Regulatory Issues in Malaria Vaccine Development

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MVW 2007
September 18, 2007

Licensure of Vaccines for Diseases not Endemic to US

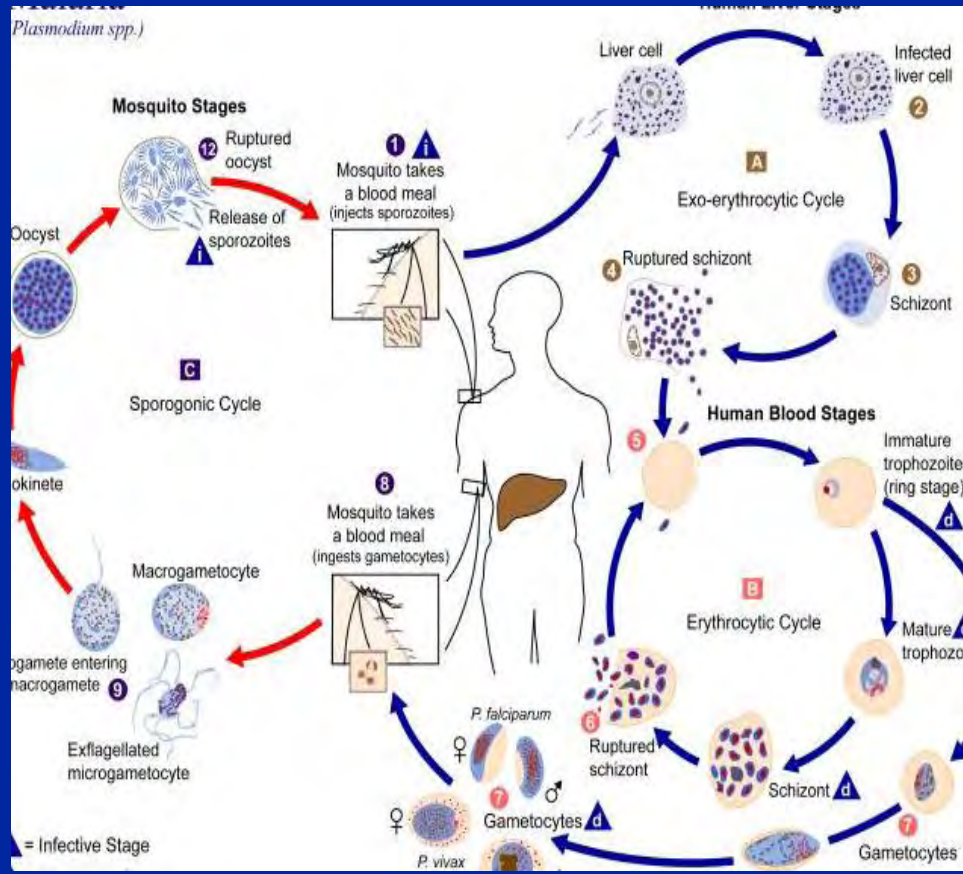
- Section 351 of the PHS Act and section 505(b) of the FD&C Act do not limit marketing approvals of products to treat, mitigate, diagnose, or prevent conditions or diseases found only in the US
- The regulatory path forward for a vaccine targeted against a disease or condition not endemic to the US is the same as for a vaccine against a disease or condition that exists in the US population

Licensure of Vaccines for Diseases Not Endemic to US

- **FDA will accept a foreign clinical study in support of an application for marketing provided certain conditions are met (*Guidance for Industry: Acceptance of Foreign Clinical Studies*, March 2001); For example, vaccines licensed using non-US clinical efficacy data include:**
  - **Acellular pertussis-containing vaccines (DTaP)**
  - **Oral polio vaccine**
  - **Typhoid Vi Polysaccharide**
  - **Japanese encephalitis**
  - **Hepatitis A**

Malaria Vaccines Studied Under U.S. IND

- >40 INDs submitted
- Stages
  - Pre-erythrocytic
  - Asexual (blood-stage)
  - Transmission-blocking
- Types:
  - Peptide
  - Conjugate
  - Plasmid DNA
  - Recombinant subunit
  - Viral-vectored
  - Prime/Boost



