

DRAFT

Centers for Disease Control and Prevention's Immunization Safety Office Scientific Agenda: Background Document

“To raise new questions, new possibilities, to regard old problems from a new angle, requires
creative imagination and marks real advance in science”

Albert Einstein

**Immunization Safety Office
Office of the Chief Science Officer
Centers for Disease Control and Prevention¹**

¹ This draft background document was prepared for the National Vaccine Advisory Committee (NVAC), Vaccine Safety Working Group. Address comments on this draft to Karen R. Broder, MD, Immunization Safety Office (ISO), CDC, Phone: 404-639-8538 Fax: 404-639-8616 Email:Kbroder@cdc.gov. See Appendix A for a list of persons on the ISO Scientific Agenda Writing and Reviewing Group.

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EXECUTIVE SUMMARY

Ensuring that vaccines are as safe as possible is a public health priority and national expectations for vaccine safety are high. Within the Department of Health and Human Services, the Center's for Disease Control and Prevention's (CDC) Immunization Safety Office (ISO) leads most of the agency's risk assessment research and surveillance activities for vaccines used in a civilian population. Four research and surveillance components work together to carry out the ISO mission of assessing the safety of vaccines used in children, adolescents, and adults: the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD) Project, the Clinical Immunization Safety Assessment (CISA) Network, and the Brighton Collaboration. VAERS is jointly operated by CDC and the Food and Drug Administration (FDA). Each of the four ISO teams has mechanisms in place to develop and prioritize its scientific activities; however no comprehensive ISO Agenda exists.

In response to a 2005 Institute of Medicine (IOM) recommendation and to guide ISO's scientific direction, ISO is developing a 5-year ISO Scientific Agenda. During 2007–2008, ISO obtained input from expert scientists through three planned meetings (with external expert scientists, federal scientists, and vaccine manufacturers' representatives) and other venues. The National Vaccine Advisory Committee (NVAC), Vaccine Safety Working Group will advise on the content and priorities of the ISO Scientific Agenda. NVAC and NVPO will lead the NVAC scientific review. CDC will finalize the Agenda and respond to NVAC feedback. The Agenda (under development) makes recommendations for the next 5 years in three scientific areas: vaccine safety research, selected surveillance, and selected clinical guidance activities. The Agenda covers topics that are part of ISO's mission, are in ISO's realm to lead, and could be implemented during the next 5 years with infrastructure generally accessible to CDC. It is not a comprehensive ISO strategic plan and does not address all issues related to vaccine safety science, such as risk perception research. The chief users of the Agenda will be ISO staff and their day-to-day research and surveillance partners. The Agenda will be useful to all ISO teams as they set priorities for projects in a coordinated manner. It will also serve as a platform to discuss collaborative vaccine safety science activities among ISO and other internal and external partners. Looking forward 5 years after CDC implements this Agenda, we would expect to find that it contributed to advancing the field of vaccine safety science and enhancing public health.

BACKGROUND

Importance of Vaccine Safety Science

Widespread use of vaccines has greatly reduced the incidence of vaccine-preventable diseases since the pre-vaccine era (Roush et al., JAMA 2007). As the rate of vaccine-preventable diseases has declined, interest in the real and perceived risks associated with vaccines has increased. Before the Food and Drug Administration (FDA) licenses a vaccine in the United States it must undergo stringent testing for safety. However, no vaccine is completely safe and adverse events following immunization (AEFI),² which may or may not be caused by vaccination, occur in populations receiving vaccines. Ensuring that vaccines are as safe as possible is a public health priority and national expectations for vaccine safety are high. Currently a federal vaccine safety infrastructure is in place to monitor vaccine safety, largely stimulated by the passage of the National Childhood Vaccine Injury Act (NCVIA) in 1986 (http://www.cdc.gov/od/science/iso/general_info/overview.htm). In parallel with improvements in vaccine safety infrastructure, the prominence of vaccine safety as a scientific field has also increased nationally and internationally. NCVIA required health professionals and vaccine manufacturers to report to the U.S. Department of Health and Human Services (HHS) specific adverse events that occur after the administration of routinely recommended vaccines, listed in the in the Vaccine Injury Table (<http://www.hrsa.gov/vaccinecompensation/table.htm>). Following NCVIA, the Vaccine Adverse Event Reporting System (VAERS) was established on November 1, 1990 to accept spontaneous reports of suspected vaccine adverse events (VAEs)² after administration of any vaccine licensed in the United States (<http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5201a1.htm>). NCVIA also established a committee from the Institute of Medicine (IOM) to review the existing literature on VAEs. During the 1990s, this group concluded that there are limitations in our knowledge of the risks associated with vaccines. Of the 76 adverse events it reviewed for a causal relationship, 50 (66%) had no or inadequate research to form a conclusion (Chen RT et al., Pediatrics 1997). During the 2000s the IOM convened a new Immunization Safety Review (ISR) committee to examine eight specific vaccine safety hypotheses (<http://www.iom.edu/?ID=4705>). Similar to

² The terms adverse event following immunization (AEFI) and vaccine adverse event (VAE) and are used interchangeably throughout this document and do not imply that an event was caused by a vaccine.

the earlier reports, the ISR found that the evidence was inconclusive to accept or reject many of the hypothesized associations; of the 30 conclusions from the report, 18 (60%) found that the evidence “is inadequate to accept or reject a causal relationship” or that there was “no evidence bearing on causality” (Appendix B). IOM recommended improving vaccine safety infrastructure to address gaps in vaccine safety knowledge and in response CDC created the Vaccine Safety Datalink (VSD) Project, the Clinical Immunization Safety Assessment (CISA) Network, and the Brighton Collaboration described below, to address vaccine safety questions (IOM, 1991 and IOM 2004).

