Prelicensure Safety Assessment and Pharmacovigilance Planning

Jerald Mullersman, M.D., Ph.D., M.P.H.

Division of Epidemiology
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research

US Food and Drug Administration

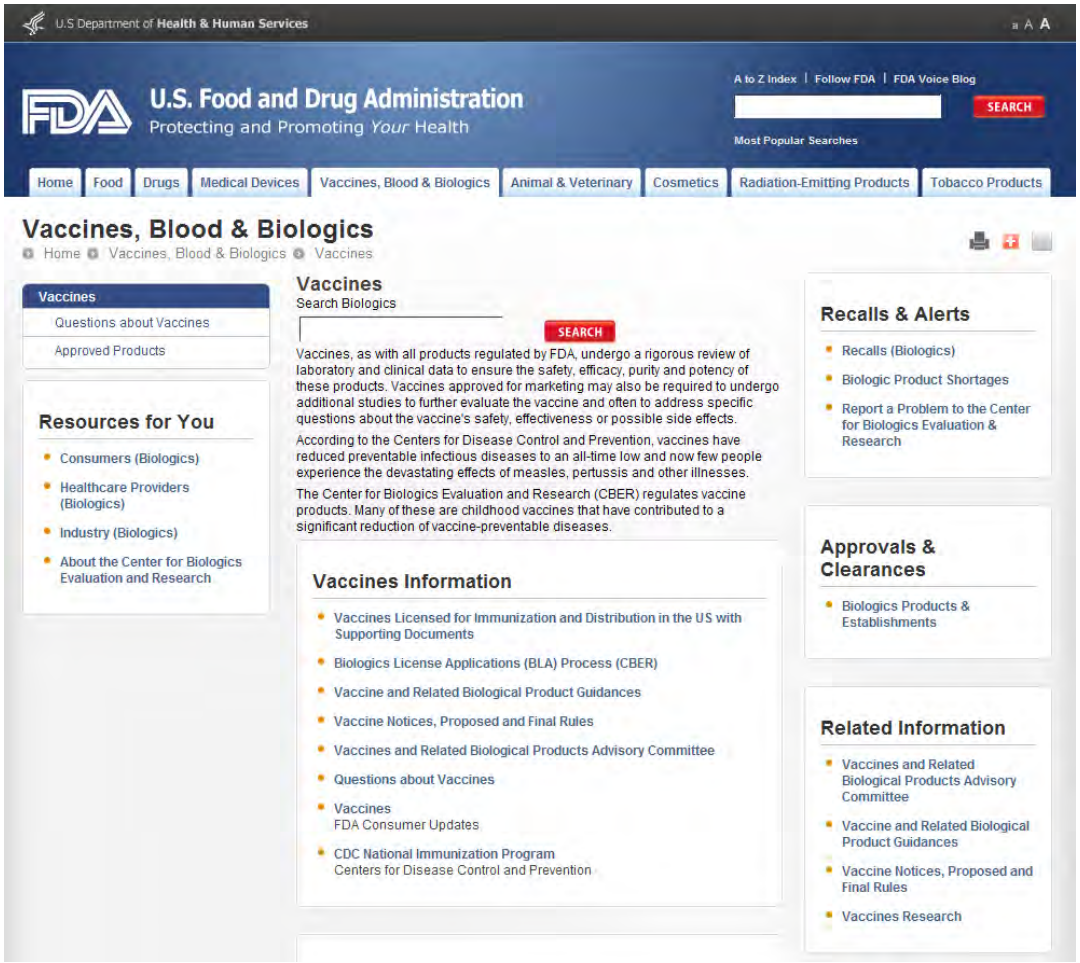
Application of Pharmacovigilance to U.S. FDA Regulatory Decisions for Vaccines

