

## Regulation of vaccines: strengthening the science base

JULIE B. MILSTIEN

### introduction

**O**FTEN heard today is the complaint that the standard of regulation of vaccines in the industrialized world serves as a barrier to entry of manufacturers into the market, especially for vaccines designed for the developing world, adding significantly to the costs of production. Vaccines play a critical role in international public health. Their development has been based on universal scientific principles; however, their regulation is centered in national regulatory authorities. The United States Food and Drug Administration (USFDA) has perhaps the longest history in vaccine regulatory activities, and has played a leading role in vaccine regulation. That role is in part traced here, with examples from activities of other regulatory authorities and the World Health Organization (WHO), as relevant.

The aim of this paper is to look at how these regulatory practices developed, the justification for their continued use, and a review of new approaches that are being put into play. Part IIA presents examples of old vaccines still in use. Part IIB traces the development of regulatory systems in the US and elsewhere. Part IIC looks at the concept of biological standardization in the regulation of biologicals. Part IID explores the evolving role of laboratories, and Part IIE presents some of the changes in regulation that are being introduced, and the implications for the older vaccines. Section III considers some of the larger issues resulting from these changes, while Section IV discusses to the future. From this review, it is apparent that in the future we need vaccine regulation guided by a strong science base for vaccine regulatory decisions; a risk-based approach to define processes and evaluations; an integrated quality management system underlying the whole procedures; and international collaboration throughout.

174 journal of public health policy · vol. 25, no. 2  
history of vaccine regulation

*Vaccines of the past*

Many vaccines still in use today are very old, having been developed 50–80 years ago, with little change in technology since then. Table 1 gives an example of some of these.

Although newer vaccines may be moving away from the older constructs that were based on extracts of bacterial or viral suspensions, some of the vaccines on the market today still use this older technology—for example, diphtheria and tetanus toxoids, whole cell pertussis vaccines, and BCG. The latter two are no longer in use in the US but remain widely used in much of the rest of the world, including some parts of Europe. Production and testing methods remain essentially unchanged from when they were first licensed. Live viral vaccines like oral polio vaccine (OPV) (still in use in much of the world, although not in the US), measles, and yellow fever vaccines have not undergone much change since the 1960s. Even a relatively “new” vaccine, recombinant hepatitis B vaccine, is almost 20 years old.

*History of vaccine regulation (1)*

The United States FDA, the agency responsible for regulatory oversight of vaccines in the US, recently celebrated its 100th anniversary, commemorating the passage of the Biologics Control Act by Congress on 1 July 1902. Like other major changes in vaccine regulation that would follow, this first step was in response to a tragic event: the death of 13 children in St Louis in 1901 who had received diphtheria antitoxin that had been accidentally contaminated with tetanus. The horse from which the antitoxin had been prepared had contracted tetanus and had been killed, but the serum was not destroyed. This was followed by a similar contamination of smallpox vaccine, also in 1901, when nine children in Camden, NJ died of tetanus after receiving this vaccine.

Prior to the 1902 law, biologics testing had been done by the Laboratory of Hygiene of the Marine Health Service, established on Staten Island, NY, in 1887, and moved to Washington, DC, in 1891. This laboratory, under the Biologics Control Act, was charged with the regulation of biologicals and the research necessary to support such regulation, under its new name, the Hygienic Laboratory of the Public Health and Marine Hospital Service.

