Ensuring the Optimal Safety of Licensed Vaccines: A Perspective of the Vaccine Research, Development, and Manufacturing Companies

abstract

Vaccine safety is increasingly a focus for the general public, health care providers, and vaccine manufacturers, because the efficacy of licensed vaccines is accepted as a given. Commitment to ensuring safety of all vaccines, including childhood vaccines, is addressed by the federal government, academia, and industry. Safety activities conducted by the vaccine research, development, and manufacturing companies occur at all stages of product development, from selection and formulation of candidate vaccines through postlicensure studies and surveillance of adverse-event reports. The contributions of multiple interacting functional groups are required to execute these tasks through the life cycle of a product. We describe here the safeguards used by vaccine manufacturers, including specific examples drawn from recent experience, and highlight some of the current challenges. Vaccine-risk communication becomes a critical area for partnership of vaccine companies with government, professional associations, and nonprofit advocacy groups to provide information on both benefits and risks of vaccines. The crucial role of the vaccine companies in ensuring the optimal vaccine-safety profile, often overlooked, will continue to grow with this dynamic arena. *Pediatrics* 2011;127:S16–S22

AUTHORS: Niranjan Kanesa-thasan, MD, MTMH,[a] Alan Shaw, PhD,[b] Jeffrey J. Stoddard, MD,[a] and Thomas M. Vernon, MD (retired)[c]

[a]Novartis Vaccines and Diagnostics, Cambridge, Massachusetts; [b]VaxInnate Corporation, Cranbury, New Jersey; and [c]Merck Vaccine Division (retired), Philadelphia, Pennsylvania

KEY WORDS

vaccine, safety, pharmacovigilance

ABBREVIATIONS

AE—adverse event
FDA—Food and Drug Administration
CGMP—current good manufacturing practice

www.pediatrics.org/cgi/doi/10.1542/peds.2010-1722D

doi:10.1542/peds.2010-1722D

Accepted for publication Nov 29, 2010

Address correspondence to Niranjan Kanesa-thasan, MD, MTMH, Novartis Vaccines and Diagnostics, 350 Massachusetts Ave, Camridge, MA, 02139. E-mail: Niranjan.Kanesa-thasan@novartis.com.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2011 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: *Drs Kanesa-thasan and Stoddard are employees of Novartis Vaccines, a company that develops, manufacturers, and markets a number of vaccines in the United States; Dr Shaw is employed by VaxInnate, a company that focuses on the development of novel vaccines; and Dr Vernon has served as a consultant to Sanofi-Pasteur.*

Downloaded from by guest on May 6, 2016

The National Vaccine Advisory Committee in 1997 published an influential article in 1997 that lauded the wonderful successes achieved by vaccines in preventing infectious diseases and the future expectations for vaccines arising from developments in molecular biology, immunology, and biotechnology.[1] It addressed the "delicate fabric of America's cooperative and collaborative relationships in vaccine research and development" required to achieve the full promise of this innovative science and technology. Three major partners were identified in the necessary collaboration: the federal government; academia; and the vaccine research, development, and manufacturing companies. As a result of this collaboration, we now accept the efficacy of licensed vaccines as a given, and today the United States enjoys historically low rates of most vaccine-preventable diseases.

As the specter of recurrent disease diminishes as a result of clear public health gains brought by vaccination, public attention has shifted from disease prevention to vaccine safety. No element of the network of collaboration is more important than achieving vaccines that are as safe as possible. Vaccines must be given to millions of healthy people, including children, to achieve their full effect. Ever more attention is being given by all of the partners to assuring the American public that vaccines are indeed safe and that opportunities to achieve even greater safety are being pursued. This attention is more acute now because safety concerns, real or perceived, have been responsible for the withdrawal or replacement of several vaccines.[2]

The role of the vaccine companies in ensuring vaccine safety is often overlooked. Among the contributions of the partners, it is the least visible to those who administer and receive the vaccines. A better understanding of the emphasis by vaccine companies on ensuring vaccine safety could be helpful to patients, parents, and practitioners. This article is an attempt by persons knowledgeable about vaccine research, development, and manufacturing to provide some insight to the tremendous efforts within the industry to achieve the maximum possible safety of their vaccines.

