

the product when administered in various dosages in healthy human subjects. In Phase II trials, the drug is tested for efficacy, as well as for specific short-term toxicities. In Phase III, the product is tested in multiple, randomized, controlled clinical trials, usually involving short-term use of the drug among 2,000 to 3,000 subjects. * Data from these three phases of clinical trials are required by FDA. (If acceptable data are available, e.g., from foreign trials, however, then FDA can reduce its requirements for one or more of the three phases.) Upon completing Phase III clinical trials, the manufacturer submits a new drug application (NDA) to FDA. Approval by FDA of the manufacturer's NDA is necessary before the company legally can introduce a new drug product into interstate commerce.

For the most part, FDA bases its evaluation of the safety and efficacy of prescription drug products on the results of rigorous premarketing clinical testing. Once satisfied on the basis of premarketing test data that a drug is safe and efficacious, though, FDA leaves further assessment of its safety and efficacy to

*The virtues and limitations of clinical trials are discussed briefly in ch. 3, 6, and 7 of this report and at greater length in another OTA report, *Assessing the Efficacy and Safety of Medical Technologies* (U.S., Cong., OTA, Sept. 1978).

medical practitioners, patients, and health insurance carriers who pay for the use of prescription drugs.

The Secretary of the Department of Health, Education, and Welfare (HEW) has statutory authority to remove an approved prescription drug from the market, providing postmarketing evidence indicates that the drug represents an "eminent hazard" to the health of its users (21 USC 355 E). Once FDA approves a prescription drug product for marketing, however, its postmarketing assessment of the product's safety and efficacy is limited.

Prescription drug manufacturers are required to report to FDA all reports they receive from health professionals regarding adverse reactions to their products. On occasion, FDA participates in postmarketing assessments of drug efficacy and safety. For example, it establishes scientific panels, sometimes in collaboration with the National Academy of Science/National Research Council, to study the safety and efficacy of selected products on the market, e.g., antibiotics and over-the-counter (nonprescription) drugs. In addition, FDA operates a passive postmarketing surveillance system to allow voluntary reporting by health professionals of cases involving adverse reactions to approved prescription drugs. At present, FDA is seeking statutory authority to expand its postmarketing surveillance activities (See chapter 7.)

Appendix 3.3 BOB'S VACCINE PRODUCT LICENSURE APPLICATION AND PRODUCT REVIEW PROCESSES'

From 1902 to 1948, responsibility for enforcing laws and establishing regulations governing the manufacture and marketing of biological products was assigned to the Public Health Service's (PHS) Hygienic Laboratory. In 1948, the Hygienic Laboratory was incorporated into the National Institutes of Health (NIH), and this responsibility was assigned to the National Microbiologic Institute. In 1955, responding to a tragedy—polio cases resulting from poliomyelitis vaccine—Congress strengthened the Federal Government's control over the manufacture and sale of vaccines in the United States by establishing at NIH a separate Division of Biologics Standards.

In 1972, the Division of Biologics Standards was transferred administratively within the Department

of Health, Education, and Welfare (HEW) from NIH to the Food and Drug Administration (FDA). The purpose of this transfer was to strengthen Federal regulatory control of biological products by separating—and thus helping to prevent potential conflicts of interest between—Federal regulatory and scientific activities. Upon being transferred to FDA, the Division of Biologics Standards was renamed the Bureau of Biologics (BOB).

BOB (technically, FDA) is authorized to help ensure the safety and efficacy of vaccine products to be used by the American public by reviewing, and either approving or disapproving, vaccine manufacturers' applications for licenses to manufacture and sell particular vaccine products. The 10 basic steps involved in BOB's vaccine licensure application and review process, the procedures and processes involved in each step, and the sources of BOB's regulatory and statutory authority are described below:

*The 10 basic steps involved in BOB's vaccine product licensure and review process described in this appendix are illustrated in figure 7 in ch. 3.

Step 1: BOB Has Established (or Establishes) General and (for Some Existing Vaccines) Specific Regulatory Requirements for Vaccine Product Licensure

Source(s) of Authority: Virtually all BOB regulations that apply to vaccine product and establishment licenses are contained in the Code of Federal Regulations (CFR), Title 21, sections 600-680. Section 600 lists several establishment standards, general provisions, and procedures for inspection of vaccine manufacturing establishments. Section 601 outlines general provisions, procedures and processes for establishment and product licensure (including foreign ones), and procedures for maintaining confidentiality of manufacturers' information. Section 610 establishes general biological standards, and sections 620-680 establish additional standards for various types of biological Products.

Legislative authority for sections 600 through 680 comes from the Public Health Service Act of 1944 (Sec. 351,58 Stat. 702, as amended, 42 USC 262).

Procedures and Processes: BOB issues two types of licenses that a manufacturer must obtain before introducing a vaccine product into commerce—a product license and an establishment license. A manufacturer must obtain an establishment license at the same time it receives its first product license.

