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# **Market Approval for Drug; and Medical Devices**



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# Market Approval for Drugs and Medical Devices

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## INTRODUCTION AND BACKGROUND

The Federal Government has been authorized to regulate various aspects of drugs in the United States since President Theodore Roosevelt signed into law the Pure Food and Drug Act of 1906 (113). That law was in part intended to help prevent adulteration and misbranding of drug products. In 1912, Congress enacted the “Sherley amendment,” which prohibited companies from making false and fraudulent curative or therapeutic claims on the labels of their products. In 1927, Congress established the Food and Drug Administration (FDA).

The 1938 Food, Drug, and Cosmetic Act, passed by Congress in response to a tragic event in which over **100** people died from ingesting a lethal drug product,<sup>1</sup> increased the Federal Government’s regulatory control over the marketing of drugs, devices, foods, and cosmetics. In addition to establishing several labeling requirements for drugs, the 1938 Act prohibited interstate commercial shipment of new drugs until they had been adequately evaluated by the Federal Government to show that they were safe under the conditions of use listed on their label. It also authorized FDA to remove from the market any drug it could prove to be unsafe. The Durham-Humphrey Amendment of **1951** defined criteria and categories based on levels of drug safety for restricting a drug to legend (i.e., prescription only) status.

Again stimulated by a disaster, this one involving fetal abnormalities caused by the drug thalidomide,<sup>2</sup> Congress enacted the Drug

Amendments of 1962 (Kefauver-Harris amendments). These amendments required drug manufacturers to provide “substantial evidence” that their products were efficacious as well as safe. The amendments also required drug manufacturers to report promptly to FDA information concerning the safety and efficacy of their marketed products and strengthened FDA’s authority to remove unsafe or ineffective drugs from the market. In addition, the 1962 amendments authorized the notice of claimed investigation for a new drug (IND) process—a legal mechanism used by FDA to regulate human investigations of drugs.

The Federal Government was given some authority to regulate medical devices in the original 1938 Food, Drug, and Cosmetic Act. Congress substantially increased this Federal regulatory authority, however, by passing the Medical Device Amendments of 1976 (116). The 1976 amendments authorize FDA to require device manufacturers to demonstrate acceptable levels of safety and effectiveness for their products. They establish three categories of products, and each category has a different level of Federal control. Medical devices that are implanted, used in supporting or sustaining human life, of substantial importance in preventing impairment of human health, or that pose a potential unreasonable risk of illness or injury, for example, usually are subjected to premarketing evaluation of safety and efficacy. The 1976 amendments permit FDA to ban or remove from interstate commerce unsafe or ineffective devices. They also allow the Agency to restrict the use of a device to persons with specific training or experience or to those in specified facilities if the device’s safety and effectiveness cannot be assured in general use.

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<sup>1</sup>Elixir of sulfanilamide made with the lethal solvent diethylene glycol.

<sup>2</sup>Use of the sedative thalidomide by pregnant women in Europe and Japan resulted in several cases of phocomelia, a fetal abnormality characterized by flipper-like limbs. The drug was not approved by FDA for marketing in the United States.



## FDA'S PRESCRIPTION DRUG MARKET APPROVAL PROCESS

Since 1962, FDA has used its statutory and regulatory authority to establish an extensive system for evaluating virtually every new prescription drug prior to its release into the general medical marketplace. By law, FDA must base its evaluation of prescription drugs on two criteria: safety and efficacy.<sup>3</sup> The procedures used by FDA in this premarket approval process, described in detail elsewhere (119,144), are briefly summarized below. To initiate human investigations involving agents legally defined as "new drugs," the drug "sponsor" (e.g., a manufacturer or an independent investigator of a new drug) must obtain FDA's approval. To obtain such approval, the sponsor submits to FDA's Bureau of Drugs (BOD) an IND, describing the qualifications of the investigators and the design of the planned trials. In the IND review process, BOD also examines data regarding the pharmacology and toxicology of the applicant drug collected in animal studies and in human studies that were not subject to FDA approval (e.g., those conducted in foreign countries). If the sponsor's IND is approved, the sponsor may proceed with clinical testing (i.e., testing in human subjects) in the United States. After completing clinical testing under IND, the sponsor files with BOD a new drug application (NDA) that describes in detail the results of IND clinical trials. The applicant drug has usually been tested in **500 to 3,000** human test subjects (**306**). By filing an NDA, the sponsor is requesting FDA's permission to market the new drug in interstate commerce.

According to Dr. Marion J. Finkel, Associate Director for New Drug Evaluation, BOD, FDA, the review process for INDs and NDAs proceeds as follows (**206**):

Each IND and NDA application is reviewed by a team of FDA scientists: a physician, a pharmacologist, a chemist, a pharmacokineticist, usually a biometrician, and when applicable, a microbiologist. Important NDA's are then presented for consideration to advisory committees, of which the Bureau of Drugs has 13, consisting of extramural [mostly nongovernmental] experts in, principally, the subspecialties of medicine, clinical pharmacology, and biometrics. The committees recommend to the FDA whether or not an NDA should be approved for marketing and, if so, under what labeling, and whether the sponsor should be requested to perform additional studies in the postmarketing phase. When recommendations are made against approval, the committees provide advice on new studies to be done by the sponsors to explore the drug's safety and effectiveness further. The use of advisory committees is the FDA's primary method for broadening the decisionmaking process.