Activities to ensure the most favorable vaccine-safety profile occur at all stages of vaccine development and manufacturing and involve multiple interacting functional groups. For descriptive purposes these activities can be characterized, and are grouped in this article, as follows: selection and formulation of candidate vaccines; manufacturing quality control; preclinical (animal) studies; prelicensing clinical (human) trials; vaccine production; postlicensure studies; surveillance of adverse-event (AE) reports; and vaccine-risk management and communication. For each of these categories, general descriptions of the activity and specific examples are included. Figure 1 shows a schematic of these activities over the life cycle of a candidate vaccine.

SELECTION AND FORMULATION OF CANDIDATE VACCINES

Safety issues are of foremost concern from the earliest steps of vaccine development. Most companies choose antigens and technologies to be consistent with their expertise and experience. The type of vaccine candidates considered (eg, live attenuated or weakened, killed whole organism, or component) as well as new technologies for vaccine development (eg, recombinant technology, cell culture, or adjuvants) are heavily influenced by safety considerations. For example, research and development of HIV vaccines have largely avoided testing attenuated replicating vaccines because of a theoretical concern that the vaccine could revert to a virulent strain and cause disease. Selection of a parsimonious approach to a particular pathogen, by using the least material needed to produce an effective immune response, is critical for both efficacy and safety. Further enhancing the design of safety of vaccines are advances in immunology that result in a better understanding of the mechanisms of the immune response to a pathogen. New discoveries about how the immune system works and how an-

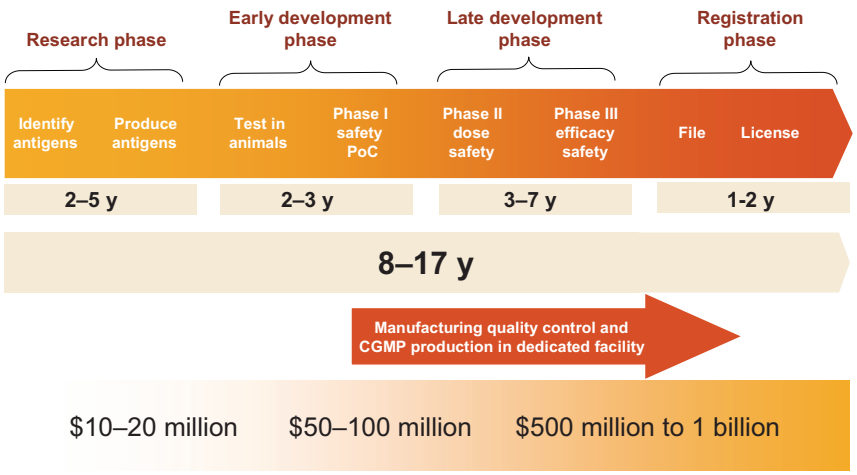

FIGURE 1
Vaccine research, development, and manufacturing activities to promote vaccine safety before licensure.

Downloaded from by guest on May 6, 2016

tigens need to be recognized in the right context influence vaccine developers around the world. For example, we now know that cells of the immune system carry an array of receptors that recognize molecular patterns unique to pathogens. Selectively targeting these immune cell receptors should result in vaccines with a better immune response and, ideally, fewer adverse effects.

Adjuvants, compounds used to enhance immune responses to vaccine antigens, are another area of vaccine development in which renewed promise has been shown.[3] The value of adjuvants is based on both empirical observations of different compounds in animals and in humans and an improved understanding of how body cells respond to foreign proteins.[4] Increasing characterization of adjuvants includes their molecular definition and extensive toxicity and safety testing, which is designed to indicate their benefit.

Because of the length of time required to discover, demonstrate, and develop new vaccines through the regulatory process (ranging from 13 to 29 years in the authors' experience), it will be a few years before they reach the public health system. How to advance these novel vaccines to licensure while ensuring safety is the central challenge for the collaboration today.