Many thanks to CDC/AJ da Silva, M Moser

FDA Review is Product-based

- Parallels prudent product development
- Dependent on characteristics of specific product
- Preclinical studies designed to support use of specific products
- Clinical trial design supported by manufacturing, preclinical data
- Supported by science, framed by regulations

IND Role in Biologics Approval Process

- Mechanism and process to collect clinical data to support the license application
  - Demonstrate safety and efficacy
  - Goal: Information for the package insert
- Chemistry, manufacturing, and controls (CMC)
  - General biological product standards
  - Process validation
- Assay validation
  - Immunogenicity/activity
  - Product quality control, lot release
- Stability data

Product Manufacture & Characterization

Licensed biological products, including vaccines, must be:

- **Safe:** "relatively free from harmful effect… when prudently administered, taking into account the character of the product in relation to the condition of the recipient at the time."
- **Pure:** "relatively free from extraneous matter in the finished product,…"
- **Potent:** "specific ability of the product … to effect a given result."
- **Manufactured consistently** according to current Good Manufacturing Practices

CGMP & Product Development

SAFETY INFORMATION

Source characterization

Raw materials qual

DS/DP Characterization

Testing/Qualification/ Clearance of impurities, contaminants

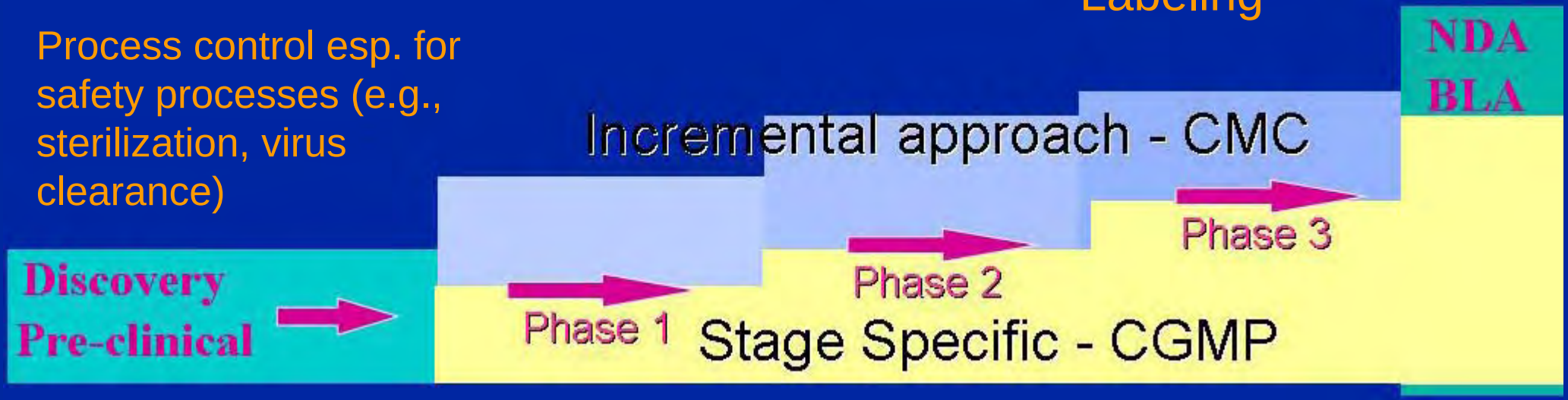
Process control esp. for safety processes (e.g., sterilization, virus clearance)

DEVELOPMENT ACTIVITIES

DS & DP Characterization
Formulation Development
Raw Material/ Component characterization
Assay Development/ Validation
Specification Development
Stability
Manufacturing Process Control & Validation

CGMP

Personnel
Quality Control
Facilities & Equipment
Laboratory Control
Component Control
Production Control
Distribution & Records
Labeling



