of Drug Labeled Furestrol, 294 F. Supp. 1307 (N.D. Ga. 1968), *aff'd,* 415 F.2d 390 (5th Cir. 1969).

The *Meritt* holding seems contrary to the intent of both the 1938 Act (see text accompanying notes 27-30, *supra*) and the 1962 Amendments (see text accompanying notes 44-46, *supra*), and at least one court has refused to follow it. United States v. 7 Cartons, More or Less . . . Ferro-Lac Swine, Formula Concentrate (Medicated), 293 F. Supp. 660, 666 (S.D. Ill. 1968).

Through a process of argumentation and litigation, both FDA and the industry came to view the entire body of on-market medications as falling into four classes that are treated differently because of the application of the basic definition to specialized fact situations.[93] The first group includes those products marketed under NDA's before 1962, but *not* generally recognized as safe (GRAS). It is conceded by the industry that these drugs became subject to removal for lack of efficacy in 1964, when the grace period provided in the 1962 Act expired.[94]

The second set covers drugs under pre-1962 NDA's which *are* GRAS. These have been viewed by industry as not coming within the definition of a new drug, because they have attained GRAS status.[95] Nonetheless, FDA considers them subject to the efficacy requirement, and this seems the more logical interpretation of the intent of the Kefauver Amendments.[96]

Third, there are the "me-too" drugs which were introduced between 1938 and 1962 without NDA clearance because they were identical to previously approved medications which had become GRAS. While it is not at all clear that the 1962 Act was intended to reach these,[97] the FDA has ordered anyone desiring to market a drug evaluated and found to be effective to submit an NDA on it.[98] Thus, what was formerly a me-too drug must now be approved through an NDA to reach the market.

This leaves for consideration those drugs marketed before 1938 when pre-marketing procedures were not in effect. Commonly referred to as "grandfathered," these drugs meet all the requirements of section 107(c)(4) and therefore, absent a change in label claims, they are completely and perpetually immune to the new drug efficacy requirements. While this may appear to dilute the overall intent of the amendments, the number of medications involved is probably so small

93. Barth, *Following the NAS-NRC Effectiveness Review, What?* 22 BUS. LAW. 1185, 1186 (1967).

94. Pub. L. 87-781, § 107(c)(3)(B), 76 Stat. 780 (1962) (reprinted *supra* note 90).

95. *Id.* at 1187.

96. D'Andrade, *The Effect of NAS-NRC Review on Me-Too and Post-'62 Drugs*, 25 FOOD DRUG COSM. L.J. 330, 332 (1970) points out that "if not covered by an effective application [section 107(d)(4)(C)] requires only that the drug have been generally recognized as safe, its addition to the requirement of 107(c)(4)(B) that the drug not have been a new drug on October 9, 1962, was unnecessary." The industry position was given support by the existence of a number of FDA "opinion letters" stating that individual drugs were no longer considered new drugs, and apparently not subject to the statutory requirements. These were all revoked, however, in a later order. 33 Fed. Reg. 7758 (1968).

97. *See* Barth, *supra* note 93, at 1187; Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 FOOD DRUG COSM. L.J. 119, 125 (1964).

98. 35 Fed. Reg. 11273 (1970).

as to be immaterial and they are still vulnerable to misbranding charges if the label claims are false or misleading.[99] Thus, under the existing law the FDA can require efficacy, as well as safety, of every drug on the market.

Once a product successfully completes the IND procedures and has been determined to be a new drug, it will be subject to the provisions of section 505 and the FDA's NDA procedures. Section 505(b) sets out with specificity the highly detailed information required in the application.[100] Following the submission of an application, the FDA must within six months either approve it or, after a hearing, reject it on the grounds that it contains insufficient information to evaluate safety or efficacy. In the event it is rejected, it will be returned for resubmission with more complete data.[101] To be sufficient such data must comprise "substantial evidence" that the drug will be safe and effective for use.

In light of the complexity of applications, six months appears to be a reasonable waiting period. If applications are rejected and resubmitted with regularity, however, the approval of drugs will be delayed for extreme periods.[102] The substantial likelihood of delay is indicated by the claim that there exists "a climate for the seeming automatic rejection of [NDA's] on the first response."[103] An additional delay may be encountered if the application is amended or supplemented since a substantive amendment sets the official filing date as the date of the amendment.[104] These delays do not affect pre-

99. *See* United States v. Allan Drug Corp., 357 F.2d 713 (10th Cir. 1966), *cert. denied*, 385 U.S. 899 (1966), in which a judgment that a drug was misbranded gave it new drug status.