## milstien · regulation of vaccines

175

table 1

## Development of Commonly Used Vaccines

<i>Vaccine</i>	<i>Year first developed</i>	<i>Comments</i>
Smallpox	1798	Used since 1800 in US, routinely since beginning of 20th century; current formulation available in 1950s; new formulations being developed for bioterror stockpiles
Rabies	1885	Human diploid cell culture vaccine developed in 1967; current cell culture vaccines available in US since 1980's
Bacille Calmette-Guérin (BCG)	1921	In France
Diphtheria toxoid	1921	Licensed in 1926 and used in early 1930s in US; widespread use after 1948 as part of DTwP
Pertussis	1926	Introduced in US in 1948 as part of DTwP (whole cell); acellular pertussis vaccine licensed for infants in 1996
Tetanus toxoid	1924	Licensed in US in 1933 and introduced in 1948 as part of DTwP
Yellow fever	1937	Current leucose-free thermostable formulation grown on chick embryo cells developed in early 1980s
Inactivated polio (IPV)	1955	Enhanced formulation licensed in 1987 in US
Oral polio (OPV)	1955	Introduced in US in 1961 and trivalent formulation licensed in 1963
Measles	1963	Current strain licensed in US in 1968
Rubella	1969	Current formulation licensed in 1979
Hepatitis B	1981	Plasma derived strain. Recombinant product licensed in US in 1986, and in 1991 recommended for widespread infant use

## 176 journal of public health policy · vol. 25, no. 2

The Act authorized the laboratory to issue regulations to ensure *safety, purity, and potency*, which was done in 1903, 1909, and thereafter. The Laboratory established standards and licensed smallpox and rabies vaccines, (and later other biological products). In 1934, the Laboratory, called the National Institute of Health since 1930, issued a regulation stating that licenses would depend on evidence of *efficacy* as well. All these provisions were codified in the Public Health Service Act of 1944 (2).

The FDA put into place a parallel regulatory structure for oversight of drugs (which before 1972 implicitly, but not explicitly, covered biologicals). In 1938 Congress enacted the Federal Food, Drug and Cosmetic Act following deaths caused by the diethylene glycol used in an elixir of sulfanilamide. This act required sponsors of Investigational New Drugs (INDs) to submit safety data about the candidate product prior to receiving approval to market it (3). In 1941, 300 people were injured and some died as a result of contamination of sulfathiazole tablets with phenobarbital, which led to the definition of Good Manufacturing Practice (GMP) (4).

A milestone vaccine regulation followed the so-called “Cutter incident” in 1955, when 260 cases of paralytic polio and 11 deaths were caused by inactivated polio vaccine that had not completely inactivated by its manufacturer, Cutter Laboratories. The US Surgeon General 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. As a result of the Cutter incident, the Laboratory of Biologics Control in the National Institutes of Health, was raised to division status as the Division of Biologics Standards, an independent entity with seven laboratories. In addition, the Centers for Disease Control put in place a system of adverse event monitoring (5).

In 1960, thalidomide was marketed in Europe as a sleeping pill and to treat morning sickness. Never approved in the US, it was nonetheless used extensively in research, causing more than 10,000 cases of children with severe limb deformations. The 1962 Kefauver amendments to the Food and Drug Control Act, required efficacy data as well as safety data to support IND applications. The thalidomide incident encouraged better definition of reporting requirements for adverse reactions, both in clinical trials and in routine use of licensed drugs.

On 1 July 1972, the Division of Biologics Standards was moved from the National Institutes of Health to the FDA, so that most provisions of the Food and Drug Control Act, not only those specifically designed for biologicals (Section 351 of the Public Health Service Act) applied to regulatory oversight of vaccines. Failure of the Division of Biologics Standards to institute an effectiveness review of vaccines similar to that done for drugs had prompted this change. Since that time, FDA administrators have reorganized the entity that handles biological products: currently they are overseen by the Center for Biologics Evaluation and Research (CBER).

*Biologicals and the need for standardization*

The 1919, US regulations defined biologic products as “vaccines, sera, toxins, antitoxins, and analogous products,” (6) and they have ever since been treated differently than chemical medicines. Regulators appreciated that they are difficult to characterize, often contaminated, and the assurance of standard parameters such as potency, consistency, and safety poses particular challenges. Regulators have often characterized biological products as such because they demand biological testing systems (7).

*Use of references and standards.* The inherent variability of most biological products and of their biological test methods, and the lack of an agreed system for measuring potency of such impure products, led to the use of international standards or reference reagents in quality control tests. The first biological standard was for insulin, developed by Sir Henry Dale in 1923. Sir Henry describes the concept: “My intervention took the form of insisting it was complete nonsense to try to define any unit of any remedy in absolute terms of reactions in a limited number of animals; and that, from the international point of view, the only sensible thing was to obtain the remedy in perfectly stable form and define the unit in terms of an absolute quantity of such standard sample, internationally accepted, leaving the laboratory methods of its determination to be the subject of indefinite possibilities of experimental improvement . . .” (6).