MANUFACTURING QUALITY CONTROL

All vaccine companies maintain an ongoing quality-assurance program that includes stringent evaluation of all ingredients of licensed vaccines for potential contamination, pursuit of practical means to eliminate reagents of biological origin or to replace them with synthetic materials, and elimination, when feasible, of any ingredients that have even a theoretical potential to cause human harm.

The safety and quality of raw materials and reagents used in vaccine manufacturing are ensured by scrutinizing the sources of the materials, including those supplied by outside vendors. Vendors must provide a certification that demonstrates specifications and standards of the raw materials. The companies apply quality-control tests to confirm the vendor's certification, and the vendor's facilities are regularly audited to ensure that quality standards are met. Validation procedures help ensure that the products adhere to their specifications at all stages of manufacturing. The inactivation process (when applicable) is validated to provide an additional level of assurance of the absence of live microbial organisms in the raw materials used in the manufacturing of vaccines.

Particular emphasis is placed on products of animal origin to prevent animal viruses from being introduced into the product and transmitted to the human population. As an example of such caution, 1 company developed its own source of embryonated chicken eggs (used as the source of cells in the manufacture of some virus vaccines) as an alternative to the purchase and evaluation of eggs from outside vendors. Concern about the eggs used in vaccine production emerged when avian leukosis virus was identified in most chickens. The presence of such viruses was seen as an unnecessary risk, and a closed flock of avian leukosis-free chickens is now maintained to meet needs for egg production.

Similar tight restrictions and quality controls are used in the manufacture of vaccines produced in cell culture.[5] These cells are certified for use in production and must meet stringent criteria for release for production. One advantage of cell culture is it provides a closed system, maintained under defined sterile conditions, and is less prone to contamination. A number of these cell substrates are now used to produce classical and newly licensed vaccines.

Manufacturers continually strive to improve vaccine quality. An aspect of quality control of raw materials in the manufacturing process is the replacement or reduction of animal-derived components, antibiotics, and preservatives whenever possible.[6] One example is the use of human serum albumin (HSA) instead of bovine serum albumin (BSA) as a vaccine component because of concerns with mad cow disease. HSA was prepared originally from plasma pools derived from blood donations and treated to remove any potential viral contamination. To avoid any potential risk related to the use of a raw material of human origin, a special effort was undertaken to replace HSA from people with HSA made by recombinant DNA methods in yeast. This seemingly trivial change of source required several years of human clinical trials of the new albumin alone and several years of clinical studies of the vaccine made with it.

The safety of raw materials and reagents is further ensured by conducting quality-control tests for chemical purity and adventitious agents, including polymerase-chain-reaction testing for known viruses. General tests such as reverse-transcriptase tests are not virus specific but can indicate the presence or absence of retroviruses (as well as endogenous nonreplicable retroviral fragments) that have not been identified or tested for by other means. The test used is sensitive to the level of 1 molecule of reverse transcriptase. Polymerase-chain-reaction testing, in contrast, is highly specific for individual virus agents.

The area of quality control is continually evolving to reflect the new vaccines being created and tested. For example, the advent of recombinant or vectored viruses has resulted in test-

Downloaded from by guest on May 6, 2016

ing for genetic stability of the engineered sequences to ensure that they are maintained without mutations over time during many growth cycles. Advances in methodology have also led to assays that are more discriminating, accurate, and precise. One such example is the application of mass spectrometry to vaccine analysis and release. Until recently, there was an upper size limit for this method that precluded application to vaccine antigens, and when applied to relatively small vaccine antigens, the precision was ~50 atomic mass units. Advances in this technique now allow for analysis of large biomolecules with a precision of 1 to 2 atomic mass units.

PRECLINICAL (ANIMAL) STUDIES

Three types of toxicology studies are routinely used for vaccines under development: acute toxicity; pyrogenicity; and tolerability. First, candidate vaccines are subjected to acute toxicity tests in laboratory animals before human use. These tests involve escalating doses administered by the route expected to be used in humans and must include doses higher than those intended for use in humans. These acute toxicity tests provide information to help predict a safe starting dose for the first phase (phase I) of human clinical trials. Evaluation of the test animals includes behavioral changes, examination for injection-site inflammation, and laboratory evaluation. Candidate vaccines are then subjected to in vivo pyrogenicity and tolerability studies, typically in rabbits and/or guinea pigs. Safety studies are then completed in rats and, when appropriate, primates, before human use. These sensitive animal tests include histologic organ (gross and anatomic) studies and help screen for findings that would raise cautionary flags for subsequent clinical and postlicensure studies.