100. In Toole v. Richardson-Merrell, Inc., 251 Cal. App. 2d 689, 705, 60 Cal. Rptr. 398 (1967), the California court determined that both favorable and adverse information must be reported:

> We think the purpose of Section 355(b)(1) [section 505(b) of the FDCA] is to require submission of all relevant data bearing upon the safety of the drug proposed to be marketed, and that the question of adequacy of such tests and of the data submitted is strictly for the determination of the administrative agency.

A complete list of all components, including any substance used in preparation of the drug, must be furnished under section 355(b)(2). Section 355(b)(4) requires that the application must also describe the methods, facilities, and controls employed in the manufacture, processing and packaging of the drug. Finally, samples of the drug and copies of the labeling to be used with it are to be submitted with the application. *Id.* § 355(b)(5). Orabilex, for example, failed to list renal damage causation in its labeling; by the time knowledge of this adverse reaction filtered back to FDA, causing withdrawal of the NDA, the drug had been associated with 18 deaths. *Nelson Hearings, supra* note 49, at 7221.

101. 21 C.F.R. § 130.11 (1971).

102. One observer foresees a 7- to 10-year period of development and testing before the FDA will approve a drug. *A New Antibiotic Finally Gets Born*, BUSINESS WEEK, Oct. 16, 1971, at S6.

103. Beyer, *New and Investigational Drugs*, 20 FOOD DRUG COSM. L.J. 75 (1965).

104. CCH F.D. COSM. L. REP. ¶ 71,307 (1971).

marketing research, since that function is performed under an effective IND, but they do postpone post-marketing research. Actual utilization of a drug in a wide patient-sampling spectrum provides the truest test of safety and efficacy. The presence of a drug in the mass market is an integral element of ongoing research regarding that drug. Hence, any delay in application procedures after successful IND testing will not only prevent a helpful product from being used, but will also cause a lapse in research. In this sense, procedural delays deprive the scientific community of vital data.

Prompt approval of an NDA assumes added importance for manufacturers desiring to market a completely new drug. The gestation period for a new drug from discovery to marketing may be from 7 to 10 years.[105] This means that a manufacturer able to market a drug may have a substantial lead time over others wishing to profit through introduction of a similar drug, enabling him to secure a substantial portion of the market. The lead time is protected by the FDA's policy of nondisclosure of NDA data. In this respect, the effective NDA acts much like a patent.[106]

Once a drug is marketed it will be allowed unhindered sale unless its NDA is revoked. The only procedural distinction between rejection and revocation of an NDA lies in the burden of proof. An applicant carries the burden of proof until the NDA becomes effective;[107] thereafter, the burden of proving the drug unsafe or ineffective rests with the FDA.[108] The power of the FDA to withdraw approval of an NDA implies that all new drugs remain on the market at the sufferance of the NDA regulatory system, subject to recall at any future date. While counter-balanced by the weighty burden on the FDA, the impact on manufacturers of potential withdrawal of marketed drugs emphasizes the importance of the section 505 procedures.

There are several grounds for withdrawal of approval, but the primary basis for withdrawal is a finding supported by existing information that the drug is lacking in safety or efficacy as evaluated under the same benefit-risk ratio utilized in the initial approval.[109] Any untrue statement of a material fact will also result in suspension of

105. *See* note 102 *supra.*

106. *Nelson Hearings, supra* note 49, at 743. The NDA does not of course provide the exclusivity protection of a patent. *See* 35 U.S.C. 154 (1970). The intricacies involved in the question whether drugs are patentable is beyond the scope of this paper.

107. *See* Ubiotica Corp. v. F.D.A., 427 F.2d 376 (6th Cir. 1970).

108. *See* Bell v. Goddard, 366 F.2d 177, 181 (7th Cir. 1966).

109. 21 U.S.C. § 355(e)(1) (1970). For example, sulfapyridine is allowed despite rare occurrences of toxicity because it has a demonstrated capacity for saving lives.

an NDA.[110] A suspension on the amorphous basis of misstatement of a material fact often results in both a protracted hearing and judicial review. Nevertheless, this standard appears preferable to any others, despite its implicit requirement that the judiciary sift through a myriad of highly technical facts to discover whether a misstatement was "material." For example, a standard based on deliberate misstatement would be virtually unenforceable since proof of the intent would be required. Proof of willful intent would appear a far more cumbersome thing for the court than the present "material" standard. Moreover, use of the intent standard would still involve a standard of materiality as well, to cover instances of deliberate-but-unimportant errors. Despite its definitional problem, the materiality test is the most reasonable and most workable.