The importance of international biological standardization was recognized early in the 20th century in the work of the League of Nations, leading to the creation of the Permanent Commission on Biological Standardization, (8) whose work was eventually taken over by the Expert Committee on Biological Standardization (ECBS) of the

178 journal of public health policy · vol. 25, no. 2

World Health Organization, with its secretariat in the Biologicals Unit (now Quality Assurance and Safety of Biologicals).

*Difficulties of bioassays.* The CBER Vision Newsletter, Special Commemorative Issue describes test development for whole cell pertussis vaccine by Dr Margaret Pittman at the National Institute of Health (later the Division of Biologics Standards) (9). A potency test for pertussis vaccine had not been developed due to lack of an animal model for pertussis infection. In 1944, Dr Pittman was, by intracerebral injection, able to infect mice with pertussis, a method that became the basis for the mouse protection test. The test measures the 50% dose—the dose of vaccine that would result in the survival of 50% of mice infected with a certain number of pertussis bacteria. She also developed an opacity standard to estimate the number of bacteria in a certain volume of vaccine. The US and other countries and the WHO ECBS, then adopted biological standards for pertussis vaccines, having assigned potency units (10).

Unfortunately, to date, no better method for determining pertussis potency has been validated, yet this test is fraught with variability. A summary of testing results for biological products at the National Institute of Biological Standards and Control in 1994–1995 (7) showed the highest rate of noncompliant results, over 8%, for the bacterial vaccines.

The abnormal toxicity test was developed to detect any possible contamination in a final lot of product, and springs from the era when contamination of biological products was a severe problem, as described above. Two guinea-pigs and five mice are injected with the product and are observed for seven days. None of the animals should show toxic signs. Many question the relevance of the abnormal toxicity test as its importance has been diminished by required compliance with Good Manufacturing Practice; it is nonspecific; and it is not mandatory for most pharmaceutical products (11). Many pharmaceuticals now omit it (most European countries) but others retain it.

#### *The role of the laboratory in regulation*

In the early days of vaccine development the role of the laboratory was key—the complexity of vaccines as impure biological products meant that testing, for the most part animal testing, was the means of ensuring that the product complied with specifications. A developing system of biological standardization improved the use of these tests;

nevertheless, they are far from ideal. Two trends are now changing the way the laboratory works in regulation of vaccines (12): the evolution of concepts of regulation, and the changes in the products themselves. The changes in regulation will be considered in Part IIE.

*Better characterized and more highly purified vaccines.* Products recently developed, such as component acellular pertussis vaccines, contain purified antigens, and others, such as the conjugated polysaccharide vaccines, depend on sophisticated chemical conjugation reactions and precise physical characterization. Products using recombinant DNA and viral vector technology are common. We often characterize these by physical techniques such as gel electrophoresis, mass spectroscopy, and polymerase chain reaction tests. Although unlikely to demonstrate potency directly, these tests show consistency of the products tested, compared to lots that have been shown to be safe and effective in clinical trials (13).

*Limitations of testing.* As a quality control method, testing vaccines has its limitations. For a sterility test, for example, it may be difficult to test enough samples to get a truly representative result. To test a product for a particular characteristic, a portion of that product must be used up. To test for a potential sporadic contaminant, the amount of sample that must be tested is defined by the formula,  $0.4\sqrt{N}$ , where  $N$  is the number of vials in a lot. Testing that number of samples does not assure that a "contamination event" would be picked up; for that reason strict process controls are also imposed to ensure sterility of biological products.

Regulators are defining new tests that have enhanced sensitivity, but they may be difficult to interpret. For example, new sensitive tests can detect potential reverse transcriptase activity in some chicken-cell derived vaccines or DNA tumor virus, SV40, in poliovaccine (14,15,16). No evidence has indicated a public health relevance of these findings (12). For some products (e.g. acellular pertussis vaccine) and for potential contaminants, such as transmissible spongiform encephalopathies (TSE), no single test has been found to predict clinical efficacy or safety (12). Finally, any test method must be appropriately validated to ensure the reliability of the results on which public health decisions might be based.