June 2, 2012

Plan for Talk

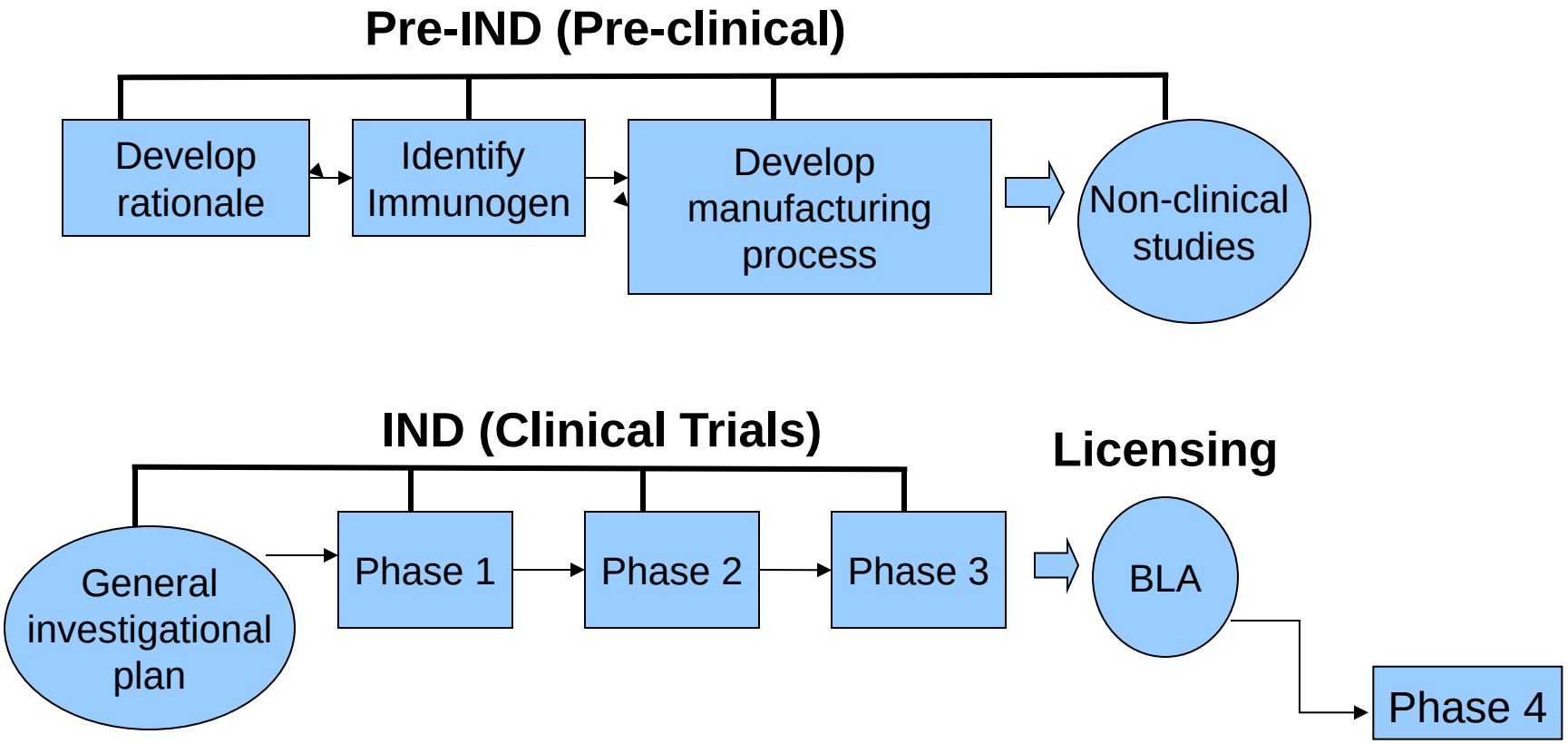
- Phases of vaccine development and use
  - Pre-Investigational New Drug (IND) application stage
  - IND studies
  - Biologics License Application (BLA) approval
  - Post-marketing period
- Safety of vaccines throughout the life cycle
- Key decisions in pharmacovigilance planning

FDA Vaccines Web Page



http://www.fda.gov/BiologicsBloodVaccines/Vaccines/default.htm

Vaccine Development Life Cycle



IND: Investigational New Drug Application
BLA: Biologics License Application

U.S. Regulatory Definition of Safety

21 CFR 600.3:

"relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time"