Two other grounds for suspension complete the spectrum of section 505(e).[111] First, if the Secretary of HEW is dissatisfied with the methods of production affecting the identity, strength, quality or purity of the drug, he can require changes in those processes. If these changes are not made, suspension may follow. Second, suspension is permitted if the labeling for a drug remains false or misleading after the Secretary has ordered it changed.[112]

Suspension procedures also bear on safety and efficacy, although in an indirect manner. The adverse effects resulting from permitting the previously discussed factors to continue unchecked appears to justify a militant use of the FDA suspension procedures, which complete the spectrum of the FDA's present regulatory procedures. With the rationale and content of those procedures in mind, an analysis of proposals to modify that system is in order.

PROPOSED CHANGES—REGULATORY PROCEDURES

In addition to proposals for modifying standards of efficacy and safety, there have been numerous proposals for altering the structure of the FDA. Again Senator Nelson has offered the most radical suggestions to date. Under one of his proposals,[113] a sponsor which has

110. 21 U.S.C. § 355(e)(4) (1970). Approval may also be withdrawn from an NDA if the applicant fails to establish and maintain a satisfactory recording and reporting system. Reports to be made are of three types: clinical reports, periodic reports, and immediate reports of unexpected or unusual occurrences connected with the drug.

111. *Id.* § 355(e)(1-21) (1970).

112. Though approval may be suspended, withdrawn or refused, these actions are not absolute. Under section 505(f) the Secretary may of his own volition, or upon application, reapprove a drug previously subject to negative action.

113. S. 2812, 92d Cong., 1st Sess., § 513(a) (1971).

completed basic research on a new drug would submit his product to the FDA along with sufficient information to enable the FDA to perform the necessary laboratory and clinical testing. The agency would then be responsible for testing the drug on human subjects as well as for decisions regarding the drug's safety and efficacy. Since this proposal presents such a divergence from present procedure, its ramifications must be thoroughly studied to determine its worth.

Under the Nelson proposal, the FDA would be required to develop, from pure research, data sufficient to justify authorization or denial of a drug within one year.[114] As with NDA's, however, extensions would be available in increments "as needed for such purpose."[115] If a sponsor objected to the extension, he would be able to require that the issue of an extension or the length of the extension be submitted to a drug-testing-review panel for resolution;[116] the panel's decision would be final.

A second modificative feature of the Nelson Bill would allow investigators outside FDA to perform evaluative work under contract in conjunction with FDA personnel. Under the present statute, allocation of drugs for experimental purposes is confined to "qualified experts"[117] who are not employed by the government in any fashion. Although the significance of the term is unsettled,[118] "qualified expert" generally "refers to physicians who have experience in drug investigation and are specialists in the field applicable to the new drug."[119] While apparently adopting the present standard for "qualified experts" the Nelson proposal will change the employers of these experts from the private to the public sector.

Under the same proposal the FDA would implement the revised testing system through the establishment of a National Drug Testing and Evaluation Center.[120] It would be the function of the center to conduct experiments independent of the manufacturer to test the validity of his findings and projected effect on human subjects. Presumably, this clinical testing could be carried directly by the FDA, or be contracted to independent firms.

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114. *Id.* § 513(d).
115. *Id.*
116. *Id.* These review panels, authorized under the proposed section 513, would be empowered to resolve any disputes arising out of objections by the applicant regarding the testing of his drug. Objections specifically noted in the bill relate to the manner, scope, or procedures of the FDA investigation.
117. 21 U.S.C. § 355(i) (1970).
118. Gibson, *The Effect of the Investigational Drug Regulations on Drug Research and Development*, 19 FOOD DRUG COSM. L.J. 153 (1964).
119. Meyers, *The Food and Drug Administration's View of Investigational Drugs*, 18 FOOD DRUG COSM. L.J. 391 (1963).
120. The bill does not attempt to set out a personnel structure for the proposed center.