During the NDA review process, FDA reviewers analyze the sponsor's summaries of data—and when needed the actual raw data—generated from clinical investigations. A major task for BOD during this review process is to ensure that clinical experimental data support the sponsor's claims for the drug's safety and efficacy that appear in the drug's labeling. The NDA review process usually entails deliberations between FDA and a drug's sponsor regarding claims for safety and efficacy. If FDA concludes that an NDA is deficient, it usually will require the sponsor to generate new data, modify its NDA with additional information, and resubmit the application to the Agency. Once a sponsor obtains an NDA approval from FDA, it is authorized to market the drug in interstate commerce for only the specific indications (uses) that have been authorized by FDA.

<sup>3</sup>Food, Drug, and Cosmetic Act S505, 21 U.S. C. S 355 (1976) part 314 (1979). The Act uses the term "effectiveness" instead of "efficacy."



## FDA'S MEDICAL DEVICE EVALUATION PROCESS

The Medical Device Amendments of 1976 (Public Law 94-295) require FDA's Bureau of Medical Devices (BMD) to classify each medical device—on the basis of the level of regulation necessary to ensure safety and efficacy—into one of three regulatory classes. Products placed in the class I category—those requiring the least controls to ensure their safety and efficacy—are subject only to general controls, including premarket notification, registration of the manufacturer, prohibition of product misbranding or adulteration, adherence to FDA-promulgated good manufacturing practices, and compliance with various recordkeeping requirements. Class II products—those for which general controls are deemed inadequate to ensure their safety and efficacy—must comply with performance standards either established or recognized by BMD when existing information permits development of such standards. General controls also apply to class II devices unless superseded by a standard. Class III devices—those for which neither general controls nor performance standards alone are sufficient to ensure their safety and efficacy—are subject to premarketing approval. (BMD can also require premarketing approval of devices for which insufficient information is available for the development of applicable performance standards.) Class III devices are subject to general controls.

The process BMD uses to evaluate the safety and efficacy of new class III medical devices is similar to that used by BOD in its NDA reviews. BMD, however, is required by law to use its advisory panels during a product's review, whereas BOD'S use of advisory panels is discretionary. BMD is also authorized to use another premarketing approval process, the product development protocol (PDP). PDP was designed to encourage the development of, and to streamline the approval process for, innovative medical devices. During a PDP process, investigation of a device and the development of information necessary for its premarket approval are merged into one regulatory mechanism. BMD works closely with the manufacturer while information to support the device's safety and effectiveness is being developed. The 1976 Medical Device Amendments also include an investigational device exemption (IDE) provision. IDE allows FDA (technically, the Secretary of Health and Human Services) to exempt a new device from other provisions of the amendments to permit controlled testing of new devices prior to commercial marketing. The IDE process is similar to the IND process that BOD uses.<sup>4</sup>

<sup>4</sup>45 FR 3732.

## SAFETY AND EFFICACY CRITERIA

The Food, Drug, and Cosmetic Act mandates FDA to require a drug sponsor to: 1) collect, by all methods reasonably applicable, data that demonstrate a drug's safety, and 2) generate "substantial evidence" from controlled trials to show that the drug is efficacious for use under the conditions set forth in the proposed labeling (144). Although the Act provides no definitions and little guidance for the meanings of safe and

effective,<sup>5</sup> it does describe "substantial evidence" of effectiveness as follows (144):

<sup>5</sup>OTA differentiates "efficacy" and "effectiveness" as follows (465):

*Efficacy*: The probability of benefit to individuals in defined populations from a medical technology applied for a given medical problem under ideal conditions of use. *Effectiveness*: Same as efficacy except that it refers to "... average conditions of use."

Although the FDA statutes use the terms "effective" and "effectiveness," the definitions implicit in the statutes appear to mean "efficacy." Thus, "efficacy" is used in the present report.



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The term “substantial evidence” means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such 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 labeling or proposed labeling thereof.

Because no drug is absolutely safe or always effective under all conditions of use, FDA weighs a drug’s benefits in comparison to its risks. In FDA’s evaluation process, an applicant drug’s safety and efficacy are compared to the safety and efficacy of approved products or medical procedures used to achieve similar therapeutic objectives. Comparisons are also made with the effects of inert substances (placebos). According to Dr. Marion J. Finkel of FDA (204):

A drug cannot be considered safe if it is less effective and has more side effects than other drugs labeled for the same indication. It might be safe for certain subpopulations or certain restricted indications, however.

According to Dr. Robert Temple of FDA (594):

We’re not supposed to refuse approval because of lesser effectiveness, but we can on grounds of lesser safety which reduces the benefit/risk ratio. Relative effectiveness can be noted in labeling.

FDA also uses such comparisons when selecting NDAs for its priority review or “fast track” review process.

FDA has published 25 clinical guidelines that define the types of studies it deems appropriate to use to establish safety and efficacy of a drug. The performance criteria used to evaluate an individual drug’s safety and efficacy, however, can vary among different pharmacological classes. This variance results from the imprecise nature of pharmacologic intervention in disease. The benefits and risks of a drug can vary from disease to disease, from population to population, and from clinical situation to clinical situation. Drug-induced hair loss, for example, is often viewed as an acceptable risk of taking a drug that is an effective treatment for cancer, especially when no other effective therapy exists. The same side effect, however, would probably not be acceptable for a drug that reduces the severity of a minor, self-limiting condition.

The complete risk-benefit analysis of a drug, therefore, is not based solely on statistical evaluation of data on safety and efficacy generated from clinical trials but also on “the context of the disease for which [the drug] is intended, the availability of other therapeutic modalities, including other forms of pharmacologic therapy, and public health implications of its availability” (144).

The task of evaluating the safety and efficacy of drugs, as well as FDA’s ability to perform this task, has been subjected to extensive analysis and debate (119,144,242,613).