During the next five years, the importance of vaccine safety as a scientific field is likely to continue to increase for several reasons. Advances in vaccine research and development are leading to an increasing number of licensed vaccines in the United States. In October 2007, 59 vaccines were licensed (<http://www.fda.gov/cber/vaccine/licvacc.htm>) and several are currently under review by the FDA or in phase 3 clinical trials (<http://clinicaltrials.gov/> and <http://aapredbook.aappublications.org/news/vaccstatus.shtml>). With a greater number of licensed vaccines available, the US immunization schedule is becoming more complex. For example, in 1998, seven vaccines were routinely recommended for children and adolescents (<http://www.cdc.gov/mmwr/preview/mmwrhtml/00053300.htm>). By contrast, in 2008, 13 vaccines were routinely recommended for this age group. Vaccines are also being used more frequently in new populations, such as adolescents or older adults. These populations may have higher background rates of certain clinical conditions than children who have historically been the main focus of the US immunization program, leading to more frequent coincidental VAEs. (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a8.htm?s_cid=mm5701a8_e). In addition, new technologies are being used. For example, in 2003, the first US intranasal vaccine (live, attenuated influenza vaccine [FluMist[®]]) was licensed. Vaccines containing novel adjuvants such as agonists of toll-like receptors are likely to be licensed in the near future.

Concerns about national preparedness for an influenza pandemic or bioterrorism event may necessitate emergency use of vaccines that have undergone limited pre-licensure testing (<http://www.cdc.gov/eid/content/13/7/1046.htm>). Consistent with the past experience, public perception about vaccine safety will also continue to drive the need to provide evidence regarding vaccine risks. Unlike efficacy, vaccine safety requires different scientific methods, and cannot be assessed directly. Communicating accurate information about vaccine risk to the public is challenging. Finally, the Department of Health and Human Services 2007-2012

strategic plan has identified “personalized health care” as a strategic priority. Since individual host factors, including genetic factors, may influence the risk for VAEs, vaccine safety research in this area would be relevant to achieving this HHS goal.

Immunization Safety Office, Centers for Disease Control and Prevention

ISO Organization

Within the Department of Health and Human Services, the Centers for Disease Control and Prevention (CDC) is one of five agencies and programs involved in vaccine safety research, surveillance or programmatic activities; the others are the National Vaccine Program Office (NVPO), Food and Drug Administration (FDA), National Institutes of Health (NIH), and the Health Services and Resources Administration (HRSA), primary through its National Vaccine Injury Compensation Program (VICP). The Department of Defense (DoD) also conducts vaccine safety activities. At CDC, the Immunization Safety Office (ISO) leads most of the agency’s vaccine safety research and surveillance activities for vaccines used in the civilian population. CDC’s Immunization Safety Office (ISO) serves as a national and international resource for vaccine safety science and has played a major role in advancing the field during the past two decades. Since 2005, the Immunization Safety Office (ISO) has been a part of CDC’s Office of the Chief Science Officer (OCSO), Office of the Director (<http://www.cdc.gov/od/science/aboutus/>) and its mission is distinct from other immunization programs within the agency (see below). Most other CDC immunization activities are located in the Coordinating Center for Infectious Diseases (<http://www.cdc.gov/about/organization/ccid.htm>). Several CDC programs outside of ISO also conduct vaccine safety activities; a prominent example is the Vaccine Safety Analytic Unit (VAU). The VAU is collaboration between CDC and DoD and its research focuses on anthrax vaccine safety; the VAU has developed its own research agenda (Payne, Pharmacoepidemiology and Drug Safety, 2006). ISO collaborates on an ongoing basis with other vaccine programs at CDC, other federal agencies and programs, and outside the federal government.

Four federal advisory committees advise HHS on issues related to vaccine safety: the National Vaccine Advisory Committee (NVAC), the Vaccines and Related Products Advisory Committee (VRPBAC), the Advisory Committee on Immunization Practices (ACIP), and the Advisory Commission on Childhood Vaccines (ACCV). Of these, ISO formally participates in three: ACIP, NVAC, and ACCV. The reader is referred to the websites for more information

about these committees; a brief review of the CDC's ACIP is described below

(<http://www.hhs.gov/nvpo/nvac/index.html>,

<http://www.fda.gov/cber/advisory/vrbp/vrbpmain.htm>, <http://www.cdc.gov/vaccines/pubs/ACIP-list.htm>, <http://www.hrsa.gov/vaccinecompensation/accv.htm>).

ACIP advises the Secretary, HHS, the Assistant Secretary for Health, and the Director, CDC on recommendations for vaccine use after licensure. ISO has substantial representation on ACIP workgroups and the ACIP Steering Committee.³ Working Groups routinely consider safety evidence when developing immunization policies. ACIP updates its recommendations routinely and along with professional societies these recommendations set a standard of care for healthcare providers nationwide (<http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm> and <http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm>).