Safety Considerations for Preventive Vaccines

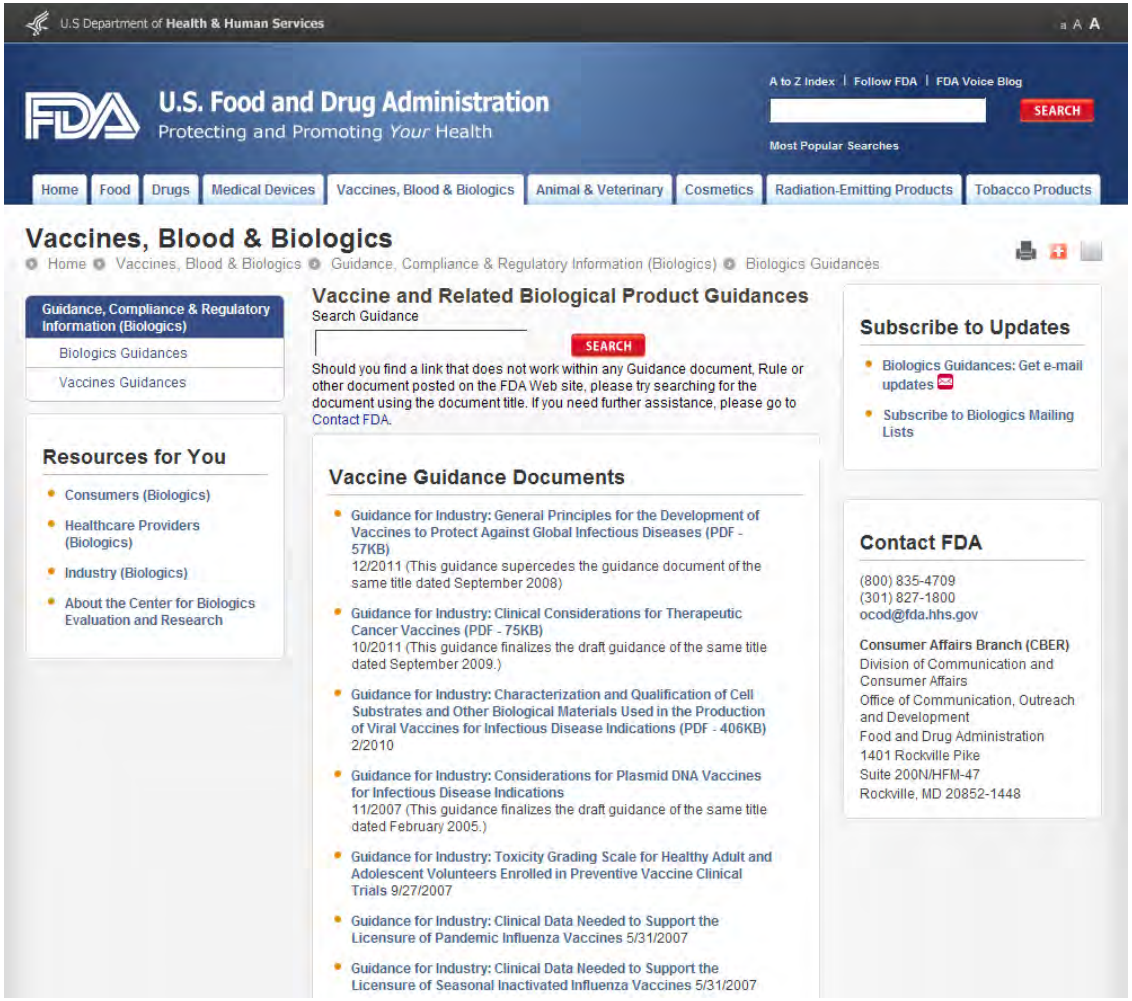
Safety *"in relation to the condition of the recipient. . ."*

- Target population: millions of healthy people, including young infants and children, each year
- State governments mandate many vaccines for children attending public schools or day care centers
- Individual risk for disease prevented by vaccination may be low (e.g., diphtheria, polio)

…thus, low tolerance for vaccine-associated risks

- FDA requires new vaccines to be studied in the context of concomitant use with other recommended vaccines that are given on the same or overlapping schedule

FDA Vaccine Guidances Web Page



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Vaccine and Related Biological Product Guidances

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Should you find a link that does not work within any Guidance document, Rule or other document posted on the FDA Web site, please try searching for the document using the document title. If you need further assistance, please go to Contact FDA.