## **CURRENT ECONOMIC CONSIDERATIONS IN FDA’S DRUG AND MEDICAL DEVICE APPROVAL PROCESSES**

FDA does not directly use economic criteria in its approval processes for drugs and medical devices. The Agency’s primary statutory authority, the Food, Drug, and Cosmetic Act, neither authorizes nor prohibits the use of economic criteria in FDA’s evaluation of applicant drugs and devices. The legality of using cost effectiveness to help evaluate new drugs and devices has not been tested.

Although FDA does not formally assess the potential economic impact a drug or medical device might have on the allocation of health care resources, some FDA actions may be based indirectly on—or taken in spite of—economic considerations. Further, some FDA actions certainly have economic impacts. Several examples are cited below.



**Classifying the Potential Therapeutic Importance of New Drugs:** FDA sets priorities for its review of new drugs according to the potential therapeutic usefulness of each applicant drug. This priority-setting process supposedly begins within 6 months after a sponsor submits an IND to FDA (206). On the basis of preliminary information about a drug's pharmacological effects and on data from clinical trials, a drug is assigned a number and a letter derived from the following classification schemes (221):

*Numerical Classification*

- 1 = New molecular entity not previously marketed in the United States.
- 2 = New salt, ester, or derivative of an active moiety marketed in the United States.
- 3 = New formulation of a compound marketed in the United States.
- 4 = New combination of two or more components not previously marketed together in the United States.
- 5 = Product duplicates a drug marketed by another firm in the United States.
- 6 = Product already marketed by some firm in the United States; approval being sought for new indication of use.

*Letter Classification*

- A** = major therapeutic advance over other currently available drugs, etc.
- B** = modest (or moderate) therapeutic advance over other currently available drugs, etc.
- C** = little or no appreciable therapeutic advance over other currently available drugs, etc.

The purpose of using a drug classification scheme of this type is to expedite the review of data for drugs that represent important new therapeutic entities. FDA seeks to review NDAs submitted for drugs it assigned a 1A or IB rating as expeditiously as possible; such reviews receive high priority by BOD (206).

Even though the criteria used to classify a new drug are based on scientific data relating to a drug's clinical safety and efficacy, there are indirect economic consequences of FDA's selection process. The expeditious review and resultant early marketing of a new drug that repre-

sents a major therapeutic breakthrough in the treatment of a heretofore uncontrollable disease could help reduce the use of existing treatment measures, such as hospitalization and surgery. The recently introduced drug cimetidine, for example, appears to provide safe, effective, and relatively inexpensive (compared to hospitalization or surgery) treatment for duodenal ulcers; using cimetidine, some ulcer patients may avoid hospitalization (203,632). FDA rated cimetidine as a 1A drug. If indeed the use of cimetidine reduces ulcer patients' hospitalizations and surgery, then an expeditious FDA review and approval of the drug could help reduce medical expenditures for the treatment of duodenal ulcers. A complete analysis would include calculations of the potential economic impacts of delaying the review of one or more other INDs or NDAs, in order to expedite cimetidine's application review.

According to FDA's Dr. Marion J. Finkel (205):

NDAs for 1A and IB drugs are full NDAs, containing all of the safety and efficacy data required for any NDA. Expeditious review of these merely means that the NDAs do not wait their turn in the pipeline but are reviewed before NDAs with lesser classifications . . .

Rarely, FDA will accept an NDA for a 1A drug without as much long term human (or animal) safety data required for NDA approval.

In at least some cases, however, the expeditious review of an important new drug might result in an incomplete assessment of the drug's safety, and an unexpectedly significant level of adverse reactions to the drug might occur. To help prevent such an occurrence, FDA can—and sometimes does—ask a sponsor to conduct post-marketing surveillance as a condition of approval for a new drug (131).

**Use of Abbreviated New Drug Applications (ANDAs) and "Paper" NDAs:** Two examples of the indirect use of economic considerations in FDA's drug approval processes are the ANDA and the so-called "paper" NDA. The ANDA process enables a drug manufacturer to obtain from FDA marketing approval for a "generic" drug product that is purported to be an identical version of an already approved product, usually



after the originator's patent has expired. Because of FDA's earlier interpretation of the Food, Drug, and Cosmetic Act, ANDAs are currently only used for products originally approved by FDA between 1938 and 1962. FDA is preparing a policy, however, that will permit the use of ANDAs for products approved after 1962. A manufacturer can obtain an ANDA essentially by demonstrating that it complies with FDA's current good manufacturing practices and labeling requirements and that it can make a product that is at least chemically equivalent and supposedly bioequivalent to the originators. Although evidence of chemical equivalence is always required, the FDA Commissioner can forgo requiring evidence of bioavailability in the ANDA process for a given drug.

"Paper" NDAs are designed to permit a drug manufacturer to meet the requirements for submitting evidence of the safety and efficacy of its post-1962 product by citing existing data from published clinical trials involving a chemically equivalent, previously approved product. The legality of "paper" NDAs was challenged in court by the Pharmaceutical Manufacturers Association (PMA) and a few major drug manufacturers (473). The court dismissed the suit on the grounds that the plaintiffs had not exhausted their administrative remedies within FDA, so PMA has filed a petition that: 1) questions FDA's authority to implement a "paper" NDA policy, and 2) requests that if such a policy is implemented by FDA, it be done through the official notice and comment rulemaking procedure.