An illustrative example is the early development of the first conjugated *Haemophilus influenzae* type B vaccine, PRP-D. Because there was no precedent for a vaccine based on covalent coupling of a polysaccharide to a protein, preclinical animal-safety studies were critically important. One safety study involved administering high doses of the conjugated vaccine to groups of weanling rats on each of 14 successive days; the comparison groups received either a matched amount of diphtheria toxoid or placebo. Over the course of the study, animals received >16 000 times a human dose on an equivalent weight basis. The animals were examined daily for any physical symptoms and also weighed daily. At the end of the study, animals were killed by a veterinarian and examined for any gross pathology. Samples of the injection site and all major organs were examined by a board-certified veterinary histopathologist. Similar extensive and intensive animal testing is conducted before human administration of any prospective vaccine. Other specialized preclinical safety studies that may be performed include reproductive toxicology studies in pregnant animals and in vivo testing of recombinant vaccines, and detailed attempts are made to retrieve the vaccine from excretions and in the environment.

PRELICENSURE CLINICAL (HUMAN) TRIALS

Clinical trials in humans are of the utmost importance in determining the safety profile of vaccines and are among the most expensive and time-consuming components of vaccine development.[7] Before the initiation of clinical trials, the investigational product and trial protocols are reviewed and cleared by the US Food and Drug Administration (FDA) or other regulatory agency. All clinical trials are also reviewed and approved before trial initiation by an investigational review board or ethical committee that is wholly independent from both the manufacturer and health authorities. For large studies, an independent data safety-monitoring board is often established with the mandate to monitor trial safety on an ongoing basis. A data safety-monitoring board is empowered to order a stop to the study if its members believe that it is warranted. Clinical trials are also governed by a standardized code of good clinical practice developed by the International Council on Harmonization.[8] These good-clinical-practice guidelines are updated continually and supported by FDA regulations.[9]

The vaccine companies design the protocols for vaccine clinical trials but often delegate the actual conduct of the trials to institutions or to contract research organizations under the company's supervision. This 2-step approach to trials uses the strengths of each: the company's expertise in the technology and product, methodologic issues, and clinical experience regarding FDA requirements for licensure and the operational expertise and objectivity of investigators conducting the actual trials. Once these studies are completed and successful in demonstrating safety, efficacy, and manufacturing consistency, the data are provided to the FDA to support licensure.

Clinical trials are conducted in incremental and graduated phases to minimize risk and to optimize the information obtained (in subsequent phases): initial safety (phase 1); dose-ranging (phase II); efficacy (phase III); and general safety of licensed products in human populations (phases IV and V). This strategy of incremental, phased trials in humans reduces to a minimum the number of persons who might be exposed to unknown risks at

Downloaded from by guest on May 6, 2016

the earlier phases. The sample sizes in later-phase trials are increased to gather additional information about the safety profile. Common AEs such as injection-site reactions are easily identified in early clinical trials; further studies both before and after licensure are also useful in identifying relatively uncommon AEs that occur at a frequency of <1 in 1000. Because of the nature of the before-licensure trial populations and achievable sample sizes, even relatively large trials with tens of thousands of participants cannot adequately evaluate rare AEs.[10] Likewise, AEs that affect certain subpopulations, or those that are more likely to occur in persons excluded from clinical trials in phases I through III (eg, those on certain medications and/or with certain concurrent medical conditions), may not be identified in prelicensure trials, because strict inclusion and exclusion criteria generally allow only healthy volunteers.