Step 2: Manufacturer Submits to BOB an IND Application To Test an Experimental Vaccine in Humans

Source(s) of Authority: BOB's regulatory authority to require a manufacturer to file an investigational new drug (IND) application for new vaccine products is contained in section 601.21, Title 21, CFR. Specific regulations that apply to IND procedures are found in section 312 (New Drugs for Investigational Use) of Title 21 of the CFR (21 CFR 312).

Authority for section 312 comes from the 1962 amendments to the Food, Drug and Cosmetic Act of 1938 (sec. 215, 58 Stat. 690, as amended, 42 USC 216; sees. 502, 503, 505, 701, 52 Stat. 1051, 1052, 1053, 1055, as amended (21 USC 352, 353, 355, 371); 5 USE 554).

Procedures and Processes: The extent to which BOB requires a manufacturer to complete an IND application depends on the amount of existing data concerning a particular product that BOB will accept from foreign and intrastate studies. If no such data are available, then the manufacturer will have to supply a substantial amount of data collected from IND-

approved studies. If it so chooses, however, BOB can waive this step entirely from the licensing process.

Step 3: BOB Evaluates and Either Approves or Rejects Manufacturer's IND Application

Source(s) of Authority: Same as those cited in Step 2.

Procedures and Processes: During the 30-day period subsequent to the filing of its IND application, the manufacturer may conduct no clinical investigations of its product. BOB during this period conducts a two-part review of the manufacturer's IND application. First, BOB staff scientists review sections of the application and comment on the validity of submitted data and research protocols. Second, BOB's IND Branch reviews the appropriateness of the total application. For its evaluation, the IND Branch may seek the advice, not only of BOB scientists, but of scientists in governmental agencies such as the National Institutes of Health (NIH) and the Center for Disease Control (CDC).

On the basis of its two-part review, BOB decides to allow the manufacturer to proceed as proposed, to require the manufacturer to modify its application, or to reject the IND application totally. If BOB objects to any part of the IND application, it must inform the manufacturer within **30** days and specify corrective actions that are necessary for BOB's acceptance. If BOB does not object to the IND application within **30** days, the manufacturer can proceed with its clinical investigation of the product described.

Step 4: Manufacturer Tests the Experimental Vaccine in Humans and Submits Its Data and Application for Product Licensure to BOB for Evaluation

Source(s) of Authority: Same as those cited in Step 2.

Procedures and Processes: Clinical investigation authorized under an IND is performed, at maximum, in three phases, each involving progressively more extensive testing. For vaccines, Phase I testing involves a small number of human subjects and is used primarily to assess safety. This phase is required when a product has been tested only in vitro and in animals. In Phase II, the manufacturer continues safety testing, using a larger number of subjects, and also begins efficacy testing for specific medical conditions. In Phase III, more rigorous testing methods

such as well controlled clinical trials, are used to evaluate clinical safety and efficacy in a large number of subjects. There are no requirements for minimum numbers of subjects included in any phase.

BOB can 1) require a manufacturer to go through this phase-by-phase process, 2) modify IND requirements, that is, abbreviate or waive one or more phases, or 3) waive such testing, depending on the availability of valid data from prior clinical investigations. Apparently, modification is the most commonly used alternative. A manufacturer is required to submit to BOB new research protocols for each phase of testing and annual progress reports. BOB weighs safety data with efficacy data in an effort to achieve an equitable balance of caution and progress.

Once an IND application has been accepted by BOB, it usually remains open until closed by the manufacturer. Thus, the manufacturer can continue to conduct clinical investigations with the product, informing BOB of major changes in proposed research protocols.

To facilitate market entry of a product, a manufacturer can begin the product licensure process before completing clinical investigations authorized or required under the IND process.

Step 5: BOB Evaluates Safety and Efficacy Data From Clinical Trials and Processes Manufacturer's Application for Product Licensure

Source(s) of Authority: Parts **600, 601, 610, 620, 630,** and **680** of the CFR delineate BOB's authority to use selected procedures, processes, and standards to conduct prelicensing evaluations of new vaccine products. Sections in the CFR pertaining to regulatory functions include the following:

<i>CFR Section Citation</i>	<i>Content of Regulation</i>
21 CFR 600.3	Establishes definitions used throughout Title 21, e.g. safety, sterility, purity, potency, and labeling.
21 CFR 601.2	Outlines procedures for filing application for product licensure.
21 CFR 601.4	Gives FDA Commissioner authority to approve or deny an application.
21 CFR 601.20	Requires products and manufacturing processes to comply with all applicable standards established in Title 21.
21 CFR 601.25	Establishes general definitions and criteria to be used to evaluate a product's safety, effectiveness, risk-to-benefit ratio, and labeling requirements, also outlines procedures to be used to evaluate products and to handle manufacturers' responses.

(Note: Section 601.25 technically refers to the review only of products licensed prior to July 1, 1972, but apparently is used by BOB to evaluate new products, as well.)

21 CFR 601.51	Establishes conditions and procedures for maintaining confidentiality of selected data submitted by manufacturers.
21 CFR 610	Establishes general standards and procedures for tests conducted on biological products to help ensure their general safety, potency, sterility, purity, identity, and stability.
21 CFR 620	Establishes additional standards for bacterial products.
21 CFR 630	Establishes additional standards for viral vaccines.
21 CFR 680	Establishes additional standards for miscellaneous products.