The primary purpose of both the ANDA and "paper" NDA modifications in the new drug approval process is to facilitate the marketing approval of drug products identical to those that FDA has previously found to be safe and efficacious on the basis of data supplied in a product's original NDA. These mechanisms are designed to prevent unnecessary work burdens on FDA's resources. The use of ANDAs and "paper" NDAs is supposed to increase the availability of FDA staff to review NDAs submitted for innovative drugs, e.g., those categorized by FDA as 1A. The use of these mechanisms also eliminates the need for sponsors to conduct duplicative

clinical trials. Thus, manufacturers' expenses associated with entering some existing drug product markets can be reduced.

**Removal of Diethylstilbestrol (DES) From Animal Feed:** The estrogenic compound DES was used by poultry and other livestock raisers for many years to increase the muscle and fat content of their animals. FDA first approved such use of DES in 1954.<sup>6</sup> After that, DES was used in animal feed to reduce the total feed intake necessary to achieve maximum animal weight gain. Furthermore, some studies showed that the use of DES in animal feed helped reduce the cost of raising poultry and other livestock. Theoretically, therefore, the use of DES may have helped contain poultry and meat prices for consumers.

Ingestion of DES by humans, however, was eventually correlated with an above-normal risk of developing certain types of cancer, such as adenocarcinoma of the vagina or the cervix.<sup>7</sup> Because of DES's cancer-producing potential, FDA attempted several times to remove this substance from animal feed.

The authority for its efforts was the Delaney clause,<sup>8</sup> a proviso added to the 1958 food additive amendment to the Food, Drug, and Cosmetic Act:

. . . no additive shall be deemed to be safe if found to induce cancer when ingested by man or animal . . .

This clause was reiterated in the 1968 animal drug amendments to the same Act.<sup>9</sup> Under the animal drug amendments, approvals for the use of new animal drugs, which are used in the livestock industry for the treatment and prevention of disease and as growth promoters, are to be granted only after a two-part evaluation by FDA. First, FDA must determine that the drug is safe and effective for use in animals. Second, it must assess the safety of potential residues that might occur in food derived from treated animals. 10

<sup>6</sup>44 FR 54853.

<sup>7</sup>44 FR 54852.

<sup>8</sup>Sec. 409(c)(3)(A), Food, Drug, and Cosmetic Act, 21 U.S.C. 348(c)(3)(A).

<sup>9</sup>Sec. 512, 21 U.S.C. 360b.

<sup>10</sup>Sec. 512, 23 U.S.C. 360 b(d)(1).



After evaluating and finding DES to be a carcinogenic substance, in 1972, FDA attempted to ban its use in animal feed. That effort terminated in a litany of legal proceedings with the livestock industry and animal feed manufacturers. " On January 12, 1976, therefore, FDA once again initiated a legal process to remove DES from animal feed. This time, the Agency also issued an inflation impact statement regarding its proposed ban of the use of DES. <sup>11</sup> The statement concluded:

1. There are no satisfactory alternatives to the Agency's proposed action which are consistent with the legal constraints imposed by the Federal Food, Drug, and Cosmetic Act as amended.
2. Operating expenses to feedlot producers of cattle for feed and other items are estimated to decrease by \$156 million during the first year following a DES ban. These increased costs are expected to fall substantially over the longer term as substitutes to DES become available in greater quantities.
3. Retail prices of beef are estimated to rise by about 2 cents per pound, meaning the per capita cost of beef to consumers at current levels of consumption would increase from \$2 to \$3 annually. The aggregate consumer impact is estimated at \$.503 million.
4. A ban on DES would not cause major inflation impacts, as defined by the HEW/OMB criteria, in the areas of competition, productivity, supplies of materials, or use of energy.
5. The benefits from implementing the proposed action will be the elimination of any risk of any cancer associated with the consumption, via the edible tissues of food-producing animals, of residues attributable to DES.

According to former FDA Chief Counsel, Richard Cooper, FDA's mandate under the Delaney clause and the 1968 animal drug amendments prevented the Agency from considering any economic benefits of DES in its decision to ban the drug from use in animal feed (127a).

On June 29, 1979, then FDA Commissioner Donald Kennedy ordered the withdrawal of approval of the new animal drug application for DES. <sup>12</sup> In taking this action to ban the use of DES, Commissioner Kennedy stated:

FDA is not authorized, under the Food, Drug and Cosmetic Act, in considering the question of whether a new animal drug has been shown to be safe for use, to weigh the "socio-economic" benefits that that drug provides against a health risk to the ultimate human consumers of treated animals. Even were I to attempt to weigh the benefits of DES against its risks, this record would not provide sufficient information to compute the risk associated with DES or to determine whether, and to what extent, use of DES provides any health benefit or even any economic benefit to society.

This case study illustrates one situation in which FDA interpreted the Delaney clause of the Food, Drug, and Cosmetic Act (its primary statutory authority) to mean that in its decisions concerning the removal of carcinogenic substances from the market, it cannot consider the results of economic analyses.

**Evaluation of an X-Ray Equipment Performance Standard Established by the Bureau of Radiological Health (BRH):** This case illustrates FDA's use of cost-benefit analysis to evaluate one of its regulations.

In 1972, FDA's BRH promulgated regulations containing a performance standard for medical diagnostic X-ray systems and their major components. <sup>14</sup> These regulations, among other things, required X-ray equipment manufacturers to certify that all specified components manufactured after August 1, 1979, comply with the new standard. Another provision stated that after August 1, 1974, no uncertified components could be assembled or reassembled into an X-ray system. <sup>15</sup> The purpose of these regulations was to help ensure the radiation safety of diagnostic X-ray systems. <sup>16</sup>

In 1974, BRH estimated the costs and benefits associated with these regulations. The Bureau

<sup>11</sup>44 FR 54854.