Therefore, to summarize, laboratory tests on vaccines are important, but they must be standardized and validated. But tests alone cannot predict clinical efficacy or safety of these products.

*Concepts of vaccine regulation have changed*

1. *Empirical approach.* Vaccine regulation in the past relied mostly on laboratory testing, with very little action in the control of process.

The Cutter incident mentioned above is a case in point (1). On April 12, 1955, the Laboratory of Biologics Control in the US issued licenses to six manufacturers to manufacture inactivated poliovirus vaccine, based on written protocols for vaccine production and safety testing. Soon afterwards, cases of polio were reported in recipients of the Cutter Laboratories vaccine. Investigators found live poliovirus had survived the inactivation procedure in two batches of vaccine, and that the manufacturer had discarded other vaccines because of the presence of live viruses. This had not been reported, but there was no reporting requirement at that time.

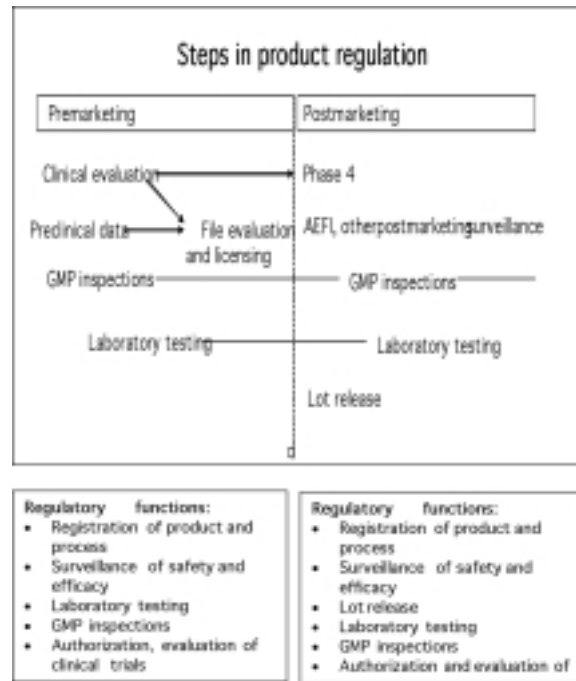
In contrast to the safety precautions used in field trials, where all safety tests were repeated in three different laboratories, no similar controls nor confirmation of consistency of production or inactivation were required for commercial manufacture. The only legal requirements for licensing of the six polio vaccine manufacturers were written protocols for vaccine production and safety testing. The protocols filed by the manufacturers did not contain enough detail to evaluate vaccine safety.

Current GMP procedures would have prevented the Cutter incident, through requirements for test validation, complete protocols for safety evaluation, manufacturer inspection, and required reporting of lots not meeting specifications. Regulation based on testing alone would not suffice.

2. *Regulatory approach.* At its 42nd meeting, the WHO Expert Committee on Biological Standardization approved *Guidelines for national authorities on quality assurance for biological products* (17), codifying for the first time at the global level the expectations of the regulatory process. This was followed by *Regulation and licensing of biological products in countries with newly developing regulatory authorities* in its 45th Report (18), which prioritized activities for countries just beginning

figure 1

Steps in product regulation pre- and post-marketing



to develop regulatory authorities. The WHO document defined five essential regulatory functions in addition to laboratory testing: licensing and registration; surveillance for field impact (including adverse events and lack of efficacy); lot release; enforcement of GMP compliance; and clinical trials authorization and evaluation. A subsequent report, based on country inputs, spelled out performance indicators for each of these functions (19). A similar range of functions has been outlined in recent guidelines on combination vaccines issued by the FDA (20), as well as in other documents found in reference 2. Figure 1 illustrates how the regulatory functions follow the product development and use process.