The statutory authority for these regulations is derived from the Public Health Service Act of 1944 (see, 351, 58 Stat. 702, as amended, 42 USC 262).

Procedures and Processes: BOB uses at least seven basic procedures to process a manufacturer's application for licensure of a vaccine product.

1. BOB's Licensing Branch screens the entire application to ensure completeness and compliance with all elements of CFR sections 601.2 and 601.
2. BOB forms an Ad Hoc License Review Committee comprised of BOB scientists, which assesses data produced from clinical trials and other testing procedures. Examples of scientific disciplines represented on the committee are microbiology, virology, bacteriology, immunology, epidemiology, and pathology. This committee is responsible for assessing various aspects of a product, including its safety and effectiveness, and relies on data from IND clinical investigations. If no IND investigation has been conducted, the committee may rely on data from clinical trials conducted in foreign countries.
3. BOB's Division of Control Activities conducts several types of tests on samples submitted from at least three lots of the experimental product. Tests are conducted to assess sterility, potency, stability, and biological and chemical purity and pyrogen content. Other BOB laboratories may conduct tests to confirm the manufacturing process.
4. BOB staff conduct a prelicensing establishment inspection. They investigate manufacturing procedures (e. g., processing, testing, storing, dispensing, and recording), inspect the manu-

facturer's equipment and facilities, and interview appropriate personnel.

5. Upon review of all test data, manufacturing procedures, and inspection findings, the chairman of the Ad Hoc License Review Committee recommends to BOB's Licensing Branch, with the concurrence of appropriate scientific division directors within BOB, either issuance or denial of the product license application.
6. BOB's Licensing Branch ensures that all data, including labeling, have been submitted by the manufacturer and reviewed by BOB. It conducts an administrative review for compliance with regulatory standards. In addition, the Licensing Branch ensures that, prior to issuance of the license, the manufacturer has prepared a batch of the new vaccines for release on the market.
7. If the Licensing Bureau concurs with the findings of the Ad Hoc License Review Committee, it recommends licensure to the BOB Director, who then makes a recommendation to the FDA Commissioner regarding the manufacturer's application.

In addition to relying on in-house procedures to review a manufacturer's product application, BOB often, on an informal basis, enlists the aid of scientists and clinicians from other Government agencies, e.g., the Center for Disease Control (CDC), the National Institute of Allergy and Infectious Diseases (NIAID), and from selected professional organizations, e.g., the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and certain infectious disease groups in medicine. The BOB Director also may seek the services of outside advisory panels, such as those established under section 601.25.

In addition to using the general standards described in sections 601 and 610, and the additional standards in sections 620 and 630 of Title 21 of the CFR, to evaluate new vaccine products submitted for licensure, BOB uses specific guidelines issued by its staff and minimum requirements (particularly for potency) established at NIH before 1972.

Step 6: BOB (FDA) Issues Product License to Manufacturer

Source(s) of Authority: Section 601.4 of Title 21 of the CFR authorizes the FDA Commissioner to issue or deny either a product or an establishment license. This authority, and its accompanying procedures were published in the *Federal Register* (FR) on January 25, 1977 (42 FR 4718), and published as amended on May 22, 1977 (42 FR 15676), and on April 12, 1977 (42 FR 19142).

Procedures and Processes: If the FDA Commissioner approves the manufacturer's product application, BOB completes the license forms, and licensure remains valid until suspended or revoked. If the FDA Commissioner denies the application, however, he or she must inform the manufacturer of the reasons for denial and offer the manufacturer a public hearing on the matter.

Step 7: Manufacturer Markets the Newly Licensed Product

Source(s) of Authority: Not applicable.

Procedures and Processes: Not applicable.

Step 8: Manufacturer Is Required, Once Having Marketed the Licensed Vaccine Product, To Remain in Compliance With at Least Four Regulations That Help BOB Monitor the Product

Source(s) of Authority: As a condition of product licensure, BOB requires manufacturers' continuing compliance with the following regulations:

<i>CFR</i>		
<i>Section</i>	<i>Citation</i>	<i>Content of Regulation</i>
21 CFR	610.1	Requires manufacturers to test samples from each lot of vaccines for compliance with BOB's standards for selected product qualities, e.g., potency, sterility, and labeling, and to report all deficiencies to BOB.
21 CFR	610.2	Requires manufacturers to submit samples and data from, and to obtain BOB's approval to release, each lot of vaccines produced.
21 CFR	601.12	Requires manufacturers to obtain BOB's approval to change selected aspects of vaccine production, e.g. manufacturing methods and product labeling.
21 CFR	600.12 and 21 CFR 600.22	Requires manufacturers, for 5 years, to maintain records of clinical reports of adverse reactions to their vaccines, and to give FDA inspectors access to these records.

(Note: BOB is attempting to establish its regulatory authority to require manufacturers to submit reports of adverse reactions to vaccines.)²

Procedures and Processes: No comment.

²See chs. 6 and 7.