<sup>12</sup>FDA docket No. 76N-002, Inflation Impact Statement DES, Office of Planning and Evaluation, January 1976.

<sup>13</sup>44 FR 54900.

<sup>14</sup>21 CFR 1020.30, 1020.31, 1020.32.

<sup>15</sup>21 CFR 100.16.

<sup>16</sup>44 FR 22755.



estimated, for example, the expected numbers and costs of X-ray systems which would be marketed under the new performance standards. Upon reviewing 3 years of experience with the regulations for diagnostic X-ray systems, BRH realized that their earlier estimates of certain costs and benefits were incorrect. In 1978, using data not previously available, BRH conducted a second analysis of costs and benefits derived from the 1972 regulations. On the basis of this second analysis, BRH concluded: 17

1. The provisions of section 1000.16 that are effective after August 1, 1979, will affect only a small fraction of the uncertified X-ray systems currently in use.
2. The total impact of this regulation, in terms of increased cost for the X-ray equipment or interruption of health care delivery, may be significant.
3. For those uncertified systems that would be affected, by virtue of their sale and relocation, section 1000.16 is not likely to be a cost-effective approach to improve the radiation safety performance of X-ray systems.

Based on these conclusions, BRH, through the rulemaking process, modified its earlier regulations by, among other things, permitting the installation of uncertified components into existing systems whose components are all uncertified and permitting the continued reassembly of uncertified equipment. It also clarified certain aspects of its performance standard for X-ray systems. 18

<sup>17</sup>Ibid.

<sup>18</sup>144 FR 49667.

**Incorporating Costs-Savings Studies Into Vaccine Approval Decisions:** In its recently published report on viral and rickettsial vaccines, FDA's Panel of Review of Viral and Rickettsial Vaccines identified economics as a major consideration in the evaluation of vaccines.<sup>19</sup> The panel noted that because adequate data are often lacking, economic considerations are often ignored in such evaluations.

The panel stated:

These data would contrast the cost of a vaccine and its administration plus the costs (medical care, rehabilitation, impairment of ability to earn income) of vaccine-related disease with costs of a similar nature that would have accrued from cases of the natural disease.

The panel further stated:

For an "acceptably safe" and effective vaccine against a serious disease, . . . the ratio should be highly favorable. However, if the preventable disease occurs chiefly in young children and is infrequently associated with permanent sequelae, a different answer might result. The question then might become "how much cost can be justified to prevent one crippling or lethal case of disease?" This clearly requires societal rather than scientific judgment.

This panel has strictly an advisory capacity within FDA, and its reports do not reflect official FDA policy. The panel's discussion of economics in the vaccine evaluation process, however, does illustrate some concern among FDA's advisors for evaluating the potential economic impacts of vaccines.

<sup>19</sup>45 FR 25665.

## POTENTIAL APPLICATION OF CEA/CBA

In order to facilitate the discussion presented in the next section of this chapter on the implications of including cost-effectiveness criteria in the market approval process, OTA has developed the hypothetical model of a cost-effectiveness analysis (CEA) outlined below. It is very important to keep in mind that the use of the model for illustrative purposes does not negate or diminish any of the weaknesses or possibilities for misuse involved in formal cost-effec-

tiveness analyses/cost-benefit analyses (CEA/CBAS) that seek a single, quantitative bottom-line, such as a cost-effectiveness ratio. Such a ratio is used in the model because 1) it points out some of the data and other problems related to use of bottom-lines, and 2) it is possible, given the quantitative nature of FDA's regulatory process, that use of a CEA ratio might be seriously considered by the agency if CEA were added to its mandate.



OTA's model is simplistic by intent and does not address the numerous assumptions and variations that are possible. Several caveats and assumptions should accompany an analysis such as the one presented. Potential methodological problems associated with the use of CEA in general are explained in detail in a background paper of this assessment.<sup>20</sup> Additional problems with its use in market approval processes are explained below. One problem, for example, is that data for some important variables would be difficult, if not impossible, to obtain.

In assessing a drug's cost effectiveness, FDA might first assess the agent's efficacy and safety and quantify its effects into measurable units of "net health effect." Let us assume, for example, that an NDA is submitted for applicant drug "D," which is used to treat high blood pressure (hypertension). Let us also assume that in pre-marketing clinical trials, drug "D" consistently lowered by 10 percent blood pressure in 50 percent of tested hypertensive patients, and that such a drop in pressure could be correlated with a 5-percent reduction in morbidity and mortality (e.g., heart attacks, strokes, and kidney disease). Suppose drug "D" also produced undesirable side effects that in premarketing clinical trials accounted for a 2-percent increase in days of disability in the tested population. Let us also assume that the tested population accurately represents the general hypertensive population.

To calculate the "net health effect" of drug "D," all such positive effects (e.g., 5-percent reduction in mortality) and negative effects (e.g., 2-percent increase in disability caused by side effects) would have to be converted into a uniform and measurable unit of health.<sup>21</sup> The "net health effect" of drug "D" could then be calculated for each indication listed on the proposed drug labeling (e.g., treatment of moderate hypertension in ambulant patients). Specific conditions of use (e.g., in conjunction with other drugs) and peculiar effects in special pop-

ulations (e.g., the elderly) could be accounted for in the calculation of net health effects.