Vaccine Guidance Documents

- Guidance for Industry: General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases (PDF - 57KB)
  12/2011 (This guidance supercedes the guidance document of the same title dated September 2008)
- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (PDF - 75KB)
  10/2011 (This guidance finalizes the draft guidance of the same title dated September 2009.)
- Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (PDF - 406KB)
  2/2010
- Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications
  11/2007 (This guidance finalizes the draft guidance of the same title dated February 2005.)
- Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 9/27/2007
- Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines 5/31/2007
- Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines 5/31/2007

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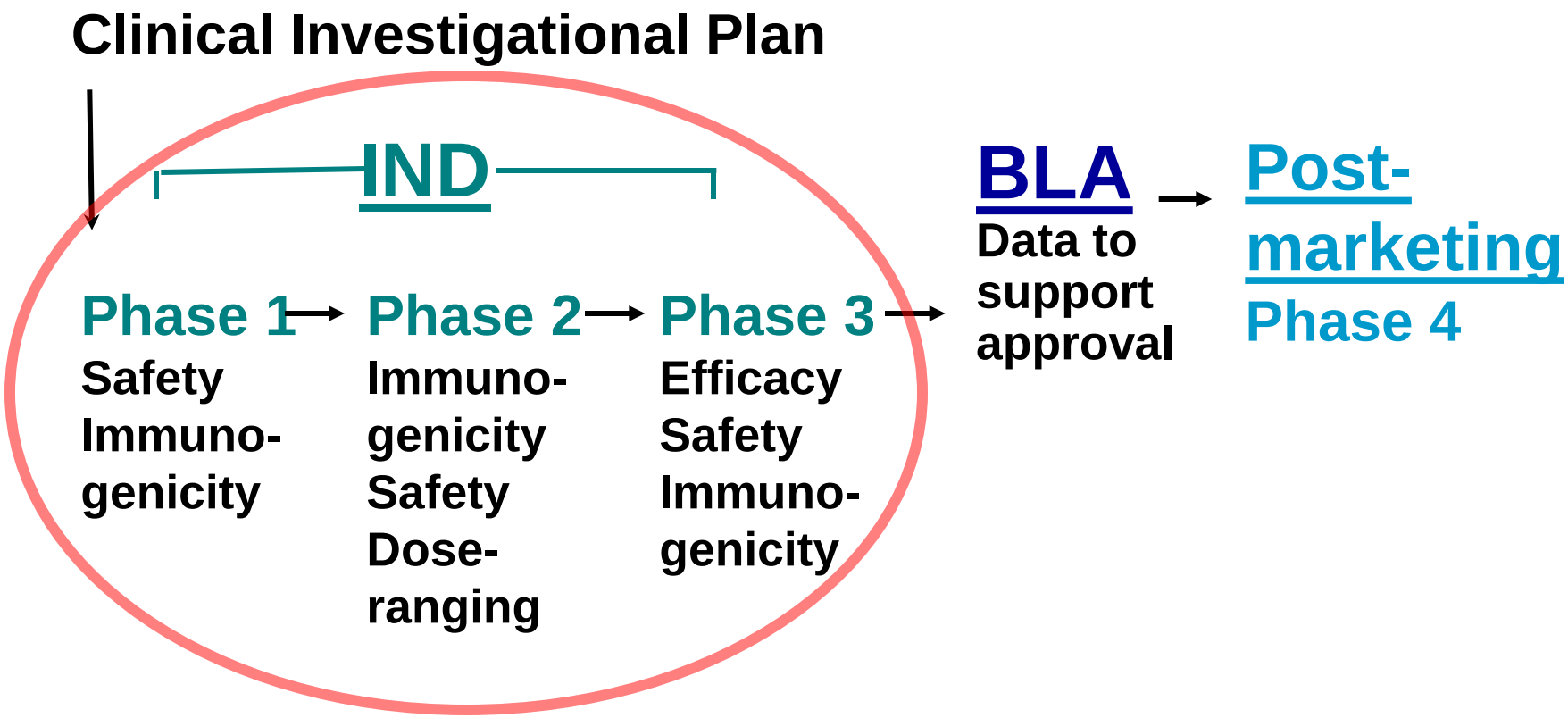
(800) 835-4709
(301) 827-1800
ocod@fda.hhs.gov

Consumer Affairs Branch (CBER)
Division of Communication and Consumer Affairs
Office of Communication, Outreach and Development
Food and Drug Administration
1401 Rockville Pike
Suite 200N/HFM-47
Rockville, MD 20852-1448

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/default.htm

Stages of Vaccine Evaluation and Regulation



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Primary Objectives of IND Review