Lot Release Testing

- Sterility – bacterial or fungal contaminants
- General safety test - guinea pigs and mice to detect extraneous toxic contaminants
- Identity test - e.g., SDS-PAGE, Western blot, immunologic assay or amino acid analysis
- Purity - e.g., % moisture, SDS-PAGE, HPLC, endotoxin
- Potency - *in vivo* or *in vitro* test to assess immunogenicity, antigen content, or chemical composition
- Tests for removal of process contaminants

Stability

- Defines product shelf-life (1 – 2 yrs)
- Stable product needed for clinical trials
- Establish program to evaluate stability at specific time intervals
  - Potency
  - Moisture
  - Sterility

DNA Vaccines - Manufacture

- Process development and QC issues
  - Cell origin, genotype & phenotype
  - Genetic stability (WCB)
  - Source of process components
  - Process contaminants in final product
  - Adventitious agents (e.g., bacteriophage) in MCB & WCB
- Genetic characterization
  - Verify DNA sequence of entire vaccine (vector plus insert) present in MCB
  - Changes to insert gene or vector sequences
    - - additional preclinical studies or a new IND may be required

DNA Vaccines - Safety

- Local reactogenicity & systemic toxicity
- Nature of the immune response
- Tissue localization, persistence & integration
- Challenge/protection studies (demonstrate rationale for vaccine use)
- Prime/boost studies (support dose, schedule, route of each component)
- Cytokine expression (immunomodulation)

DNA Vaccines - Integration

- **Potential Consequences of:**
  - **Genome instability**
  - **Inactivation of specific genes (tumor suppressors)**
  - **Activation of dominant oncogenes by insertion of promoters/enhancers**
  - **Germline alteration**
- **Biodistribution - if no signal (plasmid <30,000 copies per µg host DNA) is detected at study termination (typically Day 60), an integration study is not required**

DNA Vaccines - Integration

- **Biodistribution studies might be waived for DNA vaccines:**
  - **When a novel, but related, gene is inserted into a plasmid vector previously documented to have an acceptable biodistribution/integration profile**
  - **If minor changes are made to the vector**

Live Attenuated & Vectored Malaria Vaccines

- Characterization of cell banks – draft guidance at http://www.fda.gov/cber/gdlns/vaccsubstrates.htm
- Contaminants (e.g., host cell proteins)
- Level of attenuation/reversion
- Neurovirulence or Tumorigenicity (some viruses)
- Adventitious agents (e.g., viral, mycoplasma)

Live Attenuated & Vectored Malaria Vaccines

- Dose & route of administration
- Immune status
- Person to person spread (shedding)
- Colonization & ease of elimination
- Survivability in environment

Vectored Malaria Vaccines

- Construct characterization
- Persistence of expression *in vivo*
- Safety of extended antigen expression (e.g., BCG vectors)
- Potency
- Transfer of antibiotic resistance
- Combination vaccine?

Device-Delivered Malaria Vaccine Issues

- Antigen dose/persistence
- Antigen delivery (bioavailability)
  - Substrate inertness
  - Antigen adsorption
- Vaccine denaturation
    - Molecular shearing/viscosity changes
- Contamination
- Cross-contamination of patients with disease agents

Plant-expressed Vaccines: Product Manufacture Issues

- Transgene/antigen stability
- Containment (APHIS/USDA permit may be required)
- Host cell protein contamination
- Post-translational modification: function, immunogenicity, neoantigen presentation
- Consistency, endogenous/adventitious agents, health status at harvest

Plant-expressed Vaccines: Oral Dosage Issues

- Consistency of dose
- Batch uniformity
- Allergenicity
- Antigen delivery (bioavailability)
- Immune tolerance
- Plant toxins, pesticides, herbicides, fungicides, & heavy metals
- Potency, stability, bioburden
- Packaging (but not labeling) – recommend also conforming to food regulations
- By-products intended for human or animal feed

Live Biotherapeutic

- Contains whole, live microorganisms such as bacteria or yeast, and
- Used with the intention of treating, preventing or curing a human disease or condition
- Product strains
  - Frequently isolated from healthy, human hosts
  - May be genetically modified/engineered
  - Generally proposed to colonize a mucosal site & interfere with growth of pathogenic organisms or stimulate other beneficial cellular processes there
- Includes “probiotics for clinical use”
- Regulated as a biological product