Once the drug's effects were converted into measurable units of "net health effects," the "net cost" of achieving a desirable level of health effect (e.g., a 5-percent reduction in mortality and morbidity) would have to be calculated. A "net cost" could include such items as the cost of purchasing the drug, the cost of treating drug-induced side effects, and perhaps the cost of treating other illnesses in the persons whose lives are saved by the use of drug "D." Subtracted from such costs could be savings resulting from any reduced costs of hypertension treatment (e.g., lower use of previously approved drugs or decline in hospitalizations and in physician office visits) resulting from the use of applicant drug "D."

At the conclusion of this phase of the analysis, one could construct a ratio of net cost in dollars to one unit of "net health effect" achieved through the use of drug "D" in the treatment of hypertension, e.g.:

$$\text{Cost-effectiveness ratio} = \frac{\text{Net cost}}{\text{Unit of net health effect}}$$

In the next phase of the analysis, the net cost (in dollars) of achieving a desired net health effect through the use of drug "D" would be compared with the net cost of achieving the same net health effect by using an existing approved treatment modality (e.g., another drug, surgery, or biofeedback) to lower blood pressure. Such a comparison of costs would require that cost-effectiveness ratios, i.e., net cost (in dollars)/unit of net health effect, be derived for each hypertension treatment modality. The following hypothetical ratios for example, might be derived:

Hypertension treatment modality	Net cost/uniform unit of net health effect
Applicant drug "D" . . . .	\$400
Approved drug "A" . . . .	\$250
Surgical procedure "X" . .	\$3,000
Biofeedback . . . . .	\$100

Let us assume that no other treatment of hypertension was available at the time of the analysis.

The final phase of such an analysis would be to establish criteria for judging the cost-effec-

<sup>20</sup>Background Paper #1: Methodological Issues and Literature Review, prepared by OTA.

<sup>21</sup>As discussed in Background Paper #1: Methodological Issues and Literature Review, some analysts have used the unit termed quality-adjusted life year for this purpose (652).



tiveness ratios for each treatment modality and for using such ratios to help determine if applicant drug “D” should be approved. In the example above, if a criterion for market approval were that the applicant drug had to produce one unit of “net health effect” at a cost lower than the cost of using any other approved antihypertensive drug, then drug “D” might not be approved. If such a criterion included comparison with other approved forms of hypertension treatment, then drug “D” would presumably be approved if compared with surgery, although it might not be approved if compared with biofeedback. When one considers in this hypothetical evaluation process the need for a variety of available treatment modalities to meet individualized patient situations, then the relatively small differences in cost effectiveness between applicant drug D, biofeedback, and approved drug A become much less important.

Cost effectiveness might be used in formal review processes of drugs that have been marketed for a number of years, instead of those for new drugs. FDA conducts at least three such re-

view processes, and to date, the Agency has not used cost effectiveness in any of them. First, in its drug efficacy study implementation project, FDA is conducting a one-time review of the efficacy of drug products approved between 1938 and 1962 (131). The Agency categorizes products according to their documented clinical efficacy, has removed from the market some products for which efficacy documentation is lacking (e.g., selected fixed-dosage antibiotic combination products), and is attempting to remove other such products. Second, in its Over-the-Counter (OTC) Drug Review Program, FDA is conducting a one-time review of the safety and efficacy of several hundred ingredients used in OTC or nonprescription drug products. Third, FDA (technically, the Secretary of Health and Human Services) has authority to remove from the market a drug that represents an “imminent hazard” to the public’s health. When this authority was exercised to remove the antidiabetic drug phenformin from the market, FDA extensively reviewed the drug’s safety and to some extent its efficacy.

## **IMPLICATIONS OF CEA/CBA IN MARKET APPROVAL: GENERAL FINDINGS**

As described in chapter 2, CEA is an analytical device that can be used to help decision-makers allocate resources, usually in the public sector. The primary purpose of FDA’s drug and medical device market approval processes is to protect the public from unsafe and ineffective products. FDA’s marketing approval processes do, however, indirectly influence the allocation of public resources in at least two ways. First, the types of regulations and procedures established by FDA affect the allocation of its operating budget. Second, many—if not most—of the drugs and medical devices approved by FDA eventually are used in health care services that are paid for through publicly financed programs, such as medicare and medicaid.

The use of cost effectiveness as a criterion in FDA’s market approval processes for drugs and medical devices would require a substantial shift

in the Federal Government’s approach to regulating the medical care marketplace. At present, no Government effort is designed explicitly to reduce medical expenditures by directly slowing down or stopping the market introduction of medical goods and services. The Federal Government does not extensively evaluate the cost effectiveness of drugs or medical devices in any of its efforts to contain health care costs. Conceivably, such evaluation could take place in the National Center for Health Care Technology, which advises the Health Care Financing Administration (HCFA) on reimbursement policies for selected medical technologies. Results of CEAS involving drugs and medical devices could be incorporated into HCFA’S policies for reimbursing the use of selected drugs and medical technologies under medicare, medicaid, and any other federally operated health insurance program.



## Potential Positive Effects

There are at least two hypothetical positive effects of incorporating CEA into FDA's market approval process for drugs and devices.

First, manufacturers could formally incorporate cost-effectiveness criteria, based on societal values, into their research, development, and marketing strategies. Manufacturers most likely do use some form of CEA/CBA to allocate their R&D expenditures. The primary criteria used in such allocations, however, may emphasize such items as total sales, market portions, and return-on-investment. If FDA used criteria such as reduced treatment costs, improved levels of health, and improved efficiency in disease prevention or treatment, then more manufacturers might develop new products and seek new markets where existing treatment or prevention measures are ineffective or inefficient. Some industry representatives claim that the leading drug research firms currently include such public health criteria in their research priorities. The existence of orphan drugs (i.e., existing agents for which there is a small, demonstrated clinical need but no manufacturer), however, indicates that at least for certain products, profitability takes precedence over societal need. Conceivably, such use of CEA could help the Government encourage participation by drug and medical device manufacturers in public efforts to develop more cost-effective medical technologies.