The need for such a Center rests in a negative aspect of the profit motive:

> Since drug firms are anxious to get new drugs on the market and to increase their sales volume, there is an inevitable tendency—no matter how conscientious the firm—to emphasize the positive features and de-emphasize the negative. Many of the people they engage to do their testing are equally anxious to secure additional contracts for drug testing. FDA has found that the accuracy and objectivity of some of these drug testers leaves much to be desired.[121]

An instance substantiating such conclusions about poor input for IND's is the drug MER/29.[122] After being granted an exemption to proceed with clinical testing of the drug, the sponsor wilfully failed to report data showing that MER/29 caused cataracts to form in the eyes of test animals[123] and made false statements when questioned by the FDA. This vicious conduct only resulted in 6-month's probation for the company and two officers, a company fine of $60,000, and a successful class action by private persons suffering eye damage.[124] The company activities continue to be profitable, however, and in 1971 it reported annual sales of $408 million.[125] The point, of course, is not that a drug company should be irretrievably damaged, but that the penalties are inconsequential to a firm that stands to derive substantial profits until the defects in the product are discovered.

The concept of governmental or government-sponsored testing of investigational drugs has merit insofar as it should provide accurate data for those drugs which the FDA chooses to test through its own facilities. Such accuracy may not become reality, however, due to flaws within the proposal. The conflict of interest problems present among investigators under the present IND format[126] may not be solved by the Nelson proposal. Although sponsors would be unable to choose their own investigators, an admittedly substantial factor in misinformation situations, investigators may still be subject to industry

121. 117 CONG. REC. 17,600 (daily ed. Nov. 4, 1971).
122. *See* Toole v. Richardson-Merrell, Inc., 251 Cal. App. 2d 689, 60 Cal. Rptr. 398 (1967).
123. *Id.* at 697.
124. CCH FOOD DRUG COSM. L. REP. ¶ 72,045 (1971), *citing* FDA Report on Enforcement and Compliance.
125. STANDARD AND POOR'S CORPORATE RECORDS 7827 (Sept. 1971).
126. A recent example is the March 13, 1972, indictment of "a former Food and Drug Administration official . . . on conflict of interest charges for allegedly working for both government and industry on the same birth control research contract." Arizona Republic, March 23, 1972, at 14, col. 1.

pressures. As long as investigators are merely contracted for by FDA, there remains the possibility, however slight, that it will receive distorted or false information. So while the drug center proposal will improve matters somewhat, unless measures can be devised to prevent sponsors from learning the identity of those testing their drug, the misinformation problem experienced by the FDA might still exist under the Nelson proposal.

The proposal will also be costly to manufacturers since the sponsor will have to fund "a proportionate share of the cost of staffing, maintaining, and equipping the center."[127] As the bill stands, this proportionate share is applicable only to participating sponsors—those who have submitted IND's—rather than all members of the industry, despite the fact that the information developed will be available to all. This plan is apparently based on the presumption that all members of the industry will eventually sponsor a new drug or drugs, thereby bringing to bear the capital resources of the entire industry. In one sense, the industry will be paying for the information made available, as well as testing to protect the public. Considering the capital outlay required, however, this appears to be an unnecessary duplication of research facilities.

The deleterious effects of this proposal would more than offset the benefits likely to be produced. The government's investigation costs would be borne by the drug's sponsor.[128] This mode of funding will doubtless meet with much opposition because the sponsor would be required to pay costs he could not control for research he did not plan. Such a situation would almost inevitably have a deterrent effect on the development of new drugs. It is true that in the absence of conjunctive price control the profit motive would still provide impetus for development, but the loss of confidentiality of data—and the resultant loss of the quasi-patent protection—decreases its impact. A viable intermediate approach would be to establish guidelines for submitting research proposals to be approved and implemented by the government, or government monitoring of the manufacturer's research. This would allow a modicum of control by manufacturers that is presently lacking under the Nelson proposal.

Two distinct consequences flow from the existing qualification

127. S. 2812, 92d Cong., 1st Sess. § 513(i)(1) (1971). Another hidden cost is the late-payment interest charge of 6 percent yearly. This interest would be assessed for nonpayment of any charges incurred under all other sections of the Nelson proposal. Additionally, charges unpaid for over a year would be subject to a further delinquency payment of 10 percent of the delinquent amount.