182 journal of public health policy · vol. 25, no. 2  
the current regulatory situation

*Changes in the regulatory process*

Thanks to vaccines against many killer diseases of childhood, the incidence of these diseases has greatly decreased. As risk from disease has declined, the public has increasingly expected “zero risk” from the protective measures as well, at least in the industrialized world. This has led to a litigious atmosphere, escalating regulatory decisions, and a tendency for the more developed regulatory agencies to be extremely conservative in their approaches, exemplified by rigid application of guidelines, a tendency to higher expectations from manufacturers, larger clinical trials, and greater margins of safety.

Regulators also put more emphasis on raising GMP compliance levels, even if the required changes may not be strictly necessary for a pure, safe and efficacious product. This usually increases the cost of compliance for manufacturers. Accordingly, several manufacturers have left the industry rather than make the necessary investments for full compliance.

Another change is the increasing reliance on extensive clinical safety and efficacy data. In fact, a whole new industry of Clinical Research Organizations (CROs) has grown up to service this need for more and better monitored clinical trials. Trials demand better documentation as well as increased power to detect rare adverse events. They are more expensive.

Clinical trial data must be linked to the laboratory. Early phase trials can help determine serological correlates of protection, and correlate potency measures with efficacy. Such correlates greatly simplify product release and assessment of combinations and the impact of variances.

Other regulatory changes may also simplify the regulatory process. The FDA Modernization Act of 1997 (FDAMA) (21) eliminated the requirement for an establishment license for biologicals production, bringing regulation of biological products into closer harmony to that for drugs. In August 1996, the FDA removed certain biological regulations no longer considered necessary (22). And in July 1997, FDA amended the biological regulations on reporting changes to an approved registration file, and created three categories based on the potential of the change to affect substantially, moderately, or minimally adversely product safety, purity, potency, or effectiveness (2,23). This amendment clarifies how manufacturers should report changes,

table 2

Examples of current regulatory practices  
(see text for explanation of terms)

<i>Possibly not cost-effective</i>	<i>Likely cost-effective</i>
– Outdated animal tests (e.g. pertussis)	– New test methods (e.g. to replace polio neuroviru- lence test), standardized and validated
– Extremely large phase 3 trials	– IND system for clinical tri- als; phase 4 trials
– Spiraling cGMP	– Risk based GMP
– Specific product decisions based on “perceived” risk (e.g. thiomersal removal)	– ICH for harmonization

and when a change needs to be approved in advance before it can be put in place.

*Examples of beneficial and non-cost-effective changes*

Table 2 provides some examples of regulatory practices as they exist now which may not be cost-effective, and other approaches which might address some of the problems noted above.

*Test methods.* Animal tests associated with older vaccines may be neither precise nor predictive. The mouse weight gain test, for example, used to determine the safety of whole cell pertussis vaccine varies in practice and may measure phenomena other than the presence or absence of pertussis toxin. For acellular pertussis vaccine, the test is insufficiently sensitive to demonstrate residual pertussis toxin (24).

The abnormal toxicity test is not relevant for oral vaccines, as it uses intraperitoneal injection, nor for products with inherent toxicity which could interfere with its interpretation. Furthermore, as pointed out in part IIC, its utility is superseded by the requirement for GMP compliance. The FDA is currently exploring whether to eliminate this requirement (25). The WHO Expert Committee on Biological Standardization, at its 50th meeting in 2002, noted that data from one region of the world indicated that the abnormal toxicity test did not provide additional assurances of the quality and asked that the Secretariat investigate this globally with a view to harmonize approaches

184 journal of public health policy · vol. 25, no. 2

(26). In many countries, including much of Europe, this test has been eliminated, especially for products where other animal testing is done. For other products, the test might be done on bulk lots rather than on the final product (11).

*Clinical trials.* In the US, all products for trials in humans fall under the IND (Investigational New Drug) provisions, which means that there is an approval process for each trial. The system is flexible, allowing maximal control where there are questions, but with the ability to abbreviate the process in some cases. The US IND system is generally considered a good one for products in clinical trial. Phase 4 trials, which are done after licensing, post-marketing, constitutes a useful concept. Sometimes a phase 4 trial is designed to allow definition of potential safety issues in a large monitored population under actual use conditions.