ISO Mission

ISO's mission is to assess the safety of vaccines received by children, adolescents, and adults.⁴ ISO seeks to accomplish its mission by working closely with partners nationally and internationally to develop, provide and support high quality activities in three areas. The first is research and surveillance in the vaccine safety field to identify VAEs and assess causality and risk factors. The second is communication of the office's work in a clear and transparent manner that allows partners to incorporate vaccine safety findings into public health policy decisions and for the public to be well informed about vaccine risks and benefits. Third, ISO strives to develop and advance scientific methodology and standardized case definitions for VAEs. ISO values scientific excellence, integrity, transparency, informed decision-making, trust and respect.

ISO Infrastructure for Vaccine Safety Research and Surveillance

ISO has four principle research and surveillance components that conduct vaccine safety science activities. These include the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD) Project, the Clinical Immunization Safety Assessment (CISA) Network, and the Brighton Collaboration. We describe a brief summary of each component below; more information is also available at http://www.cdc.gov/od/science/iso/about_iso.htm.

³ As of March 21, 2008, ISO staff serve on 10 ACIP Working Groups and the Acting Director ISO serves on the steering committee.

⁴ As of March 21, 2008, the ISO mission is provisional and does not represent CDC or HHS policy; the mission will be finalized after the ISO Scientific Agenda is complete.

In addition to the activities above, ISO includes the Vaccine Technology Development (VAXDEV) activity⁵ and communication and policy activities that are not reviewed in this document.

Vaccine Adverse Event Report System (VAERS)

The Vaccine Adverse Event Reporting System (VAERS) is a national passive surveillance program that collects information about adverse events that occur after the administration of US licensed vaccines. The primary function of VAERS is to detect early warning signals or generate hypothesis about possible new VAEs or the frequency of known VAEs (Varricchio F et al. *Pediatric Infect Dis J*, 2004). NCVIA mandated that all health care providers report certain adverse events that occur following vaccination. As a result, in 1990 CDC and FDA jointly established VAERS. Specific objectives are VAERS are: 1) to detect new, unusual, or rare VAEs, 2) monitor increases in known VAEs; 3) determine potential patient risk factors for particular VAEs, 4) identify vaccine lots with increased numbers or types of reported VAEs, and 5) assess the safety of newly licensed and/or recommended vaccines (<http://www.cdc.gov/mmwr/PDF/ss/ss5201.pdf>). VAERS demonstrated its public health importance when the system detected a signal for intussusception after RotaShield[®] rotavirus vaccine in 1999; later epidemiologic studies confirmed an increased risk and these data contributed to the product's removal from the US market (Varricchio PIDJ 2004).⁶ VAERS is subject to underreporting and other previously described limitations (Varricchio PIDJ 2004).

CDC and FDA VAERS teams establish priorities through routine interagency scientific planning calls. FDA vaccine licensure, CDC's ACIP vaccine recommendations, and public health emergencies largely drive VAERS priorities. VAERS is ISO's front-line system for detecting VAEs and commonly conducts investigations for potential vaccine safety concerns. For example, in 2007, VAERS conducted a rapid review of reports after Merck voluntarily recalled 1.2 million doses of *Haemophilus influenzae* type b (Hib) conjugate vaccine, because *Bacillus cereus* was isolated from the manufacturing equipment (no contamination of the vaccine was found). This initial review and subsequent VAERS analysis provided additional reassurance that no cases of *Bacillus cereus* infections occurred in persons who had received the recalled Hib vaccine (<http://www.cdc.gov/vaccines/recs/recalls/hib-recall-faqs-12-12-07.htm>).

⁵ The VAXDEV activity is under a separate CDC review to determine its optimal organizational placement at CDC; it is not included in the ISO Scientific Agenda.

⁶ A different rotavirus vaccine, Rotateq[®], is currently licensed and recommended for use in the United States.

Vaccine Safety Datalink (VSD) Project

CDC established the Vaccine Safety Datalink (VSD) Project in 1990 to improve the evaluation of vaccine safety through the use of epidemiologic studies and surveillance (http://www.cdc.gov/OD/science/iso/research_activities/vsdp.htm and Chen Pediatrics 1997). The VSD Project is a collaboration among CDC's Immunization Safety Office and eight large managed care organizations (MCOs).⁷ The goals of the VSD Project are to conduct population-based research and surveillance on immunization safety questions; evaluate immunization safety hypotheses that arise from the medical literature, passive surveillance systems, adjustments to immunization schedules, and introduction of new vaccines; and to guide national immunization policy decisions.

The VSD Project use administrative data sources and provides comprehensive medical and immunization histories for more than 5.5 million people annually. The data are derived from participating MCOs that contain more than 9 million members. Of the eight sites, six cover persons of all ages and two cover children and adolescents aged <18 years. Each participating site gathers data on vaccination (e.g., vaccine type, date of vaccination, concurrent vaccinations), medical outcomes (e.g., outpatient visits, inpatient visits, urgent care visits), birth data, and census data.