Vaccine-pivotal trial sample sizes have increased in recent years, and these increases in size have been driven by safety-assessment considerations. For example, clinical trials that involved >70 000 children each were necessary to demonstrate (successfully) that 2 rotavirus vaccines were not associated with bowel intussusception at a rate that is higher than the not-uncommon background rate of 1 to 4 per 1000 live births.[11,12] It is often suggested that the size of clinical trials be increased even further, but trials of a magnitude to link uncommon or rare AEs to a vaccine are technically unachievable. To detect a twofold increase between vaccinated and unvaccinated subjects of a rare AE that occurs at a rate of 1 in 100 000 (power = .80, $\alpha = .025$), the necessary sample size in a randomized clinical trial would be >9 million subjects.[13] Identifying and quantifying rare AEs that may potentially be vaccine-associated require special postlicensure studies and studies in response to surveillance of AE reports. These studies have increasingly been used after introduction of new vaccines and are described in more detail below.

TABLE 1 Elements and Purpose of Process Validation

Element of Validation	Purpose
Installation qualification	To verify that equipment used is the correct piece of equipment by design and has been installed properly
Operational qualification	To verify that equipment will operate as designed
Performance qualification	To document that the equipment operates as required
Cleaning validation	To verify that cleaning procedures will consistently reduce residuals and cleansing agents to acceptable levels
Sterilization validation	To verify that sterilization processes result in the sterility of all items
Automation validation	To verify that computer hardware and software systems used to automate processes, complete calculation, etc can consistently perform as intended
Analytical methods validation	To verify that analytic methods used during the testing process consistently perform their intended function and fulfill their purpose
Biological validation	To ensure that predetermined specifications for the biological manufacturing process are established during the development phase and that these specifications are consistently met during the transfer to manufacturing and during full-scale operations

Prospective validation is required for all new products and any major changes. Continuing validation includes an annual revalidation effort to ensure that the validation cycle is maintained. Retrospective validation of an existing process is based on continual review of process data.

VACCINE PRODUCTION

Ensuring the optimal safety of vaccine manufacture is supported by adherence to current good manufacturing practices (CGMPs) and testing for sterility and purity.[14] CGMPs include manufacturing processes and standard operating procedures; manufacturing consistency; product quality control (monitoring specifications, sterility, and stability); process validation; safety and environmental aspects; data quality control and oversight; state-of-the-art technology; and rigorous inspection and certification by regulatory agencies.

Although a comprehensive review of CGMPs is beyond the scope of this article, the importance of process validation is often underappreciated and will be used as an example of the utility of following CGMPs. According to FDA guidelines, the general principles of validation are "establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."[14] Table 1 lists the basic elements and purposes of process validation throughout the long cycle of vaccine development and manufacturing.

Vaccine manufacturing uses an "onion-skin" theory of safety (safety procedures are layered on top of each other so that if 1 procedure were somehow removed or found to be ineffective, there would be a duplicate safety measure directly below it). There are many multiple systems and attributes with built-in redundancies to ensure safety. Every step of the manufacturing process has a counter check and confirmation process that includes tests for potency, general safety, sterility, and purity. The FDA provides a final countercheck with further testing of sampled lots and releases the product for use only after this testing and their approval.

POSTLICENSURE STUDIES

Vaccine companies sponsor and conduct studies after FDA licensure (phase IV studies) that are designed to investigate causality of uncommon but

Downloaded from by guest on May 6, 2016

potentially vaccine-associated AEs that occur among the much larger number and greater diversity of persons who receive a vaccine after licensing and marketing. FDA licensure may be contingent on these studies to further elucidate the vaccine's safety profile in actual use (eg, pediatric studies required by law or studies designed in response to signals generated from passive postmarketing surveillance of AE reports). Large postlicensure safety-surveillance studies are now routinely required after vaccine approval. An example of a special safety-surveillance study was the large postmarketing evaluation of the safety (and efficacy) of the varicella vaccine conducted by the Kaiser Permanente (Northern California) Vaccine Study Center with the vaccine company's sponsorship. This study included 89 753 adults and children and investigated 3200 potential vaccine-associated AEs. The result of the study was a timely and favorable affirmation of the safety profile for the vaccine as well as confirmation of the rates of varicella-like rash and breakthrough cases that had been observed in the smaller clinical trials.[15] Frequently, postlicensure clinical studies in pediatric and geriatric populations are requested by the FDA; if not conducted before approval, pediatric studies are required by law (Pediatric Research Equity Act of 2007). On occasion, additional studies are conducted in special populations that may have been excluded from prelicensure studies, such as immunocompromised people.

