Vaccine Safety Scientific Agenda

Vaccines are one of the most important measures available to support and protect public health. While vaccines have substantial benefits, it is also important to assess their safety during discovery and development, regulatory approval, recommendations for use, and subsequent post-marketing surveillance. In the U.S. vaccine safety evaluation is overseen and coordinated by federal departments and agencies. The key federal departments with a role in vaccine safety activities include the U.S. Department of Health and Human Service (**HHS**, which includes the Centers for Disease Control and Prevention, **CDC**; the Food and Drug Administration, **FDA**; the Health Resources and Services Administration, **HRSA**; the National Institutes of Health, **NIH**; the Centers for Medicare and Medicaid Services, **CMS**; the Indian Health Service, **IHS**; the National Vaccine Program Office, **NVPO**, and the Biomedical Advanced Research and Development Authority, **BARDA**), the U.S Department of Defense (**DoD**), and the U.S. Department of Veteran Affairs (**VA**). While no medical intervention is 100 percent safe, the many components of the safety system provide multiple and overlapping levels of assurance of the safety of vaccines in the U.S.

NVPO's **National Vaccine Advisory Committee (NVAC)** advises the HHS' Assistant Secretary for Health on prevention of human infectious diseases through vaccine development, provides advice regarding how to evaluate and prevent adverse reactions to vaccines, and has recently evaluated and made recommendations on the state of the U.S. Vaccine Safety System (NVAC, 2011). NVPO also coordinates the **Immunization Safety Task Force (ISTF)** which promotes collaboration among all federal partners invested in vaccine safety activities. Highlighting the importance of vaccine safety, the 2010 National Vaccine Plan called for the development of a vaccine safety scientific agenda that would summarize the contributions of the federal partners to the overall safety of vaccines in the U.S. This document outlines the efforts of federal agencies on vaccine safety and the ongoing and planned associated scientific activities and interagency coordination that contribute to the safety system.

Pre-licensure (Discovery/Research and Development) Vaccine Safety Scientific Activities

The evaluation of vaccine safety is an important component of vaccine research and development. The NIH is the main federal partner during this stage, focusing on and supporting the basic and applied research that forms the foundation of vaccine development. As promising ideas develop into potential vaccine candidates, safety is considered during every step of the vaccine development pipeline. Consistent with FDA regulations and guidance documents, vaccine candidates are evaluated for safety in relevant animal models and other laboratory assessments before moving into clinical trials. All trials include a rigorous assessment of vaccine safety as a primary study objective, and study participants are closely monitored for any adverse events associated with vaccination (commonly referred to as adverse events following immunization or AEFIs). In addition to research on new vaccines, the NIH devotes substantial resources to developing improved vaccines that are more effective and have fewer side effects than currently licensed vaccines.

During the pre-licensure phase of vaccine development, when clinical trials are underway, the U.S. FDA's **Center for Biologics Evaluation and Research (CBER)** also plays a critical role in helping assure safety for research subjects, the quality of the scientific investigation, and that the vaccine clinical trial designs are adequate to permit an evaluation of vaccine safety and effectiveness. CBER's **Office of Vaccines Research and Review (OVRR)** research programs develop testing methods, reference materials, and

other tools to evaluate the safety of vaccines, including the cell substrates used to manufacture vaccines. OVRR also develops and evaluates predictive pre-clinical models and other methods to screen novel vaccine components for potential adverse effects prior to clinical trials.

A summary of the scientific activities at this stage of vaccine development is shown in Table 1 (please refer to the web links for updated and additional information)

Table 1.Pre-licensure Vaccine Safety Scientific Activities

Leading Institution	Vaccine Safety Activity	Scientific Agenda
NIH	*Identification and development of vaccine candidates*	*Develop and provide resources to facilitate basic and applied research including the ability to assess vaccines for safety and immunogenicity* http://www.niaid.nih.gov/about/organization/vrc/Pages/default.aspx http://www.niaid.nih.gov/labsandresources/labs/aboutlabs/lid/Pages/default.aspx http://www.niaid.nih.gov/about/organization/dmid/Pages/default.aspx
NIH	*Design of novel vaccine strategies*	*Support research to explore novel vaccine technologies and strategies to improve the immunization profile* http://www.niaid.nih.gov/about/organization/dait/programs/Pages/basicImmunology.aspx
NIH	*Investigate the variability in human immune responses*	*Support research to understand the range of variability in the human population that impacts responses to vaccines and potential associations with AEFIs*
NIH	*Improving vaccine immunomodulators, administration, and formulations*	*Discover and develop novel adjuvants, alternative routes of administration, and formulations*
FDA	*Vaccine development*	*Develop pre-clinical models, and vaccine efficacy and safety screening methodology* http://www.fda.gov/BiologicsBloodVaccines/default.htm http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm350562.htm http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/ucm133096.htm
FDA	*Study of pathogenicity*	*Study molecular mechanisms of pathogenicity and determine biomarkers of virulence that might improve the safety profile*