The VSD Project allows for planned immunization safety research studies and surveillance. In addition, the VSD Project contributes to public health response and conducts timely investigations of hypotheses that arise from review of medical literature and IOM, reports to VAERS, changes in immunization schedules, or the introduction of new vaccines. The VSD Project has established five strategic priorities: 1) to evaluate the safety of newly licensed vaccines, 2) to evaluate the safety of new vaccine recommendations for existing vaccines, 3) to evaluate clinical disorders following immunization, 4) to assess vaccine safety in special high-risk populations, and 5) to develop and evaluate methodologies for vaccine safety assessment. Studies are prioritized on the basis of the public health importance of the topic, alignment with the VSD Project strategic priorities, and availability of resources. The VSD Project disseminates

⁷ The MCOs are: Group Health Cooperative of Puget Sound, Seattle, WA; Kaiser Permanente Northwest, Portland, OR; Kaiser Permanente Medical Care Program of Northern California, Oakland, CA; Southern California Kaiser Permanente Health Care Program, Los Angeles, CA; HealthPartners Research Foundation, Minneapolis, MN; Marshfield Clinic Research Foundation, Marshfield, WI; Kaiser Permanente Colorado, Denver, CO; and Harvard Pilgrim Healthcare, Boston, MA.

study results through presentations to the ACIP and professional meetings, publication in CDC's Morbidity and Mortality Weekly Report (MMWR) and peer reviewed journals.

The VSD Project has proven to be a highly effective tool for evaluating immunization safety and providing critical guidance for vaccination policy. Since its inception, the VSD Project has published more than 85 articles in peer reviewed journals. The VSD Project has addressed important vaccine safety questions including landmark studies on the effect of early thimerosal exposure and neuropsychological outcomes at 7 to 10 years (Thompson et al, NEJM 2007) and the risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella (MMR) vaccine (Barlow et al., NEJM 2001). Additional studies include examining the risk of anaphylaxis after vaccination, the safety of trivalent influenza vaccine among children, as well childhood vaccination and the risk of type 1 diabetes (http://www.cdc.gov/od/science/iso/vsd/vsd_publications.htm). In addition, the VSD Project has developed dynamic data files and applied sequential analysis to allow for near real-time surveillance of VAEs through its "rapid cycle analysis (RCA)" project (Lieu, Med Care 2007).

Clinical Immunization Safety Assessment (CISA) Network

CDC established the Clinical Immunization Safety Assessment (CISA) Network in 2001 to conduct clinical vaccine safety research (http://www.cdc.gov/OD/science/iso/research_activities/cisa.htm and http://www.cdc.gov/od/science/iso/cisa/cisa_publications.htm). The CISA Network's goals are: 1) to develop research protocols for clinical evaluation, diagnosis, and management of adverse events following immunization (AEFI); 2) to improve the understanding of AEFI at the individual level, including determination of possible genetic and other risk factors for predisposed individuals and high-risk subpopulations; 3) to develop evidence based guidelines for vaccination of individuals at risk of serious adverse events following immunization; and 4) to serve as a resource for clinical vaccine safety inquiries. The network consists of the six academic sites.⁸ CISA also collaborates with the Vaccine Health Centers (VHC) Network of the DoD (<http://www.vhcinfo.org/>). CISA is well suited to study postlicensure vaccine safety in special populations due to its access to both the special populations and the specialists who care for them.

⁸ The sites are: Northern California Kaiser, Stanford University, CA; Vanderbilt University, TN; Boston University Medical Center, MA; Columbia-New York Presbyterian Hospital, NY; and Johns Hopkins University, MD

The CISA Network uses a registry for clinical consultations to conduct its research. It also has created standardized protocols to evaluate specific AEFI. CISA provides a national service function by advising clinicians on how to evaluate, diagnosis, and manage patients who experience AEFI; information from these consultations helps generate hypotheses that may lead to further research. These data also will be used to improve the scientific understanding of adverse events and lead to new or improved protocols and guidelines for health care professionals to use to evaluate and manage patients who experience AEFI. CISA selects and prioritizes research topics through discussion among ISO scientific staff and CISA investigators. In determining the priority of a research study, the Network assesses the project's scientific merit, relevance to CISA's mission, and feasibility.

Key achievements of the CISA network include establishing the first national registry and a biologic specimen repository for persons experiencing VAEs. Patients with rare and serious AEFI can be referred to CISA for inclusion in the CISA Vaccine Consult Registry and Repository so that these persons may be enrolled in future vaccine safety studies. In January 2008, CISA hosted the first interdisciplinary US workshop on understanding the genetic basis of vaccine safety that was funded by the National Vaccine Program Office. A summary of the meeting is in progress and will guide future scientific activities in the emerging field of vaccine safety genomics.

The Brighton Collaboration

The Brighton Collaboration is an international voluntary collaboration, administered by CDC. It develops globally accepted and standardized case definitions for AEFI for use in surveillance and research. It also establishes guidelines for collecting, analyzing, and presenting vaccine safety data. The Brighton Collaboration's goal is to enable comparability of vaccine safety data across different surveillance systems and studies within different geographical populations. The collaboration began in 2000 as a joint effort of the CDC and University Children's Hospital, Basel with the formation of a steering committee and working groups. These working groups are composed of international volunteers with expertise in vaccine safety, patient care, pharmaceuticals, regulatory affairs, public health, and vaccine delivery. The Brighton Collaboration prioritizes AEFIs based on severity, frequency of reporting, enhanced public interest, and emerging scientific needs. As of November 2007, Brighton had completed a total of 24 case definitions; these include definitions on anaphylaxis, intussusception,

unexplained sudden death in the first and second years of life, and thrombocytopenia (<http://www.brightoncollaboration.org/internet/en/index.html> and Kohl, Gidudu Vaccine 2007). In addition, several case definitions are under development including one for Guillain-Barré Syndrome (GBS).