Adjuvants

- Adjuvant - An agent added to, or used in conjunction with, vaccine antigens to augment or potentiate (and possibly target) specific immune responses to those antigens.
- To date, aluminum compounds are currently the only adjuvants included in U.S.- licensed vaccines.
- Investigational: cytokines, montanides, oil-in-water emulsions, liposomes, QS-21, MPL, CpG.
- Specific vaccine/adjuvant formulation is licensed, not the adjuvant alone.
- Demonstrate the added value of the adjuvant in humans at an early stage of vaccine development

Non-Clinical Testing

GLP Preclinical Safety Assessment of Malaria Vaccines

- Evaluate antigen/adjuvant formulation that is representative of clinical lot
- Use clinical route of administration
- N + 1 doses
- Episodic dosing (e.g., weeks apart)
- Dose per injection ≥ intended human dose (as feasible)

GLP Preclinical Safety Assessment of Malaria Vaccines

- Body weight and food consumption
- Laboratory parameters
  - Serum chemistries
  - Hematology
- Local/systemic events
- Necropsy (histopathology)

Assays in Malaria Vaccine Development

Potency

- Specific capacity to effect a given result
- Often shows that a vaccine induces an appropriate immune response
- May not directly correlate with product efficacy
- Measured by *In vivo* or *in vitro* assays
- Measure of manufacturing consistency and stability

Examples of Vaccine Potency Assays

- Mouse immunogenicity assay
- Toxin neutralization
- Viable counts (cfu or pfu)
- DTH response
- Antigen content (ELISA, RIA)
- Saccharide/protein ratio – polysaccharide conjugates
- Chemical content
- Physico-chemical attributes

Assays in Malaria Vaccine Development

Importance of Assays:

- To assess product quality
- To detect vaccine-elicited immune response(s)
- To assess efficacy endpoints, e.g. define a disease case prevented by the vaccine
- Considerable R & D may be necessary
- Functional antibody assays (e.g., GIA, TBA/MFA, ADCI) may be needed in addition to binding alone (e.g., ELISA)

Assays in Malaria Vaccine Trials

- **Assay performance data**
  - **Specificity, sensitivity, ruggedness, reproducibility, e.g., procedures to minimize false positive PCR**
  - **Important for early trials**
  - **Critical for pivotal trials, e.g., efficacy trials (assay validation is critical)**
- **Typical results reported & analyzed as**
  - **Percent responders**
  - **Geometric Mean Titers (GMT)**

Malaria Vaccine Challenges

Malaria Vaccine Challenges

- Selection of safe and effective formulation
  - Choice of adjuvant, if needed
  - Single or multiple antigens
  - Antigens from a single or multiple stages of life cycle
- Selection of safe and effective dose & route of administration/regimen
- Phenotypic variation due to differential *var* (PfEMP1) gene expression
- Antigen polymorphism (e.g., MSP1)

Malaria Vaccine Challenges

- **Development of rapid diagnostic tests to supplement "gold standard" microscopy**
- **Insufficient suitable animal models of malaria infection/disease permissive for *P. falciparum***
- **Potential reduction in efficacy due to concurrent infection by different *Plasmodium* species or other pathogens**

Malaria Vaccine Challenges

- **Choice of appropriate comparator control group**
- **Lack of clear correlate(s) of protection**
- **Choice of appropriate case definition for malaria disease**
  - **High sensitivity**
  - **High specificity**
  - ***Low specificity dilutes efficacy estimates***

Malaria Vaccine Challenges

- Choice of appropriate efficacy endpoints
  - clinical disease of any severity
    - First episode
    - Multiple episodes
  - Severe malaria
    - First episode
    - Multiple episodes
  - Any infection
- Lower bound of 2-sided 95% CI for malaria vaccines should be well above zero