21 CFR 312.22(a):

- In all phases of the investigation, to assure the safety and rights of subjects
- In Phase 2 and 3, to help assure that the quality of the scientific evaluation is adequate to permit an evaluation of effectiveness and safety

Phase 1 Clinical Trials of Preventive Vaccines

- Preliminary evaluation of safety and immunogenicity
- Design depends on pre-clinical data, experience with similar products
  - Often open label
  - Randomized, controlled in some cases
  - Dose escalation, in some cases
- Population
  - Small number of subjects (e.g., 20-80)
  - Adults usually studied before children
  - Inclusion/exclusion criteria to minimize risk
- Careful safety monitoring; conservative stopping rules

Phase 2 Clinical Trials of Preventive Vaccines

- Evaluation of safety (common local and systemic reactions) and immunogenicity
  - Dose ranging (some studies)
- Up to several hundred subjects per trial
- Usually randomized and controlled
- Entry criteria less restrictive, reflect target population

Phase 3 Clinical Trials of Preventive Vaccines

- Confirm clinical benefit (efficacy/immunogenicity)
- Expand knowledge of safety (including serious and less common adverse events)
- Randomized, controlled
- Often thousands or tens of thousands
  - Clinical endpoint efficacy trials provide a large safety database
  - When numbers of subjects included in efficacy trials or immunogenicity trials provide inadequate safety data, additional controlled safety trials required
- Detailed surveillance and detailed outcomes assessment (safety and efficacy/immunogenicity)

Impact of Concomitant Vaccines

- Effect of co-administered vaccines evaluated in Phases 2 and 3
- Safety of concomitant immunization
- Efficacy/immunogenicity of investigational vaccine administered concomitantly with other recommended vaccines
- Interference in responses to other vaccines when administered with investigational vaccine (some studies)

Phase 3 Safety Evaluation of Preventive Vaccines: Statistical Considerations

- Analyses usually exploratory in nature
  - Few *a priori* hypotheses, but many analyses
- No statistical adjustment for multiple testing
  - Failure to identify true safety signal more critical error than detecting a false signal
- Some trials may aim to test specific hypothesis regarding a potential vaccine-associated adverse event

Pre-Licensure Safety Database for Some Infant/Childhood Vaccines (1)

Prevnar (pneumoccoccal 7-valent conjugate vaccine) (US licensure 2000)

- Safety experience derived primarily from efficacy trial
- ~18,000 infants received ~58,000 doses of Prevnar; similar number of infants in control group
- Common adverse events monitored by telephone interviews in ~3,000 infants in each group
- Relatively rare events requiring medical attention evaluated across all doses in all study participants using automated databases

Pre-Licensure Safety Database for Some Infant/Childhood Vaccines (2)

Pentacel (DTaP-IPV-Hib) (US licensure 2008)

- Substantial previous experience with same manufacturer's DTaP and Hib conjugate vaccines
- Nearly 6,000 study participants received at least one dose of Pentacel; most received four doses in controlled clinical trials *(safety and immunogenicity)*