RATIONALE FOR DEVELOPING AN IMMUNIZATION SAFETY OFFICE SCIENTIFIC AGENDA

Each of the four ISO research and surveillance components has mechanisms in place to develop and prioritize its scientific activities with its federal and academic partners; however, no formal office wide scientific agenda setting process or comprehensive ISO Scientific Agenda exists. ISO recognizes that carrying out effective research, surveillance, and clinical guidance will benefit from establishing common scientific priorities. Developing the ISO Scientific Agenda will promote the twin principles of scientific excellence and public trust through transparency. In 2006, CDC initiated a process of developing an ISO Scientific Agenda.⁹ The rationale for developing this ISO Scientific Agenda includes the following factors: 1) part of CDC and ISO missions, 2) responsive to a 2005 IOM recommendation and 3) opportunity to contribute to vaccine safety science and patient safety initiatives. Below, we highlight how the ISO Agenda will contribute to each of these areas.

Part of CDC and ISO Missions

The mission of CDC is “to promote health and quality of life by preventing and controlling disease, injury, and disability.” (<http://www.cdc.gov/about/organization/mission.htm>). By assessing risk of vaccination and communicating its findings in a clear and transparent manner ISO enhances vaccine safety and contributes to the Agency’s mission. To guide scientific agenda development and promote collaboration across the agency and other partners to meet public health objectives, CDC has developed “Advancing the Nation’s Health: A Guide for Public Health Research Needs, 2006-2015 (<http://www.cdc.gov/od/science/PHResearch/cdcra/AdvancingTheNationsHealth.pdf>).” This Research Guide encourages programs to develop more specific scientific and research agendas. It also identifies broad thematic areas that may inform other CDC agendas. For

⁹ ISO adopted the term Scientific Agenda in December 2007. Previously the term “Research Agenda” was used.

example, the Research Guide includes a thematic area on vaccine safety. In addition, CDC is one of the lead federal agencies for the Healthy People 2010 initiative, (<http://www.healthypeople.gov/About/>). The Health People goals are “to increase quality and years of life” and “eliminate health disparities.” Improving ISO vaccine safety activities would help fulfill these goals.¹⁰

In alignment with broader agency goals and its mission, in October 2006, ISO conducted an internal Peer Review of its program with seven senior CDC scientists from outside ISO. The individual reviewers made suggestions in three main areas (<http://www.cdc.gov/vaccines/recs/ACIP/downloads/mtg-slides-jun07/11-izsafetyoffice-broder.pdf>). First they noted that ISO should strive for transparency, clearly identifiable research priorities, scientific credibility, enhancement of existing collaborations, and identification of new partnerships. Second they suggested that ISO should ensure it can perform core public health functions under both routine and emergency situations. Third, they suggested that development of the ISO research agenda should include input from stakeholders in immunization safety and an external review (e.g., through the National Vaccine Advisory Committee [NVAC]).

Responsive to an Institute of Medicine Recommendation from the 2005 “Vaccine Safety, Data Access, and Public Trust” Report

During the late 1990s, the public and Congress raised concerns about the accessibility of the VSD Project data to independent researchers. In 2002, the VSD Project established a data sharing program that is administered by the National Center for Health Statistics, CDC (http://www.cdc.gov/OD/science/iso/research_activities/vsdatasharing.htm). At the request of CDC, the IOM convened a committee¹¹ to review and make recommendations about aspects of the VSD Project’s data sharing program. The committee made 28 recommendations in four main areas: 1) independent review of the VSD Project activities, 2) the applicability of the Shelby Amendment and Information Quality Act (legislation that promotes public access to federal information) to the VSD Project data, 3) the VSD Project data sharing program, and 4) the release of preliminary findings based on the VSD Project data. In its section on independent review of the VSD Project activities, the IOM made the following recommendation (recommendation 5.1): “The committee recommends that a subcommittee on the National

¹⁰ Of the 467 objectives stated in the Healthy People 2010 guidance, two are specific to vaccine safety.

¹¹ The committee was distinct from the committees that conducted earlier IOM reviews of vaccine safety.

Vaccine Advisory Committee that includes representatives of a wide variety of stakeholders review and provide advice to NIP [National Immunization Program]¹² on the VSD Project plan annually. The subcommittee charged with this role could be the existing Subcommittee on Safety and Communications¹³ or a subcommittee created specifically for the purpose.” The report further described that the group “should represent a broad cross-section of stakeholders and be charged with thinking strategically about the VSD Project research priorities. The group should meet publicly and allow interested persons to observe the process and provide input through established mechanisms.” CDC concurred with this recommendation (CDC, unpublished document).¹⁴

Opportunity to Contribute to Vaccine Safety Science in Organizations outside ISO and Other Patient Safety Initiatives

ISO provides ongoing technical vaccine safety support to other programs and agencies and develops methodology that is relevant to the broader field of pharmacoepidemiology.¹⁵ In light of these roles, it is likely that an ISO Scientific Agenda would enhance vaccine safety and patient safety initiatives outside of the office, even if the scope were directed to cover ISO-specific activities. Within CDC, an ISO Scientific Agenda might be particularly useful to the CDC Patient Safety Workgroup (WG). Launched in August 2007, this WG is comprised of subject matter experts from 14 divisions across ten national centers at CDC. These experts specialize in the science, program and policy aspects of patient safety issues, including healthcare-associated infections and medical and biological product safety (i.e., drugs, vaccines, devices, blood, organs, and tissues); and the statistical and methodological aspects of patient safety surveillance and research. The Patient Safety WG’s mission is to provide a "central," cross-cutting forum for CDC experts to discuss and make recommendations about patient safety issues for the agency; define CDC's role in the broader context of patient

¹² In 2006, the National Immunization Program (NIP) was reorganized into other parts of CDC. Before 2005, most vaccine safety activities were in NIP.