Acknowledgements

Norman Baylor
Douglas Pratt
Donna Chandler
Paul Richman
Herbert Smith
Wallace Adams
Steve Rosenthal
Loris McVittie
Paul Kitsutani
Leonard Sacks
Julie Vaillancourt
Karen Midthun
Nancy Miller
Steve Kunder
Karen Goldenthal
Christopher Joneckis
Joan Blair
Marion Gruber
Elizabeth Sutkowski
Von Nakayama
Paul Kitsutani
Janice Soreth
Jingyee Kou
Jennifer Ross
Patricia Rohan
Jesse Goodman
Joseph Toerner

Extra Slides

- **Additional information for your reference**
  - Regulation & vaccine development
  - CBER & OVRR organization
  - Statutes & regulations
  - IND - its role & common pitfalls
  - Meetings with FDA
  - Fast track
  - Priority review
  - Accelerated approval
  - Correlates of protection
  - Biologics License Application (BLA)
  - CBER international activities
  - Summary

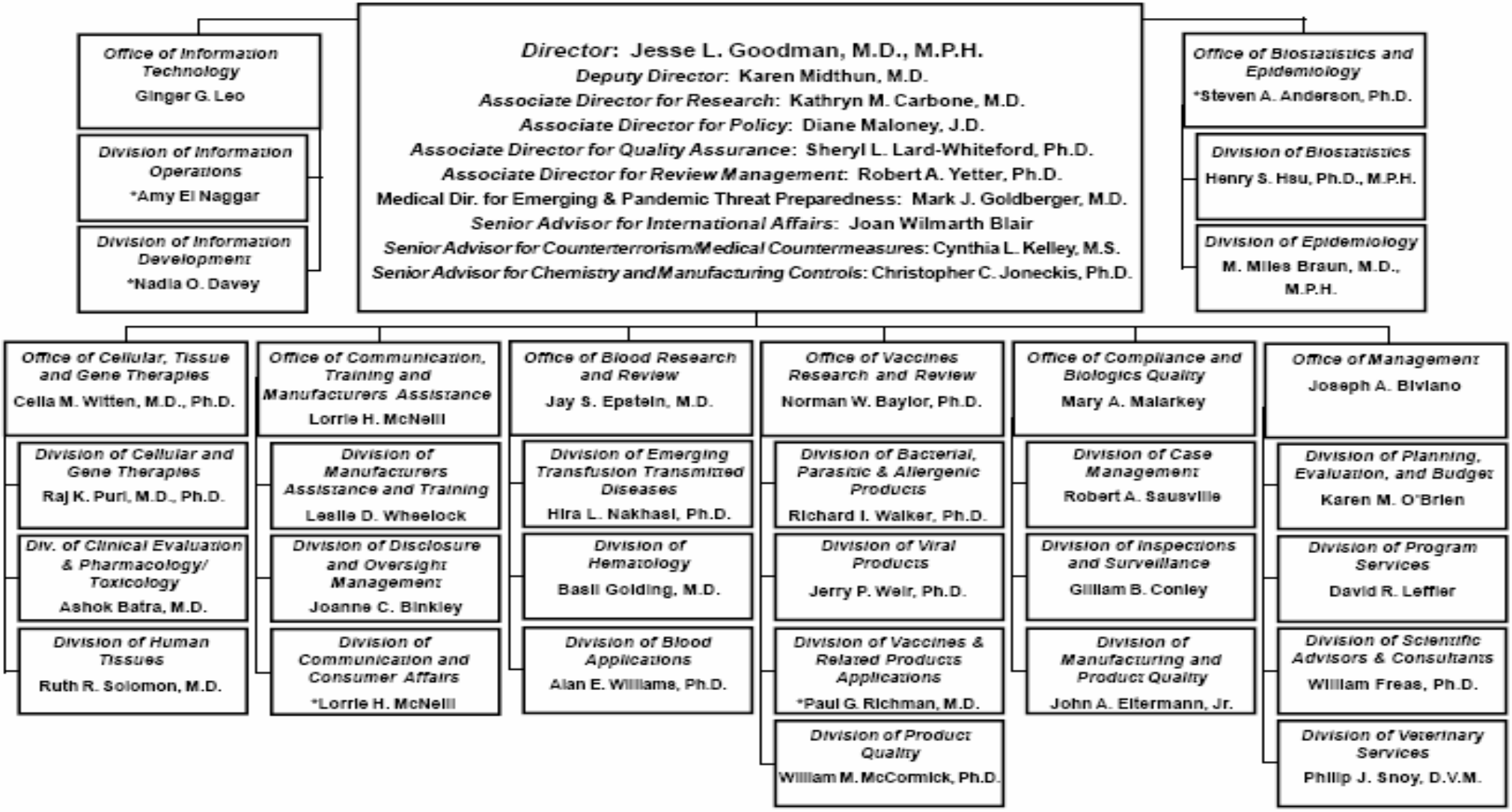
Regulation: What is the value added?