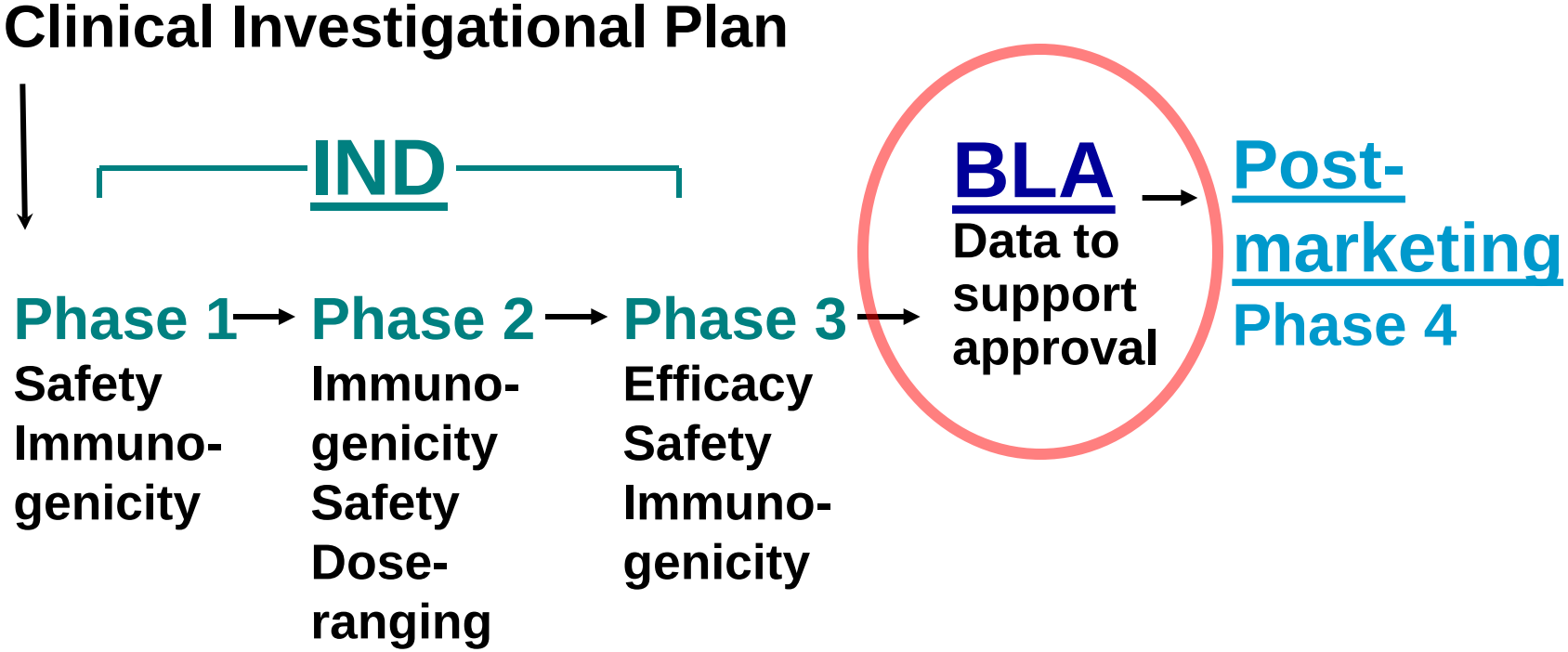
Pre-Licensure Safety Database for Some Infant/Childhood Vaccines (3)

Rotarix (Rotavirus Vaccine, Live, Oral)
(US licensure 2008)

- Increased risk of intussusception had been observed following administration of another manufacturer's rotavirus vaccine (no longer licensed in US)

- Risk of intussusception with Rotarix evaluated in a pre-licensure safety trial including ~63,000 infants (no increased risk of intussusception observed following Rotarix compared with placebo)

Stages of Vaccine Review and Regulation



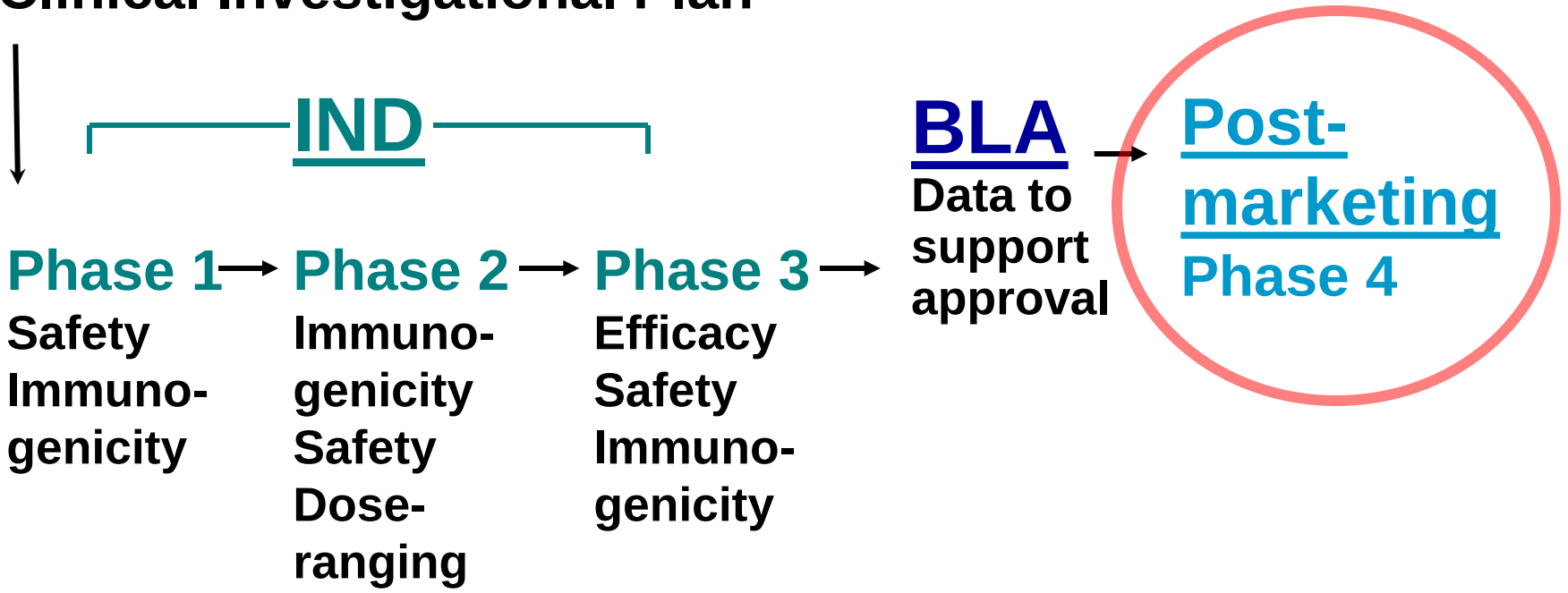
IND: Investigational New Drug Application
BLA: Biologics License Application