¹³ As of January 16, 2008, the NVAC Subcommittee on Safety and Communication are two separate subcommittees.

¹⁴ CDC response to the 2005 IOM report is available by request from the corresponding author.

¹⁵ Pharmacoepidemiology is defined as by the International Society of Pharmacoepidemiology as the study of the utilization and effects of drugs in large numbers of people and as the application of epidemiological methods to pharmacological issues (<http://www.pharmacoepi.org/aboutpe.cfm>).

safety; and identify ways to coordinate more efficiently and effectively with key patient safety partners, including FDA.

OBJECTIVE, SCOPE AND INTENDED USE OF THE ISO SCIENTIFIC AGENDA

The objective of ISO's Scientific Agenda is to recommend priority vaccine safety science activities for the next five years. Recommendations for CDC's ISO Scientific Agenda (under development), cover three vaccine safety areas: research studies, selected surveillance activities, and selected clinical guidance activities. The scope of the ISO Agenda recommendations is broader than the 2005 IOM recommendation to develop and set priorities for the VSD Project research agenda.

The ISO Scientific Agenda recommendations will include activities that are aligned with ISO's mission, are in ISO's realm to lead, and could be implemented during the next 5 years using infrastructure generally accessible to CDC. However, the ISO Scientific Agenda is not a comprehensive ISO strategic plan and does not address all issues related to vaccine safety science. Specifically, it does not cover vaccine safety science initiatives that are not clearly already in ISO's purview to lead under its current mission (e.g., risk perception activities); therapeutic vaccines or vaccines not expected to be licensed within 5 years. Recommendations also do not include routine service, formal surveillance evaluation (MMWR, <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5013a1.htm>), programmatic, or communication activities. They also do not address issues related to specifics of ISO collaboration with federal and non-federal partners.

The chief users of the ISO Scientific Agenda will be ISO staff and their day-to-day research and surveillance partners, including the VSD Project, VAERS, CISA, the Brighton Collaboration, and CDC vaccine subject matter expert investigators and scientists,. The Agenda recommendations will be useful to all ISO teams as they establish and set priorities for projects in a coordinated manner. The Agenda will help ISO to fill knowledge gaps in vaccine safety science and advance ISO's future capacity to carry out research, surveillance, and clinical guidance activities. It will also serve as a platform to discuss collaborative vaccine safety science projects among ISO and internal and external partners. A secondary purpose of this Agenda is to provide vaccine and patient safety scientists, outside ISO, with information that may be useful to other federal or non-governmental research or scientific agendas. Looking

forward 5 years after CDC implements this Agenda; we would expect to find that it contributed to advancing the field of vaccine safety science and enhancing public health.

APPROACH

General Process of ISO Scientific Agenda Development and National Vaccine Advisory Committee (NVAC) Scientific Review

Scientific Development

During 2006–2008, CDC, the National Vaccine Program Office (NVPO), and the NVAC Subcommittee on Vaccine Safety (<http://www.hhs.gov/nvpo/nvac/subcomm.html>) established and implemented a general process for developing the ISO Scientific Agenda. The parties agreed that ISO Scientific Agenda development will involve three phases and that CDC, NVPO and NVAC will collaborate closely on both development and review. In the first phase, CDC will develop a Draft ISO Scientific Agenda and provide it to the NVAC. In the second phase, NVAC will review the Draft ISO Scientific Agenda and provide input on the draft to CDC. In the third phase, ISO and CDC will consider the NVAC advice and finalize the ISO Scientific Agenda. It is important to note that CDC will lead Phases 1 and 3; final decisions about the Scientific Agenda content and priorities would be those of ISO and CDC. NVAC and NVPO will lead the NVAC scientific review. NVPO and NVAC formed a Vaccine Working Group on Vaccine Safety, including members and invited consultants with different expertise and backgrounds. CDC provided the following charge to NVPO for the NVAC scientific review and it was accepted. The NVAC reviewers will undertake and coordinate a scientific review of the Draft ISO Scientific Agenda and advise on: 1) content of ISO draft Scientific Agenda (e.g., are the topics on the agenda appropriate? Should other topics be included?); 2) prioritization of scientific topics, and 3) possible scientific barriers to implementing the Scientific Agenda and suggestions for addressing them.

Public Involvement

Trust and transparency about vaccine safety are values that CDC, NVPO and NVAC share, and involving the public in the ISO Scientific Agenda process is also responsive to the IOM recommendation from 2005 (see section on ISO mission and “Vaccine Safety Research,

Data Access, and Public Trust). ISO is committed to receiving input from the public and carefully considering this input before CDC finalizes the Scientific Agenda. In June 2007, participants attending the joint NVAC Subcommittee on Vaccine Safety and Subcommittee on Public Communication, Consultation, and Participation meeting discussed the topic (<http://www.hhs.gov/nvpo/nvac/documents/2007june/Pavia.ppt>).