SURVEILLANCE OF AE REPORTS AFTER LICENSING AND MARKETING

Systems for surveillance of AEs are managed by companies and regulatory agencies of many countries to monitor the safety profile of vaccines in use. The federal systems in the United States (eg, the Vaccine Adverse Event Reporting System or Vaccine Safety Datalink) have become more extensive and offer more rapid monitoring that can more actively detect important AEs. The value of this surveillance was demonstrated most recently during the pandemic H1N1 influenza vaccination program.[17] The companies complement these government-based systems with their own "pharmacovigilance" or drug-safety programs by seeking, accumulating, and analyzing AE information from any and all sources (including consumers), reporting it to regulatory authorities, and determining the need for further investigations.[18] Pharmacovigilance specialists interact externally and with multiple functions internally and are often set up in separate, distinct safety systems. These departments are routinely inspected by regulatory agencies, and their importance to companies has increased as key contributors to monitoring safety and assessing risk across the life cycle of a product.

Similarly, pregnancy registries are a special safety-monitoring program that is based on passive surveillance. Inadvertent or untimely immunization during or around the first trimester of pregnancy is an important vaccine-safety issue. To determine if such vaccinations pose risks for the developing fetus or to the expectant mother, pregnancy registries monitor the outcomes when vaccines are administered to pregnant women.

VACCINE-RISK COMMUNICATION

The vaccine companies are partners with government, professional associations, and nonprofit advocacy groups in communicating both the benefits and risks of vaccines. As discussed above, all safety data are reviewed by the FDA on application for licensure. In addition, companies now formally provide risk evaluation and mitigation strategies for new products to the FDA; this is also the case with licensure and registration in other countries.

The companies have an important role in communicating vaccine risks (as well as benefits) to patients and providers through package inserts (product label) and all direct communications, including promotional materials. Manufacturers take these responsibilities seriously; for example, any promotional advertisements that make any product claim are highly scrutinized with the full understanding that such communication is heavily regulated and must always be balanced by important safety information. Package inserts, although also influenced by legal considerations, outline indications for use, contraindications, warnings, precautions, interactions, dosage, storage, expiration, and adverse reactions based on evidence collected in clinical studies and after licensure. Company field representatives discuss these issues with providers, but always within the information available in the package insert as required by law. Any question beyond this scope results in a query to the company's medical services personnel to achieve a professional-to-professional communication either via a letter or a more direct contact.

CONCLUSIONS

Vaccine companies have an extremely important role in ensuring the optimal safety of vaccines. They have a long history of prudent vaccine development and ensuring that the vaccines they develop and manufacture are not only effective but have used current technology to ensure the utmost level of safety, given the vast use of vaccines and uncommon AEs. Although the vaccine companies are ultimately responsible to stockholders, ethical and public health considerations are paramount for their very survival. As re-

Downloaded from by guest on May 6, 2016

viewed in this article, safety is a vital concern in research and development, manufacture, clinical trials, and postlicensure surveillance. As stated by Dr Gordon Douglas, former president of Merck Vaccine Division, "It's good business to have a safe vaccine."[19]

Over the last 50 years, there have been tremendous strides in technologies and scientific knowledge resulting in the vaccines we use today. Safety safeguards used by manufacturers have grown apace and have been put in place through the product lifecycle, as described in this article. This dynamic arena will continue to grow, reflecting societal, scientific/technologic, and regulatory forces. The common goal among all partners in vaccine development is to maximize the powerful benefits of vaccines while minimizing to the best extent possible the risks to recipients.

ACKNOWLEDGMENT

We gratefully acknowledge review and insightful commentary by Dr Hillel Cohen (Novartis Vaccines and Diagnostics).