Regulatory Review and Licensure Vaccine Safety Scientific Activities

When an entity, usually a manufacturer, believes that a vaccine candidate has been shown to be safe and effective based on analysis of safety and efficacy in clinical trials and other data, it can submit a license application to the FDA for review. As part of the license application review process, CBER may convene the **Vaccines and Related Biological Products Advisory Committee (VRBPAC)** where the vaccine sponsor and the FDA present their findings. The VRBPAC, whose members are experts external to FDA, provides advice to the Agency regarding the safety and efficacy of the vaccine for the proposed indication. As part of its assessment of the license application, CBER conducts a rigorous review of manufacturing and product information, non-clinical pharmacology and toxicology data, and clinical studies to make a determination regarding licensure (or approval). If the data support the safety and effectiveness of the vaccine, it is licensed, which means that it can be commercially marketed. Following vaccine licensure, CBER and manufacturers conduct ongoing surveillance of the vaccine, including assessment of adverse events, lot release activities, and inspections of manufacturing facilities.

Post-Licensure Vaccine Safety Scientific Activities

Vaccine licensure does not guarantee that a vaccine will be recommended for routine use, and vaccines must undergo an additional step of expert review in order to be routinely recommended. The CDC's **Advisory Committee on Immunization Practices or ACIP** is an independent advisory committee that develops recommendations on how to use vaccines to control diseases in the U.S. (http://www.cdc.gov/vaccines/acip/index.html).

In addition, the federal agencies and departments that oversee and coordinate vaccine safety evaluation continuously monitor and conduct research on the safety of marketed vaccines being administered to the public. Continuing safety monitoring and research after a vaccine is introduced into the market and administered to the population is essential to detect rare adverse events that might have remained undetected during the developmental phase.

A summary of the routine federal vaccine safety systems is detailed in Table 2 (please refer to the web links for details on specific scientific activities related to vaccine safety conducted by these systems).

Table 2. Routine Vaccine Safety Monitoring and Research Systems

Leading Institution	Safety System	Objectives
CDC and FDA	*Vaccine Adverse Event Reporting System **(VAERS)***	*Receives reports of possible adverse events from a variety of sources, including parents, providers, manufacturers, pharmacists, and the military, and rapidly detects "signals": possible adverse events for follow up.* *http://vaers.hhs.gov/about/index*
CDC	*Vaccine Safety Datalink **(VSD)***	*Rapidly tests, and confirms or rejects VAERS-generated signals. It links databases, including vaccination and medical records and allows for near real-time surveillance.* *http://www.cdc.gov/vaccinesafety/Activities/vsd.html*
CDC	*Clinical Immunization Safety Assessment **(CISA)***	*Addresses vaccine safety issues, conducts high quality clinical research, and assesses complex clinical AEFIs* *http://www.cdc.gov/vaccinesafety/Activities/cisa/cisa_studies.html*
FDA	*Post-Licensure Rapid Immunization Safety Monitoring Program **(PRISM)***	*Monitors the safety of vaccines post licensure using a national large, linked electronic healthcare database and a variety of observational study designs, including near-real time surveillance* *http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/default.htm*
DOD	*Defense Health Agency-Immunization Healthcare Branch **(DHA-IHB)***	*Researches adverse events using electronic health records and can contact individuals when consultation for follow-up or care is needed. Can follow up on VAERS signal detections.* *https://www.vaccines.mil/*
DOD	*Armed Forces Health Surveillance Center **(AFHSC)***	*Supports post-marketing database studies* *http://www.afhsc.mil/home*

Leading Institution	Safety System	Objectives
VA	*Adverse Drug Event Reporting System* ***(ADERS)***	*Reports, tracks and monitors adverse events caused by medications and vaccines across the entire VA health care system using a passive surveillance system comparable and linked to VAERS.* *http://www.pbm.va.gov/PBM/vacenterformedicationsafety/vacenterformedicationsafetyadverseeventtrackingtools.asp*
VA	*Center for Medication Safety* ***(VAMedSAFE)***	*Obtains data from VA ADERS and VA Integrated Databases to track the safety of vaccines administered in the VA healthcare system.* *http://www.pbm.va.gov/vacenterformedicationsafety/vacenterformedicationsafetyaboutus.asp*

Following vaccine licensure, all the federal partners, HHS, DoD and VA also collaborate to conduct comprehensive product-specific safety research. Specific vaccine safety studies are developed based on questions or concerns raised from the medical literature, when there are new vaccines that have been recommended for use, if there are changes in how a vaccine is recommended, or there are reports to the Vaccine Adverse Event Reporting System (VAERS). Continued vaccine safety research is essential to advance knowledge of vaccine safety and inform clinical and public health practice.