The public has had an opportunity to learn about the Agenda plans through public presentations to NVAC and ACIP (<http://www.hhs.gov/nvpo/nvac/documents/2007june/Pavia.ppt> and <http://www.cdc.gov/vaccines/recs/ACIP/downloads/mtg-slides-jun07/11-izsafetyoffice-broder.pdf>). All in-person meetings among the NVAC scientific reviewers for the ISO Scientific Agenda and full NVAC will be open to the public. In addition, the NVAC Vaccine Safety Working Group which will conduct the review of the ISO Scientific Agenda includes two public representatives who have personal experience with vaccine and vaccine safety issues (personal communication, Dan Salmon on 1/18/2008). Following the NVAC Working Group review, ISO will solicit comments on the draft ISO Scientific Agenda, through mechanisms such as the *Federal Register* (<http://www.gpoaccess.gov/fr/index.html>) and CDC website.

The remainder of this document focuses on the CDC development of the Draft ISO Scientific Agenda (phase 1). Information about the proposed approach for the NVAC scientific review will be described in a companion draft document on Agenda recommendations. The approach that CDC will use to finalize the Agenda after the NVAC review (phase 3) will be described in the Final ISO Scientific Agenda.

CDC Development of the Draft ISO Scientific Agenda: Input Venues

External Input Meetings on the ISO Research Agenda

CDC recognized that obtaining external input before the NVAC scientific review would enhance the quality of the Agenda and help inform the NVAC scientific review. During May 2007 through November 2007 CDC and NVPO convened three meetings to obtain input from the following groups: external expert scientists, vaccine safety representatives from HHS and Department of Defense agencies and programs, and US vaccine manufacturers' representatives.¹⁶

¹⁶ The meetings were as follows: CDC Individual Simultaneous Consultation on CDC's Immunization Safety Office Research Agenda (5/2007), NVPO Interagency Vaccine Group (IAVG) Meeting on CDC's ISO Research Agenda (8/2007), and NVPO Individual Simultaneous Consultation with US Vaccine Manufacturers' Representatives on CDC's ISO Research Agenda (11/2007)

Before each meeting ISO prepared briefing materials including lists of research studies underway or planned and background presentations that were shared with participants. The charge to individual participants in each meeting was also similar. In each meeting participants were asked to: 1) identify emerging vaccine safety questions and gaps in knowledge that will be important for public health and could be studied by ISO, 2) advise on prioritization of the topics and 3) propose some potential approaches to study the topics. During each meeting one or more note takers summarized the key events and suggestions. We also asked non-ISO participants to complete feedback worksheets for ISO staff to review. We drafted separate reports from each meeting describing the approaches used and key suggestions from the participating scientists.¹⁷ Brief summaries about the organization of the three meetings are provided in Appendix C. In addition to these planned meetings, we reviewed additional external input from existing sources (e.g. a review of ACIP statements).

Ongoing Input from ISO Day-to-Day Partners

While reaching out to external groups for novel ideas, ISO has also worked closely with its day-to-day partners to obtain input on the ISO Scientific Agenda. These partners include CISA and VSD investigators, the FDA VAERS team, and non-CDC colleagues in the Brighton Collaboration. All have discussed the Agenda and will continue to have opportunities to provide input. In January 2008, OCSO convened an ISO Writing and Reviewing Group to enhance the quality of the ISO Scientific Agenda and optimize collaboration among its teams and leadership (Appendix A).

In addition to these partners, ISO scientists interact routinely with CDC immunization experts outside ISO by collaborating on scientific projects and participating in appropriate ACIP Working Groups. To ensure that CDC immunization experts and ACIP have appropriate involvement with the ISO Scientific Agenda, ISO staff are working closely with CDC's National Center for Immunization and Respiratory Diseases (NCIRD) and ACIP leadership. In June 2007, ISO presented an update on the status of the ISO Scientific Agenda to ACIP and discussed agenda development during a CDC "Vaccine Interest Group" meeting. This topic also has been discussed on monthly NCIRD calls with professional partner organizations.

¹⁷ The unpublished reports from the external input meetings about the ISO Research Agenda are available by request from the corresponding author.

FUTURE ACTIVITIES

The NVAC Vaccine Safety Working Group will convene for its first meeting on April 11, 2008 in Washington DC. During this meeting the Working Group will review and advise on the content and priorities of the draft ISO Scientific Agenda. The ISO Internal Writing and Reviewing team is currently developing draft Agenda recommendations for this review. ISO will provide these draft Agenda recommendations in a companion document before the meeting. In addition, during the meeting, the NVAC Working Group will have the opportunity to consider various approaches to prioritizing the ISO Agenda.