- Need for consistent and objective protection of the public's safety and need for trust
- Public expects safe and effective products, especially vaccines given to well individuals
- Preserving confidence in medical products and in public health leadership is critical

Vaccine Development

- The development of a vaccine is a complex process resulting in the licensure and commercialization of a product that has been demonstrated to be safe and effective and that can be manufactured in a consistent manner.
- The FDA is committed to fostering the efficient, rapid development of vaccines needed for the public health.

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH



*Acting

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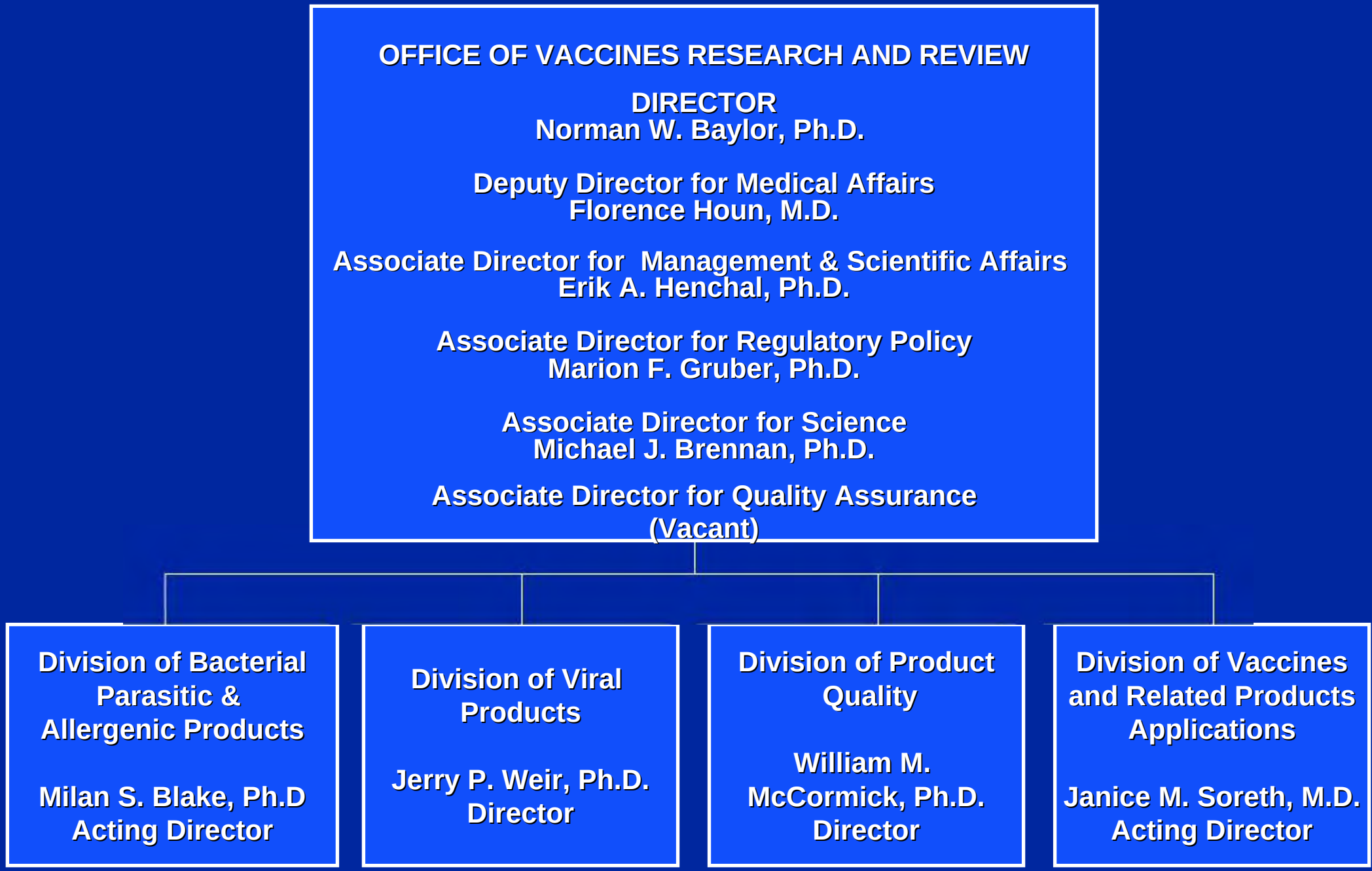
CBER's Office of Vaccines Research & Review