Some of the current key projects are detailed in Table 3.

Table 3. Post-Licensure Vaccine Safety Research of Special Interest

Leading Institution	Vaccine Safety Research Topic	Research Plan
CDC and FDA	*Vaccine recipient's individual risk factors*	*(1) improve safety monitoring and assessment by defining which sub-populations should be monitored, (2) identify individuals at increased risk for AEFIs, (3) improve the clinical approaches to treating AEFIs, (4) develop advanced vaccines with a decreased likelihood of AEFI occurrence, and (5) enhance risk communication about the safety of vaccines, particularly with regard to groups identified at higher risk for AEFIs.*
FDA	*General vaccine safety studies*	*Research potential safety concerns of newly licensed products such as autoimmune diseases or anaphylaxis*
FDA	*Concomitant and multiple dose vaccine administration*	*Study potential AEFIs that may arise after administering concomitant vaccine doses and multiple dose vaccines given at recommended intervals*
FDA	*Study of vulnerable populations*	*Vaccine safety research on special populations such as pregnant women*
FDA	*Safety evaluation methodology testing*	*Improve sensitivity and eliminate analytic bias when studying vaccine administration outcomes*
CDC	*Prevention of AEFI*	*Assessment of vaccine products, dosing and administration to identify factors that could be modified to avoid AEFIs*
CDC	*Assessing safety of new vaccines*	*CDC monitors new vaccines after their introduction using spontaneous reporting systems, and conducts population-based surveillance using electronic health data*

Leading Institution	Vaccine Safety Research Topic	Research Plan
CDC	*Assessing vaccine safety in understudied populations*	*Special populations, such as pregnant women, immune deficient patients, and special ethnicities, have been historically excluded from vaccine clinical trials. CDC evaluates vaccine safety among these populations as well*
CDC	*Continued research on statistical methods and study design*	*Because of the complexity of studying populations receiving vaccines, sophisticated statistical methods and study designs are being developed and refined for both active and passive surveillance. Continuing to refine near real-time surveillance techniques (e.g., rapid cycle analysis, RCA)*
CDC	*Communications Research*	*Research on knowledge, attitudes, beliefs, and behaviors related to vaccine safety and AEFI reporting, and continuously improving strategies for communicating risks*
DOD and VA	*Pandemic Vaccination Safety*	*Utilizes near real-time analysis to identify possible safety signals*
DOD	*Detecting AEFIs in special populations*	*Pregnancy registries are mined to assess maternal and fetal/infant outcomes after vaccination*
VA	*Seasonal flu active safety surveillance*	*Identify possible adverse outcomes in the VA healthcare system such as GBS, anaphylaxis, Bell's palsy, encephalitis, meningitis, idiopathic thrombocytopenia, optic neuritis, seizures and convulsions*
VA	*End of season analysis*	*Yearly assessment of influenza vaccine associated AEFIs in the VA healthcare system*

Final Remarks

The mechanisms employed by federal departments and agencies at each stage of a vaccine's development, its licensure, and during the post-marketing evaluation phase comprise a comprehensive vaccine safety enterprise. The individual components of the safety network are designed to overlap and complement each other to ensure the highest degree of synergy and effectiveness possible as the safety of vaccines is evaluated and monitored.

Bibliography

National Vaccine Advisory Committee-Vaccine Safety Working Group (2011). U.S. Vaccine Safety System. http://www.hhs.gov/nvpo/nvac/nvac_vswp.pdf

Abbreviations

***VRBPAC**: Vaccines and Related Biological Products Advisory Committee*
***CBER**: Center for Biologics Evaluation and Research*
***PRISM**: Rapid Immunization Safety Monitoring*
***ACIP**: Advisory Committee on Immunization Practices*
***VAERS:** Vaccine Adverse Event Reporting System*
***VSD:** Vaccine Safety Datalink*
***CISA:** Clinical Immunization Safety Assessment Network*
***NVAC**: National Vaccine Advisory Committee*
***AEFI:** Adverse Event Following Immunization*
***MILVAX-VHCN:** Military Vaccine Agency-Vaccine Healthcare Centers Network*
***AFHSC**: Armed Forces Health Surveillance Center*
***ADERS**: VA's Adverse Drug Event Reporting System*
***VAMedSAFE:** Center for Medication Safety*

RCA: *Rapid Cycle Analysis*