**Second, if FDA were able to accurately assess the cost effectiveness of an applicant medical device or drug,** the Agency might help reduce expenditures for inefficient products by keeping them off the market entirely. By evaluating the cost effectiveness of medical devices and drugs in the market approval process, the Government would be assessing a product very early in its diffusion process. Perhaps this early evaluation process would lead to better direction—and perhaps an expansion—of experimentation with new drugs and devices. At present, substantial non-FDA-approved clinical experimentation with newly approved drugs takes place in uncontrolled situations. Such early evaluation, however, would have no effect on the inefficient use of drugs and medical devices found to be cost effective in clinical trials.

## Potential Problems

Among the consumer advocates, FDA employees, and representatives of the pharmaceutical industry surveyed in this assessment, there appeared to be widespread agreement that cost effectiveness is not an appropriate criterion to use in the drug and medical device approval process. Using information and ideas obtained from several individuals, OTA developed the following analysis of potential problems.

**First, the market approval process may be too early in the life of a drug or medical device to evaluate its cost effectiveness; information regarding a product's safety and efficacy are usually available for only one or two indications of use at the time a sponsor submits an initial NDA for a new drug or an application for approval of a new device.** Data regarding a drug's safety and efficacy in medical conditions not listed in the product's official labeling are not often generated until a product has been marketed for at least a few years. If a new drug or medical device were not approved for marketing because its cost effectiveness did not compare favorably with already approved products, then the new product might never be fully evaluated, particularly in the treatment of medical problems other than the one(s) studied initially. The total benefits, risks, and cost effectiveness of drugs that are used in the treatment of more than one medical problem often may not be known for several years after the product's initial development. Examples of such products include propranolol used in the treatment of angina, migraine headaches, and hypertension; selected antibiotics used in the treatment of acne; amantadine used in the treatment of parkinsonism; and phenytoin used in the treatment of certain cardiac arrhythmias. In addition, rare or delayed-onset adverse drug reactions, for example, drug-induced cancers, would not likely be included in premarketing CEA.

James B. Russo, SmithKline Corp., offers an industrial concern about the use of CBA in the market approval process for drugs (529):

Our primary concern is over the fact that cost-benefit analysis in the drug area is a new discipline, and one which simply must not be widely



applied, particularly in the area of new drug approval, until we have real confidence in its predictive reliability . . . I don't really know how to state that point as strongly as I'd like to. Think back to probenecid. The drug was developed to slow the excretion of penicillin from the kidney, because in those days penicillin production was inadequate. By the time probenecid was shown to be safe and effective for that purpose, penicillin was coming out of the industry's ears. Had that NDA been looked at on the basis of the product's cost against its possible benefits in prolonging blood levels of penicillin, work on the drug would have been stopped in the early '50s. Of course, once it was found that it speeded the excretion of uric acid, an entirely new and a relatively important means of relieving gout became a possibility. It isn't simply a matter of NDA approval. If we knew we would have to pass that kind of test at the NDA stage, I fear that a lot of projects would be cancelled long before we had practical information on the drug's full potential.

In recent years, however, FDA has approved very few NDAs to add to a previously approved product's official labeling a new major indication that required data from new clinical trials. Between January 1, 1974, and September 30, 1979, for example, FDA approved 4 such NDAs out of a total of 484 total NDA approvals for all reasons (221). There are, however, 362 active commercial INDs for products being used for indications not currently listed in the products' official labeling. In addition, for perhaps hundreds of approved products, FDA has permitted manufacturers, through the supplemental NDA process, to make minor modifications (i.e., those not requiring manufacturers to sponsor new clinical trials) in their products' official indications for use. The extent to which marketed drugs are used for unapproved indications is not known. Manufacturers often have no economic incentives to seek FDA approval for popular, unofficial clinical uses of their products.

**Second**, the calculation of costs needed to assess the cost effectiveness of a new drug would require FDA to either: 1) use existing estimates of costs of treating illnesses using alternative forms of therapy, or 2) generate new data bases. Problems encountered in using existing data bases are discussed in a background paper of

this assessment.<sup>22</sup> At present, FDA has no intramural capability for generating new data regarding the treatment costs for selected diseases. Conceivably, FDA could ask or require drug and medical device manufacturers' to submit estimates of the costs of treatments provided during the clinical testing of a new drug. Meaningful estimates of treatment costs might be difficult to calculate, however, because the prices charged for medical care are dynamic and can vary substantially among geographical regions.

At the time FDA approves a drug or medical device, it does not know—nor can it influence—how much a manufacturer will charge for its newly approved product. FDA could ask a manufacturer to estimate a product's selling price. Apparently, however, this task would be difficult for manufacturers to accomplish at the time of market approval. Further, the price of a drug or medical device will likely change over time, and cost-effectiveness information calculated at the time of market approval would likely change.

**Third**, the effect on competition of using cost effectiveness as a criterion for market approval of drugs and medical devices is unknown. Potential implications vary substantially depending on how FDA might use the cost-effectiveness criterion.