128. *Id.* § 513(i)(1).

procedures for investigators. It has been suggested that while they are informal, they are too stringent in that they place excessive emphasis on academic degrees.[129] First, qualified investigators may react adversely to the stringent qualification process and choose either to leave the drug research field or not to enter the field at all.[130] This ramification is particularly pernicious because it may not become recognizable for years. Although these results inhibit scientific creativity, thereby hindering the flow of valuable new drugs into the market, the Nelson plan makes no changes in the current system. Only the investigator's employer and not the standards for his selection would be changed. Second, there have arisen professional research organizations that are invaluable to smaller companies wishing to sponsor IND's,[131] and more stringent standards will push more drug companies toward their use. Because of wide variance in drugs and their effects, however, the organization researcher must be closely supervised[132] to ensure that methods of testing and evaluation remain sufficiently fluid to allow tailoring of research efforts to the individual drug.[133] These organizations are not, therefore, the best source of clinical testing. While the standards are set on a case-by-case basis by the FDA, it seems that reform should be aimed at the setting of objective standards for assessing experts. These standards should be less stringent than at present and should recognize the value of non-academic researchers.[134]

A final criticism of government testing is that it cuts off the sponsor's research in midstream. Investigators employed by the spon-

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129. The applicant must submit the investigator's qualifications with the IND. The American Pharmaceutical Association, appearing before the Fountain Committee also addressed itself to rigid qualifications regulations:

> Dr. Klumpp, Mr. Chairman, Lest we lean too far in the direction of academic qualifications, I would like to point out and have it on the record that the Nobel Prize-winning observations on insulin were made by Charles Best, who at that time was a fourth-year medical student; that an unknown Lieutenant in the Army, by the name of Beaumont, made perhaps the greatest contribution to the understanding of the physiology of the gastro-intestinal tract, utilizing only one patient; and that the discovery of the effect of digitalis was made by an unknown country doctor in England by the name of Withering.

Hearings on Drug Safety Before the Subcomm. on Intergovernmental Operations, 88th Cong., 2d Sess., pt. 1, at 346 (1964).

130. *See* Gibson, *supra* note 117, at 156.

131. In the *Fountain Hearings, supra* note 31, at 345, the Committee examined the possibility of industry-employed investigators being caught in a conflict-of-interest situation. This could occur through investigators showing partiality for one manufacturer over another for other than scientific reasons. Members of the American Pharmaceutical Association disagreed with this argument, contending instead that investigators were motivated solely by their interest in research and therapy.

132. *See* Kern, *Legal Problems of the Drug Research Director*, 17 FOOD DRUG COSM. L.J. 7 (1962).

133. Kelly, *The Drug Amendments of 1962*, 18 FOOD DRUG COSM. L.J. 145 (1963).

134. *See* note 129 *supra*.

sor would be permitted to perform research only up to the clinical testing stage, with all subsequent work being done under the auspices of FDA. The manufacturer would, in essence, develop a new drug, then turn it over to the FDA, which would determine the actual effect of the drug on humans. This would largely preclude, for example, the manufacturer's research into collateral human uses. Clearly, such limitation on private research would inhibit flexibility and scientific creativity, thereby decreasing the number of new drugs reaching the market.

The foregoing discussion makes clear that the problems encountered by the present regulatory structure do not merit the alterations which have been suggested. This is not to say, however, that the current scheme cannot be substantially improved. At least three types of changes are necessary. First, FDA officials must be encouraged to keep the industry at arms' length, to regulate rather than accommodate. Periodic audits of the personal finances of policy-level officials by the Internal Revenue Service or the General Accounting Office would discourage kickbacks and illicit gifts. Further, a ban on employment in the regulated industry for a set period after leaving FDA, such as has been proposed by Senator Warren Magnuson,[135] would eliminate postponed rewards and hopes of reward for action favorable to a manufacturer.

Second, there should be instituted a system of substantially toughened and imaginative penalties for mishandling of relevant information, whether willful or negligent, by fabrication or concealment. It is as absurd today that any company should damage the sight of hundreds and escape with a fine of $60,000 as it was for the maker of Elixir of Sulfanilamide to kill 107 in 1937 and pay $26,000 for misbranding. Such a revised system might include mandatory imprisonment for responsible persons in cases of willful violations and greatly increased penalties, perhaps a percentage of all profits made on a drug whose NDA was obtained by improper means or a fine for each day a violation was found to have existed;[136] such fines are ne-

135. Magnuson, *Righting a Right*, TRIAL, Jan.-Feb. 1972, at 20.

136. *Id.* at 25:

> Another innovative provision designed to minimize bureaucratic lassitude would permit a citizen to bring suit against an employee of the consumer safety agency, alleging that the employee had failed to perform his statutory duty. Such a citizen suit would resemble a mandamus action, but the court, in addition to ordering a person to perform his duty, could fine or temporarily suspend the individual if he had acted unreasonably. Or the court could fine and/or imprison the individual if his unreasonable action had been in reckless disregard of the public health and safety.

cessary in the context of huge modern corporations. Such a program would have a doubly salutary effect: on the one hand there would be a considerably greater deterrent to improper practices, and on the other the generally excellent work of the overburdened staff at FDA would be highlighted before the public—and the industry—by meaningful prosecutions.

