First, written standards, developed by groups of experts and adopted through the ECBS, establish regulatory requirements for production and quality control criteria to assure safe and effective vaccines in immunization programs. Specific examples include new written standards for nonclinical and clinical evaluation of vaccines (3); and vaccine-specific guidelines that can serve as a basis for national regulatory decisions, such as a new written standard for human papillomavirus (HPV) vaccines adopted in 2006 by the ECBS (4). Recently developed WHO documents for specific vaccines also include guidance for clinical evaluation of such products, in contrast to earlier documents, that dealt only with production and quality control. These WHO recommendations, if adopted by member countries, can become part of their national requirements for specific vaccines. Second, physical standards developed by WHO are used globally to standardize and validate the methods used to test vaccines. These can be International Biological Standards or International Biological Reference Reagents (5). The written and physical standards provide the basis for the regulation of vaccines as biological products.

HISTORY OF EFFORTS TO ENSURE VACCINE QUALITY

Development of Vaccine Regulation in the United States (6)

The U.S. Food and Drug Administration (FDA), the agency responsible for regulatory oversight of vaccines in that country, recently celebrated its 100th anniversary, measured from Congress's passage of the Biologics Control Act on July 1, 1902. This Act was a response to the deaths of 13 children in St. Louis in 1901 after receiving diphtheria antitoxin that had been accidentally contaminated with tetanus. A similar contamination of smallpox vaccine resulted in the deaths of nine children the same year.

The Biologics Control Act charged the Laboratory of Hygiene of the Marine Health Service with the regulation of biologicals. Under the Act, the Laboratory issued regulations to ensure safety, purity, and potency; established standards; and issued licenses for smallpox and rabies vaccines, and later for other biological products. It was renamed the National Institute of Health in 1930. All issued regulations and standards were codified in the Public Health Service (PHS) Act of 1944 (7).

A milestone in the regulation of vaccines followed the ''Cutter incident'' in 1955, when 260 cases of polio and 11 deaths resulted from the use of incompletely inactivated polio vaccine manufactured by Cutter Laboratories. The Surgeon General then suspended all polio vaccinations pending a review of vaccine testing procedures and inspections of all manufacturing facilities, which resulted in stricter standards and tighter control.

On July 1, 1972, the Division of Biologics Standards was moved from the National Institutes of Health to the FDA, because of a failure to initiate an effectiveness review, so that the provisions of the Food and Drug Control Act as well as those specifically designed for biologicals (section 351 of the PHS Act) applied to regulatory oversight of vaccines. Biological products are currently overseen by FDA's Center for Biologics Evaluation and Research.

Standardization Activities of the ECBS

Section 351 of the PHS Act defines a biological product as a ''virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product,... applicable to the prevention, treatment, or cure of diseases or injuries of man'' (8). These products have been treated differently than chemical medicines because they are difficult to characterize, often contaminated, and assuring potency, consistency, and safety poses particular challenges. They involve starting materials of biological origin and often need biological testing systems (9). The issues of inherent variability and of measuring potency led to the use of an international standard or reference reagent in quality control tests. The League of Nations recognized the need for biological standardization; this led to the creation of the Permanent Commission on Biological Standardization (10). This work was eventually taken over by the ECBS. Established in 1947, the ECBS has overall responsibility for setting written standards and establishing reference preparation materials. Members of the ECBS are scientists from NRAs, academia, research institutes, and public health bodies. These scientists act as individual experts and not as representatives of their respective organizations or employers. The decisions and recommendations of the ECBS are based entirely on scientific principles and public health considerations.

In the early days of vaccine development, as has been seen, vaccines as impure biological products underwent tests, usually in animals, as the sole means of ensuring that the product complied with specifications. Despite biological standardization, they are still not ideal. Two developments have changed the role of testing in vaccine regulation (11): (*i*) the evolution of concepts of regulation, with more emphasis on assuring consistency of production, through GMP compliance, and more attention to how clinical data are obtained and assessed, both prior to and after marketing (12) and (*ii*) the changes in the products themselves, which affect the type of testing that is done.

Assuring United Nations Agency Vaccine Supply

After the Expanded Program on Immunization (EPI) was started in 1974, vaccines were provided either by multinational manufacturers or national vaccine producers exporting products through United Nations (UN) procurement agencies, including UNICEF and the Pan-American Health Organization (PAHO) Revolving Fund (RF) (13,14).[a] Vaccine quality was assumed to be acceptable, but even so it was noted that ''PAHO/WHO screen manufacturers offering vaccines for EPI use and, where possible, review protocols of the specific lots submitted for sale'' (15). In addition, much emphasis was placed on the national testing of vaccines or the use of WHO or PAHO testing centers (16). At its 84th meeting in June 1980, the PAHO Executive Committee urged all Member States to strengthen their respective laboratories for vaccine testing (17).

In 1981, WHO's ECBS published its first guideline on national control of vaccines (18), mandating a ''national control authority'' for all countries, the responsibilities of which would

[a] The PAHO RF started buying vaccines in 1978 for 1979. Suppliers of OPV, DTP, TT, measles, and BCG vaccines included Torlak (Yugoslavia), Merieux (France), SmithKline-RIT (Belgium), Connaught (Canada), Japan BCG (Japan), Evans Medical/Glaxo (U.K.). A search of the UNICEF archives failed to provide specific information such as that for the PAHO RF cited here; however, it is safe to assume that WHO activities in the area of quality assurance were comparable for both and also that the suppliers were similar for both procurement agencies.