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APPENDICES

Appendix A: ISO Scientific Agenda Writing and Reviewing Group

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Appendix B: Institute of Medicine Immunization Safety Review Summary*

Institute of Medicine Immunization Safety Reviews, 2001–2004			
IOM Immunization Safety Review	Outcome	Vaccine	Conclusion
Thimerosal-Containing Vaccines and Neurodevelopmental Disorders (2001)	Neurodevelopmental disorders (e.g. autism, ADHD, and speech language delay).	Childhood vaccines with Thimerosal	Evidence is inadequate to accept or reject a causal relationship (also see 2004 review)
Measles-Mumps-Rubella Vaccine and Autism (2001)	Autistic Spectrum Disorder (ASD)	MMR Vaccine	Evidence favors rejection of a causal relationship
Hepatitis B Vaccine and Demyelinating Neurological Disorders (2002)	Multiple sclerosis – incident	Hepatitis B Vaccine	Evidence favors rejection of a causal relationship
	Multiple sclerosis – relapse		Evidence favors rejection of a causal relationship
	Central Nervous System Demyelinating ³ Disorder – first episode		Evidence is inadequate to accept or reject a causal relationship
	Acute disseminated encephalomyelitis (ADEM)		Evidence is inadequate to accept or reject a causal relationship
	Optic neuritis		Evidence is inadequate to accept or reject a causal relationship
	Transverse myelitis		Evidence is inadequate to accept or reject a causal relationship
	Guillain-Barré Syndrome (GBS)		Evidence is inadequate to accept or reject a causal relationship
	Brachial neuritis		Evidence is inadequate to accept or reject a causal relationship
Multiple Immunizations and Immune Dysfunction (2002)	Heterologous infections	Multiple Vaccinations	Evidence favors rejection of a causal relationship
	Type 1 diabetes		Evidence favors rejection of a causal relationship
	Increased risk of allergic disease, particularly asthma		Evidence is inadequate to accept or reject a causal relationship

Institute of Medicine Immunization Safety Reviews, 2001–2004			
IOM Immunization Safety Review	Outcome	Vaccine	Conclusion
SV40 Contamination of Polio Vaccine and Cancer (2002)	Cancer	Oral polio vaccine (OPV)	Evidence is inadequate to accept or reject a causal relationship
Vaccinations and Sudden Unexpected Death in Infancy (2003)	Sudden infant death syndrome (SIDS)	Diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTwP)	Evidence favors rejection of a causal relationship
		Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP)	Evidence is inadequate to accept or reject a causal relationship
		Haemophilus Influenza (Hib), Hepatitis B (HepB), Oral Polio Vaccine (OPV), Inactivated Polio Vaccine (IPV)	Evidence is inadequate to accept or reject causal relationships
		Multiple simultaneous vaccinations	Evidence favors rejection of a causal relationship
	Sudden unexpected death in infancy, other than SIDS	Multiple simultaneous vaccinations	Evidence is inadequate to accept or reject a causal relationship
	Anaphylaxis in infants	DTwP	Evidence favors acceptance of a causal relationship
	Neonatal death	Hepatitis B vaccine	Evidence is inadequate to accept or reject a causal relationship
Influenza Vaccines and Neurological Complications (2004)	GBS	1976 Swine Influenza Vaccine	Evidence favors acceptance of a causal relationship
		Influenza vaccine administered after 1976	Evidence is inadequate to accept or reject a causal relationship
	Multiple sclerosis – relapse	Influenza vaccine administered after 1976	Evidence favors rejection of a causal relationship
	Multiple sclerosis – incident		Evidence is inadequate to accept or reject a causal relationship

Institute of Medicine Immunization Safety Reviews, 2001–2004			
IOM Immunization Safety Review	Outcome	Vaccine	Conclusion
	Optic neuritis		Evidence is inadequate to accept or reject a causal relationship
	Other Demyelinating Neurological Conditions		Evidence is inadequate to accept or reject a causal relationship
	Demyelinating neurological disorders in children aged 6-23 months		No evidence bearing on a causal relationship
Vaccines and Autism (2004)	Autism	Thimerosal-containing vaccines	Evidence favors rejection of a causal relationship
		MMR vaccine	Evidence favors rejection of a causal relationship

* Source: National Vaccine Program Office, provided by Dan Salmon and information available at <http://www.iom.edu/?ID=4705>, accessed on March 21, 2008.

Appendix C: Summary Table of External Input Meetings on the ISO Scientific Agenda¹⁸

Input Group	Sponsor	Meeting Description	Meeting Date
Immunization Safety Office External Scientific Consultancy	CDC	CDC individual simultaneous consultation with seven individual expert scientists and liaisons representing the fields of pediatric infectious diseases, adult infectious diseases, obstetrics and gynecology, immunology, genomics, and epidemiology	May 10-11, 2007, Atlanta, GA
US Department of Health and Human Services and US Department of Defense agencies and programs	NVPO	National Vaccine Program Office (NVPO) Interagency Vaccine Group (IAVG) meeting with 21 Federal scientists with expertise in vaccines	August 3, 2007, Washington DC
Non-federal partners	NVPO	NVPO-sponsored meeting with vaccine manufacturer representatives from six US vaccine manufacturers	November 16, 2007, Washington DC

¹⁸ Separate reports for each meeting are available from the corresponding author.

Appendix D: List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AEFI	adverse events following immunization
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
Hib	<i>Haemophilus influenzae</i> type b
IOM	Institute of Medicine
ISO	Immunization Safety Office
NIH	National Institutes of Health
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OCSO	Office of the Chief Science Officer
VAE	vaccine adverse event
VAERS	Vaccine Adverse Event Reporting System
VHC	Vaccine Health Center
VSD	Vaccine Safety Datalink
USPHS	United States Public Health Service