For rotavirus vaccine, postmarketing monitoring detected intussusception associated with its use—a rare event (one case per 10,000 recipients) which could not have been definitively documented in smaller phase 3 trials. For new candidate rotavirus vaccines, regulators are now recommending extremely large phase 3 trials (27) (>70,000). In the US, this number of trial participants may be feasible, but for other countries, trials of this size may approach that of an entire birth cohort, and multi-center trials may be necessary, thus adding to the expense and complexity. Moreover, as phase 2 trials are generally much smaller, this requirement could imply a large increase in the number of recipients of an unlicensed product—a situation not necessarily safer than if the product were licensed on the basis of smaller phase 3 trials and subject to careful phase 4 monitoring.

*GMP.* GMP compliance, characterized by a new concept—current GMPs (cGMPs)—is an ever changing target. Although various GMP codes do not differ much, their interpretation and enforcement by GMP inspectors in different countries does. In August 2002, the FDA announced an initiative “Pharmaceutical cGMPs for the 21st Century,” a risk-based approach designed to:

- Enhance the focus of the agency’s cGMP requirements on potential public health risks;
- Help ensure that FDA’s work does not impede innovation in the industry;
- Enhance the consistency of the FDA approach across its different centers and field components (28).

Perhaps such an approach will provide some balance to the current cGMP escalation.

*Product decisions.* Decision making based on a theoretical risk rather than solid scientific evidence is a regulatory practice that carries global implications. The decision to require removal of thimerosal, a mercury-containing preservative, from vaccines for use in the United States, because of concern about exposing infants to mercury compounds constitutes a recent example (26,29). The action, based on a perceived risk which has not been demonstrated to exist (30), cost manufacturers dearly and created a vaccine shortage in the US. (The decision threatened the global supply of vaccine had it been implemented in additional countries). Moreover, much of the developing world depends on use of thimerosal, to preserve vaccines in multi-dose vials, that help keep down the cost vaccination programs (31).

*Harmonization.* Many vaccine manufacturers raise concerns about lack of harmonization—the wide variety of requirements for registration and licensing of new products in different parts of the world. The International Conference on Harmonization (ICH), made up of regulatory agencies and manufacturers in the US, Europe and Japan, has begun to address the problem. Under harmonization, participating regulatory agencies must agree to incorporate and implement uniform guidelines. To date, useful guidelines relevant to vaccines have been developed in several areas: those on clinical trials and a common technical document are notable.

#### proposed future directions

A 1997 study commissioned by the UK National Biologicals Standards Board (7) addressed the issue of whether physico-chemical analysis and testing could replace bioassay, if not for all biological products, at least for those made by recombinant DNA and monoclonal antibody technology. The study committee concluded that physico-chemical testing and bioassay will need to co-exist for some time to come. Although for some products physico-chemical testing might provide an initial screen for consistency, only for a very few products, such as recombinant proteins and polysaccharide vaccines, are physico-chemical tests available that could correlate with biological effectiveness. In such cases, however, there can be a higher degree of confidence in their consistency, which could allow changes in the regulatory requirements. For the present, regulators must continue to

186 journal of public health policy · vol. 25, no. 2

insist on separate approaches for the regulation of vaccines. In addition, we still have the legacy of the older products that may not be amenable to these approaches.

However, there are ways to approach the increasing regulatory burden. FDA, in its announcement of a risk-based approach for pharmaceutical cGMPs, has outlined at least four underlying principles (32,33):

- Using a risk-based approach to decisions, so that for each decision it would be clear how it would lower the risk to the consumer;
- Ensuring that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science, an approach which could imply a reevaluation of outdated test procedures;
- Application of quality systems in all aspects of pharmaceutical production and regulation, which might imply, for example, accreditation of control laboratories; and
- International collaboration, with an implication for consensus standards and harmonization on cross-cutting issues.

Perhaps the committee which undertook the scientific review commissioned by the UK National Biological Standards Board (7) put it best in their summary:

*The Committee's assessment of scientific and technical developments also took into account their implications. These include a need to retain a capacity for independent scientific assessment to underpin regulation, and expertise in biological standardization and bioassay; to ensure regulatory regimes adequately reflect scientific advances; to channel national efforts into an international collaborative approach; . . . and to commit to the use of risk assessment and priority-setting to manage the increasing and increasingly complex workload in this field . . .*

There appears to be international consensus on the way forward. It remains to be seen whether it can be implemented.