REFERENCES

1. National Vaccine Advisory Committee. United States vaccine research: a delicate fabric of public and private collaboration. *Pediatrics*. 1997;100(6):1015–1020
2. American Academy of Microbiology. Vaccine development: current status and future needs. Available at: http://academy.asm.org/images/stories/documents/vaccinedevelopmentfull.pdf. Accessed December 12, 2009
3. Kenney R, Edelman R. Survey of human use adjuvants. *Expert Rev Vaccines*. 2003;2(2):167–188
4. Singh M, Ugozzoli M, Kazzaz J, et al. A preliminary evaluation of alternative adjuvants to alum using a range of established and new generation vaccine antigens. *Vaccine*. 2006;24(10):1680–1686
5. Reisinger KS, Block SL, Izu A, Groth N, Holmes SJ. Subunit influenza vaccines produced from cell culture or in embryonated chicken eggs: comparison of safety, reactogenicity, and immunogenicity. *J Infect Dis*. 2009;200(6):849–857
6. US Food and Drug Administration. Common ingredients in U.S. licensed vaccines. Available at: www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm187810.htm. Accessed December 11, 2009
7. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003;22(2):151–185
8. Center for Drug Evaluation and Research. E6: good clinical practice—consolidated guidance. Available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf. Accessed December 11, 2009
9. US Food and Drug Administration. FDA regulations relating to good clinical practice and clinical trials. Available at: www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm114928.htm. Accessed December 11, 2009
10. Black S. Perspectives on the design and analysis of prelicensure trials: bridging the gap to postlicensure studies. *Clin Infect Dis*. 2001;33(suppl 4):S323–S326
11. RotaTeq [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; December, 2010
12. Rotarix [package insert]. Rixensart, Belgium: GlaxoSmithKline Biologicals, 2010
13. National Institute of Allergy and Infectious Diseases. Task Force on Safer Childhood Vaccines: final report and recommendations. Available at: http://permanent.access.gpo.gov/lps22576/safevacc.pdf. Accessed December 20, 2011
14. Werz W, Hoffman H, Haberer K, Walter JK. Strategies to avoid virus transmissions by biopharmaceutic products. *Arch Virol Suppl*. 1997;13:245–256
15. US Food and Drug Administration. Guideline on general principles of process validation. Available at: www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124720.htm. Accessed December 11, 2009
16. Black S, Shinefield H, Ray P, et al. Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J*. 1999;18(12):1041–1046
17. Centers for Disease Control and Prevention. Safety of influenza A (H1N1) 2009 monovalent vaccines: United States, October 1–November 24, 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58(48):1351–1356
18. Wise L, Parkinson J, Raine J, Breckenridge A. New approaches to drug safety: a pharmacovigilance toolkit. *Nat Rev Drug Discov*. 2009;8(10):779–782
19. Ellenberg SS, Foulkes MA, Midthun K, Goldenthal KL. Evaluating the safety of new vaccines: summary of a workshop. *Am J Public Health*. 2005;95(5):800–807

Downloaded from by guest on May 6, 2016

Ensuring the Optimal Safety of Licensed Vaccines: A Perspective of the Vaccine Research, Development, and Manufacturing Companies

Niranjan Kanesa-thasan, Alan Shaw, Jeffrey J. Stoddard and Thomas M. Vernon

Pediatrics; originally published online April 18, 2011;
DOI: 10.1542/peds.2010-1722D

Updated Information & Services	including high resolution figures, can be found at: /content/early/2011/04/18/peds.2010-1722D
Citations	This article has been cited by 2 HighWire-hosted articles: /content/early/2011/04/18/peds.2010-1722D#related-urls
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: /site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2011 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from by guest on May 6, 2016

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Ensuring the Optimal Safety of Licensed Vaccines: A Perspective of the Vaccine Research, Development, and Manufacturing Companies

Niranjan Kanesa-thasan, Alan Shaw, Jeffrey J. Stoddard and Thomas M. Vernon

Pediatrics; originally published online April 18, 2011;
DOI: 10.1542/peds.2010-1722D

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/early/2011/04/18/peds.2010-1722D

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2011 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from by guest on May 6, 2016