If FDA assumed the responsibility for conducting CEAS, theoretically manufacturers would not be burdened with the expense of developing the capability to conduct such analyses. Most research-based companies, however, would likely establish their own capabilities; at least two pharmaceutical firms currently perform CEAS on some of their products. One company, Merck Sharp and Dohme, developed a computerized cost-benefit model to illustrate the costs and benefits of its pneumococcal vaccine (464). Another pharmaceutical manufacturer, SmithKline and French, has extensively studied the costs and benefits of the use of one of its drugs, cimetidine, in different populations (529). If FDA required each sponsor of every

<sup>22</sup>Background Paper #1: *Methodological Issues and Literature Review*, prepared by OTA.



new drug or medical device to conduct CEA as a part of the premarketing approval processes for drugs and devices, then the use of cost effectiveness would add to the financial and regulatory hurdles of new product introduction. Conceivably, that situation could reduce manufacturers' willingness to bring a new product to market and could reduce competition.

If FDA required only the original manufacturer of a new drug or medical device (i.e., one not previously marketed in the United States) to analyze the cost effectiveness of its product, then the burden of conducting such analyses would fall primarily on the leading innovating companies.

If FDA used cost effectiveness as a criterion for the marketing of only new therapeutic entities, and not for either generic or "me too" products,<sup>23</sup> and if manufacturers perceived such a task as too expensive, then manufacturers might attempt to break into existing markets for multiple source products rather than to develop new drugs and create new markets.

If FDA applied cost-effectiveness criteria to "me too" type products, then a manufacturer might lower the introductory price of its new product in order to make it compare favorably to already-approved products in the same therapeutic category. Once a product was marketed, however, its manufacturer could alter its price, and FDA has no authority to control the price of approved drugs and medical devices. Excessive increases in postapproval prices would likely be limited by competition in the marketplace for similar products.

**Fourth, the use of CEA to evaluate new drugs and medical devices would require extensive resources, substantial time, and creative application of existing data. FDA would likely have to compare the relative safety, efficacy, and cost of an applicant product with those same characteristics of marketed products. In order to perform such comparisons, FDA would have to do the following:**

- quantitatively assess the safety (risks) and efficacy (benefits) of each marketed drug and medical device;
- establish standards for clinical efficacy, safety, and cost of each available form of treatment—and possibly prevention—in numerous disease states (note: such standards could be incorporated into a monograph system such as those used for OTC drug products and antibiotics); and
- calculate cost-effectiveness information for the use of each drug and medical device in specialized populations, such as the elderly and persons with specific medical problems.

Although it is debatable whether FDA has statutory authority to evaluate new products relative to currently marketed products, a provision in the Senate-passed version of the Drug Regulation Reform Act of 1979 would allow FDA to consider formally and explicitly the "benefits and risks of available therapies" when evaluating applicant drugs in the NDA review process.

**Fifth, the cost effectiveness of different products would vary substantially depending on the forms of treatment being compared. A comparison between a new drug and a surgical procedure in the treatment of a selected medical problem, for example, could yield large differences in cost-effectiveness ratios. Such a comparison might be useful to FDA in its evaluation of the drug. The information yielded could be helpful in the evaluation of the new product, especially if the product were a new chemical entity that represented a therapeutic breakthrough. Ultimate treatment for uncontrollable malignant hypertension in a young person, for example, has been the removal of one or both kidneys (nephrectomy). Until recently, many cases of this disease have not been controllable through the use of drugs. A potent new antihypertensive drug, minoxidil, has been shown to effectively lower very high blood pressure, and in some studies, its use reduced the need for nephrectomies (482). There is no other product on the market that resembles minoxidil either chemically or therapeutically. When compared to sur-**



**gical removal of the kidneys, minoxidil would likely be quite cost effective for some patients.**

**Comparisons between two drugs**, however, especially two drugs with similar therapeutic effects, would likely yield only small differences in cost-effectiveness ratios. Small differences would be of little value. Thiazide diuretics, for example, represent another form of antihypertensive drug therapy. There are approximately 30 different single-entity thiazide diuretic products on the market, and **each one** produces very similar therapeutic and adverse effects. In cost-effectiveness comparisons among these 30 products, the differences in cost-effectiveness ratios would likely be very small; hence such comparisons would likely be of little distinguishing value in FDA's NDA review process for a new thiazide diuretic.

**Sixth**, the cost effectiveness of a drug or a medical device might be influenced more by the conditions of its use than by its demonstrated efficiency in premarketing clinical trials. Factors such as dosage regimen, route of administration, and palatability (taste) all could influence a product's acceptance by patients and hence affect its cost effectiveness. Even if FDA were able to accurately assess the cost effectiveness of a drug or medical device at the time of market approval, such an assessment might not accurately predict the efficiency of the product in general use.

**Seventh**, if FDA used cost effectiveness as a criterion in its drug and medical device market

approval processes, the Agency would have to rely on speculative and uncertain data for two important valuations. First, FDA measures the safety and efficacy of drugs and medical devices in terms of changes in physiologic functions, not in terms of changes in a person's overall health status. The efficacy of an antihypertensive drug, for example, is evaluated on the degree to which the drug reduces a person's blood pressure. FDA does not quantify the effect a drop in blood pressure would likely produce in the health status of a hypertensive patient. Second, FDA analysts would face the challenge of assessing the economic value of physiological changes—and if possible of those in health status—among persons using the medical device or drug.

**Eighth**, by using cost effectiveness as a criterion in the market approval process for drugs and devices, FDA might be extending its role beyond the scope of responsibilities Congress intended the Agency to have. FDA's primary purpose is to protect the public from unsafe and ineffective drugs and medical devices and from unsafe cosmetics, foods, and food additives. Thus far, Congress has not asked FDA to use economic criteria to regulate the choice of safe and effective products during the market approval process. Choices based on economic criteria are left to be made by consumers, health care practitioners, hospital administrators, and private and public health insurance carriers after a product has been marketed.