## REFERENCES

1. Early history of the development of regulation of biological products by the FDA was taken from the CBER Vision Newsletter, Special Commemorative Issue, July 2002, available at <http://www.fda.gov/cber/inside/centnews.htm>, accessed 3 November, 2003.

2. Baylor NW, McVittie LD. Changes in the regulations for vaccine research and development. *The Jordan Report*. 2002; 45–50.
3. Tacket CO, Rennels MB, Mattheis MJ. Initial clinical evaluation of new vaccine candidates: phase 1 and 2 clinical trials of safety, immunogenicity, and preliminary efficacy. Chapter 4, In: Levine MM, Woodrow GC, Kaper JB, Cobon GS (Eds.), *New Generation of Vaccines: The Molecular Approach*. 2nd Edition. New York: Marcel Dekker, 1997.
4. Ngai P. International Vaccine Institute Third International Course on Vaccine Evaluation in Developing Countries, 2–6 December, 2002, Singapore, PowerPoint presentation.
5. Robbins FC. Polio—Historical. In: SA Plotkin, EA Mortimer (Eds.), *Vaccines*. Philadelphia: Saunders, 1988, 98–114.
6. Jeffcoate SL, Corbel MJ, Minor P, Schild GC. *Proceedings of the Royal Society of Edinburgh*. 1993; 101B: 207–226.
7. *Biological Standardization and Control. A Scientific Review Commissioned by the UK National Biological Standards Board*. Geneva: World Health Organization, 1997. WHO/BLG/97.1
8. Hilleman MR. Vaccines and the Vaccine Enterprise: historic and contemporary view of a scientific initiative of complex dimensions. *The Jordan Report*. 2002; 29–35.
9. CBER Vision Newsletter, Special Commemorative Issue, July 2002, available at <http://www.fda.gov/cber/inside/centnews.htm>, accessed 3 November, 2003.
10. Seagroatt V, Sheffield F. *Journal of Biological Standardization*, 1981; 9: 351–365; WHO Expert Committee on Biological Standardization. Fortyninth Report. Pertussis Vaccine, 3rd International Standard. Technical Report Series. 2000; 897: 19–20; WHO Expert Committee on Biological Standardization. Pertussis vaccine. International Biological Reference Preparations Catalogue. Geneva: World Health Organization, 2001, available at <http://www.who.int/vaccines/Biologicals/P1.asp>, accessed 29 November, 2003.
11. Hendriksen CFM, Garthoff B, Aggerbeck H, et al. Alternatives to animal testing in the quality control of immunobiologicals: current status and future prospects. *ECVAM Workshop Report 4*. ATLA. 1994; 22: 420–434.
12. Milstien J. Regulatory process and three Rs alternatives. In: Brown F, Hendriksen C, Sesardic D, Cussler K (Eds.), *Advancing Science and Elimination of the Use of Laboratory Animals for Development and Control of Vaccines and Hormones*. Dev Biol. Basel: Karger, 2002; 11: 15–19.
13. Dellepiane N, Griffiths E, Milstien JB. New challenges in assuring vaccine quality. *Bulletin of the World Health Organization*. 2000;78:155–162.
14. Pyra H, Böni J, Schüpbach J. Ultrasensitive retrovirus detection by a