Biologics License Application

- **Multidisciplinary review committee**
  - **membership: medical, product, manufacturing facility, statistical, epidemiology, toxicology, labeling, other consultants as needed**
  - **evaluates product and manufacturing information and data from nonclinical and clinical studies to demonstrate safety, purity, and potency**
- **FDA advisory committee review input, if needed**
  - **provide opinion regarding adequacy of safety and efficacy data**
- **FDA decision**
  - **benefit-to-risk ratio considered**
  - **determine needs for post-marketing pharmacovigilance activities**

Stages of Vaccine Review and Regulation

Clinical Investigational Plan



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Sources of Safety Information for Pharmacovigilance Planning

- Data from the sponsor's BLA submission
- International or domestic postmarketing data
- Product class safety information
- Medical Literature

Routine Pharmacovigilance

- All-inclusive surveillance for all vaccines conducted by both FDA and sponsors
  - Continuous safety monitoring with AERS and VAERS
  - Disproportionality analyses of spontaneous reports
  - Periodic safety update reports (PSURs)
  - Signal detection, issue evaluation, labeling updates

- Contact with international public health and regulatory agencies

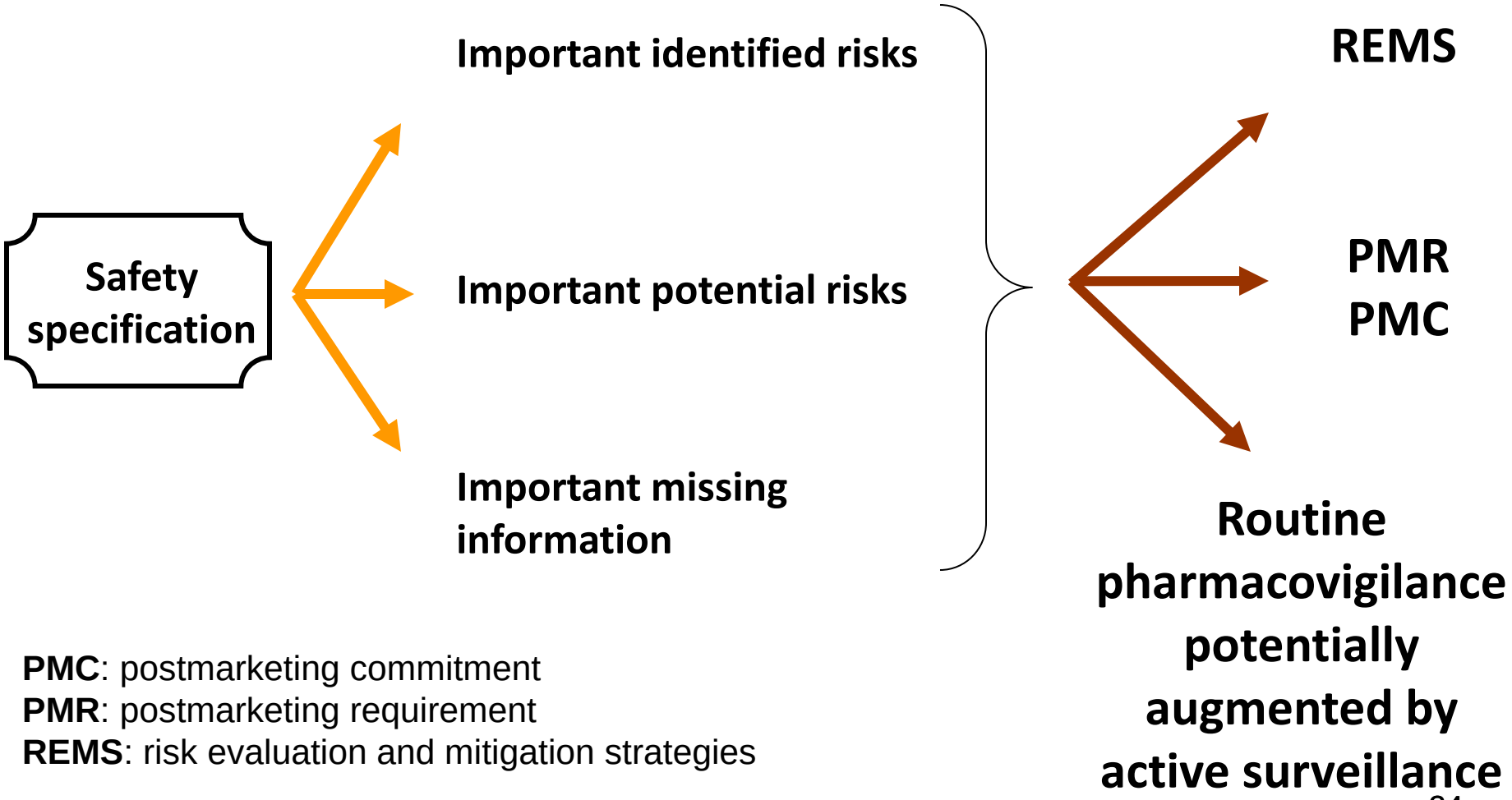
FDA Guidance for Industry: E2E Pharmacovigilance Planning, April 2005

Active Surveillance

Population based surveillance using databases containing health-related information

- Post-licensure Rapid Immunization Safety Monitoring (PRISM) component of the Mini-Sentinel program
- Centers for Medicare and Medicaid Services
- Vaccine Safety Datalink (VSD)

Key Decisions in Pharmacovigilance Planning