Finally, the number and quality of FDA employees should be increased, which will unquestionably require more funds. One step in this direction might be a system of fees for the processing of IND's and NDA's, as was recently suggested by Senator Abraham Ribicoff.[137] These propositions are founded on the belief that the present system is not essentially defective, but rather the quality of regulation suffers because of lapses of energy, willpower and resources[138] at FDA; problems not correctable by altering internal agency procedures.[139]

CONCLUSION

In the last analysis it is clear that enormous progress has been made in protecting the consumer of drugs since Congress committed

137. 118 CONG. REC. 498 (daily ed. Jan. 26, 1972).

138. Senator Nelson quotes Dr. Frances Kelsey to the effect that the administration of FDA's authority over the multitude of researchers is already nearly impossible. 117 CONG. REC. 17600 (daily ed. Nov. 4, 1971). These numbered some 25,000 in 1967. *Nelson Hearings, supra* note 49, at 771. The FDA is seeking the largest budget increase in its history for fiscal year 1972-73 in order to add about 1,100 persons to its staff. Arizona Republic, Apr. 24, 1972, at 14, col. 1.

139. Senator Nelson's presentation at the introduction of his bill, 117 CONG. REC. 17599-603 (daily ed. Nov. 4, 1971), contains a number of factual errors and considerable rhetorical slight-of-hand, but the two most pertinent examples are the drugs Flexin and Panalba. While Flexin is correctly cited as one instance where willful concealment of information resulted in patient deaths (*id.* at 17600), any mention of FDA's role in the affair is omitted. When the Attorney General was requested to prosecute Flexin's manufacturer he refused, partly because the statute of limitation had run on some of the violations, but also because "Food and Drug Administration medical officers approved the Applications, including that of September 29, 1959 [which revealed 32 cases of hepatitis in Flexin patients] without further inquiry concerning the hepatitis cases." *Nelson Hearings, supra* note 49, at 4016. The other prime example is the combination antibiotic Panalba, of which the presentation declares:

> The Upjohn Company had in its files studies done in 1959 and 1960 which showed that the fixed combination Panalba was not as effective as its ingredients given separately. . . . This information was never called to the attention of the FDA or the medical profession, and was only discovered by an FDA inspector in Upjohn's files on March 7, 1969.

117 CONG. REC. 17600 (daily ed. Nov. 4, 1971). In fact, experts in pharmacology were skeptical of the value of fixed-combination antibiotics as early as 1950, 6 years before Panalba was certified by FDA. *Nelson Hearings, supra* note 49, at 5032. This departure from established principles of chemotherapy was made during the reign of Dr. Henry Welch, FDA's Director of the Division of Antibiotics and one of the foremost advocates of combination drugs, *id.* at 5055, who was ultimately forced to resign because he received over $285,000 for his efforts as editor of two journals supported by drug company advertising. Finally, it is plainly erroneous to state that the FDA had no knowledge of Panalba's lack of value until March 1969, when a proposal to revoke its certification, based on an evaluation of "ineffective as a fixed combination," was published. 33 Fed. Reg. 19204 (1968).

itself to the task with the Act of 1906. That first limited legislative step opened the door for the thorough, systematic regulation of the Food, Drug, and Cosmetic Act of 1938 and its assurance of safety in use. The circle of protection was completed with the advent of the Kefauver Amendment efficacy requirement in 1962.

While there is no lack of proposals for altering this system of regulation, it remains to be shown that fundamental change is required. The present approach maintains the delicate balance between present health needs and the continuous struggle to develop the medications that will be required in the future, and does so while meeting the five theoretical conditions requisite to a complete plan of regulation. In short, only minor modifications, aimed at perfecting the application of regulations by fallible human beings are in order, not a wholesale procedural or philosophical restructuring.

The consumer of American drugs is the beneficiary of a system of safeguards far surpassing that governing any other line of commerce, a system resulting from 70 years of progressive judicial and legislative thinking. If the minor therapy clearly required is applied with equal vision, that particular arm of government will continue to serve him admirably for a long time to come.