## 188 journal of public health policy · vol. 25, no. 2

- reverse transcriptase assay based on product enhancement. Proceedings of the National Academy of Science US, 1994; 91: 1544–1548.
15. Anonymous. Reverse transcriptase activity in chicken-cell derived vaccines. *Weekly Epidemiological Record*, 1998; 73: 209–212.
  16. Sangar D, Pipkin PA, Wood DJ, Minor PD. Examination of poliovirus vaccine preparations for SV40 sequences. *Biologicals*, 1999; 27: 1–10.
  17. Expert Committee on Biological Standardization. Forty-second Report. Guidelines for national authorities on quality assurance for biological products. Technical Report Series, 1992; 822: Annex 2.
  18. Expert Committee on Biological Standardization. Forty-fifth Report. Regulation and licensing of biological products in countries with newly developing regulatory authorities. Technical Report Series, 1997; 858, Annex 1.
  19. World Health Organization, Immunization, Vaccines and Biologicals. Regulation of vaccines: building on national drug regulatory authorities. WHO/V&B/99.10
  20. Food and Drug Administration. Guidance for industry for the evaluation of combination vaccines for preventable disease: production, testing, and clinical studies, 1997. Docket number 97N-0029, available at <http://www.fda.gov/cber/gdlns/combvacc.pdf>, accessed 17 December, 2003.
  21. Food and Drug Administration. Biological Products Regulated under Section 351 of the Public Health Service Act; Implementation of the Biologics License; Elimination of the Establishment License and Product License. *Federal Register*. 1997; 64 (202): 56441.
  22. Food and Drug Administration. *Federal Register*, 1996; 61 (149): 40153.
  23. Food and Drug Administration. *Federal Register*, 1997; 62 (142): 39890.
  24. Granoff DM. Correlation of clinical performance of acellular pertussis vaccines: implications for development of DTaP combination vaccines. *Biologicals*, 1999; 27: 87–88.
  25. Baylor N, Falk LA, Midthun K. The role of the Food and Drug Administration in vaccine testing and licensure. Chapter 11, In: Levine MM, Kaper JB, Rappuoli R, Liu M, Good M (Eds.), *New Generation Vaccines*. 3rd Edition. New York: Marcel Dekker, in press 2004.
  26. Expert Committee on Biological Standardization. Fiftieth Report. Abnormal toxicity test. Technical Report Series, 2002; 904: 10.
  27. Foulkes MA, Ellenberg SS. Vaccine efficacy and safety evaluation. *The Jordan Report*, 2002; 51–56.
  28. Food and Drug Administration. FDA unveils new initiative to enhance

- pharmaceutical good manufacturing practices. 21 August 2002. Available at <http://www.fda.gov/bbs/topics/NEWS/2002/NEW00829.html>, accessed 24 November, 2003.
29. Notice to readers. Thimerosal in vaccines: A joint statement of the American Academy of Pediatrics and the Public Health Service, 1999. *Morbidity and Mortality Weekly Report*; 48: 563–565.
  30. Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study, 2002. *Lancet*; 360: 1737–1741.
  31. Clements CJ, Ball LK, Ball R, Pratt D. Thiomersal in vaccines, 2000. *Lancet*; 355: 1279.
  32. Food and Drug Administration. Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach, available at <http://www.fda.gov/oc/guidance/gmp.html>, accessed 8 November, 2003.
  33. Food and Drug Administration. Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach: Second Progress Report and Implementation Plan, available at [http://www.fda.gov/cder/gmp/2ndProgress-Rept\\_Plan.html](http://www.fda.gov/cder/gmp/2ndProgress-Rept_Plan.html), accessed 31 October, 2003.

#### SUMMARY

This paper aims to review the history of development of vaccine regulatory approaches, to assess practices that may be barriers to access to innovative products, and to suggest possible approaches to address these practices. Despite the appearance of new vaccines in the past few years, many vaccines are based on old technologies, and are still subject to regulatory practices devised many years ago. Vaccine regulation began with a foundation on vaccine testing, and only in response to tragedies associated with vaccine use did new concepts begin to be defined. Vaccine regulation now includes a range of functions that cover the entire continuum of vaccine development and use. However, some regulatory practices, such as the continuing dependence on outdated animal tests, have not kept pace with these changes. Other practices, such as the continual raising of the standard of Good Manufacturing Practice (GMP) compliance, or the move to increasingly larger phase 3 clinical trials, appear to be based more on perceived risks than on firm scientific principles. The future of effective regulation for vaccines that will allow innovation while protecting the public health must be based on three guiding principles: a firm science base for policies and decisions, a risk-based approach to implementation of regulatory oversight, and support for regulatory research to inform these activities. These should be implemented in a setting of international harmonization.