PMC: postmarketing commitment
PMR: postmarketing requirement
REMS: risk evaluation and mitigation strategies

ICH Guideline for Pharmacovigilance Planning E2E Nov 2004 (www.ich.org)

Clinical Postmarketing Commitments (PMCs)

- Studies conducted by manufacturer to further evaluate safety (e.g., rare adverse events) or effectiveness (e.g., duration of vaccine-induced immunity)
- Agreed upon by FDA and manufacturer prior to approval
- Progress of studies monitored by FDA

Example - Considering PMC

- **Pregnancies**: Gardasil (1894) and AAHS* (1925)
- **Overall AE rate**: Gardasil (22.6%) vs. AAHS (23.1%)
- Among pregnancies with onset <30 days of vaccination, the congenital anomaly rate was 5:1
- Question taken to VRBPAC (Vaccines and Related Biological Products Advisory Committee)
  - Diversity of anomalies did not suggest causal relationship
  - Timing of vaccine exposure not consistent with usual timing of congenital anomaly onset

Congenital anomalies → **Routine pharmacovigilance and PMC for pregnancy registry**

*AAHS = Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant
VRBPAC Meeting, May 18, 2006
http://www.fda.gov/ohrms/dockets/ac/cber06.html#VaccinesandRelatedBiological

FDA Amendments Act of 2007
Title IX Sec 901 Postmarketing Requirements

- Authorizes FDA to require postmarketing studies or clinical trials
  - at time of approval
  - post-approval if FDA becomes aware of new safety information
- FDA may consider safety information from clinical trials, adverse event reports, postmarketing studies, biomedical literature, other appropriate scientific data
- New authorities for monitoring and enforcement
- Requirements imposed when other approaches insufficient

FDA PMR/PMC Database Query Web Page

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/default.htm