- Consists of ~300 regulatory and scientific staff
- One application division and three laboratory divisions
- Mission is to assure the purity, potency, safety, and efficacy of vaccines and related biological products
  - Preventive vaccines
  - Therapeutic vaccines for infectious disease indications
  - Toxins & allergenic products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Typical OVRR Review Team

- Regulatory Reviewer (Primary Reviewer)
- Clinical/Medical Officer
- Product Reviewer(s)
- Statistician
- Pharm/Tox Reviewer
- Others, as needed (e.g., cell substrate, assay validation, facilities)
- May need additional contact with CBER facilities staff (DMPQ/OCBQ/CBER)

Statutes

- Federal Food Drug & Cosmetic Act (21 USC 301-392)
  - FDAMA, November 12, 1997
- Public Health Service Act (42 USC 262 Section 351
- Code of Federal Regulations

Regulations

21 Code of Federal Regulations (CFR):

Part 600-680	**Biologics**
Part 312	**INDs**
Part 201, 202	**Labeling and advertising**
Part 210, 211	**cGMPs**
Part 800	***in vitro* diagnostics**
Part 25	**Envir. Assessments**
Part 50	**Informed Consent**
Part 54	**Financial disclosure**
Part 56	**Institutional Review Boards**
Part 58	**GLP-Nonclinical Lab Studies**

Stages of Review and Regulation

IND =Investigational New Drug Application; BLA=Biologics License Application

Pre-IND Information

- Manufacturing process
- Product characterization
- Preclinical/nonclinical animal toxicity studies for safety, immunogenicity
- Data to support the IND clinical studies, e.g., dose selection for initial Phase 1 study
- Focus: Initiate first Phase 1 clinical study
- Pre-IND meeting with FDA strongly recommended

IND Submissions – Common Pitfalls: Manufacturing

- Insufficient information
- Variable conditions
- Lot release test results lacking
- Potentially toxic substances - validation of removal or assay for residual component
- Adventitious agents - inadequate testing or inadequate information on source materials

IND Submissions - Common Pitfalls: Lot Information

- Lots not clearly identified
- Test results not submitted
- 21 CFR 312.23(a)(7)(i): assure proper identification, quality, purity and strength
- 21 CFR 610: potency, general safety, sterility, purity, identity
- Summary table - stage of manufacture, test, acceptance criteria, test result, data attached

Vaccine IND Submissions: Common Pitfalls: Preclinical

- **Preclinical Issues:**
  - **Pyrogenicity**
  - **Attenuation (live organisms)**
  - **Inactivation/reversion**
  - **Immunogenicity (potency) data lacking**
  - **GLP safety study (Phase 1)**
- **Experimental details lacking**
    - **Need information on lot, dose, route, assays to evaluate immune response**
- **Support dose proposed for clinical trial**

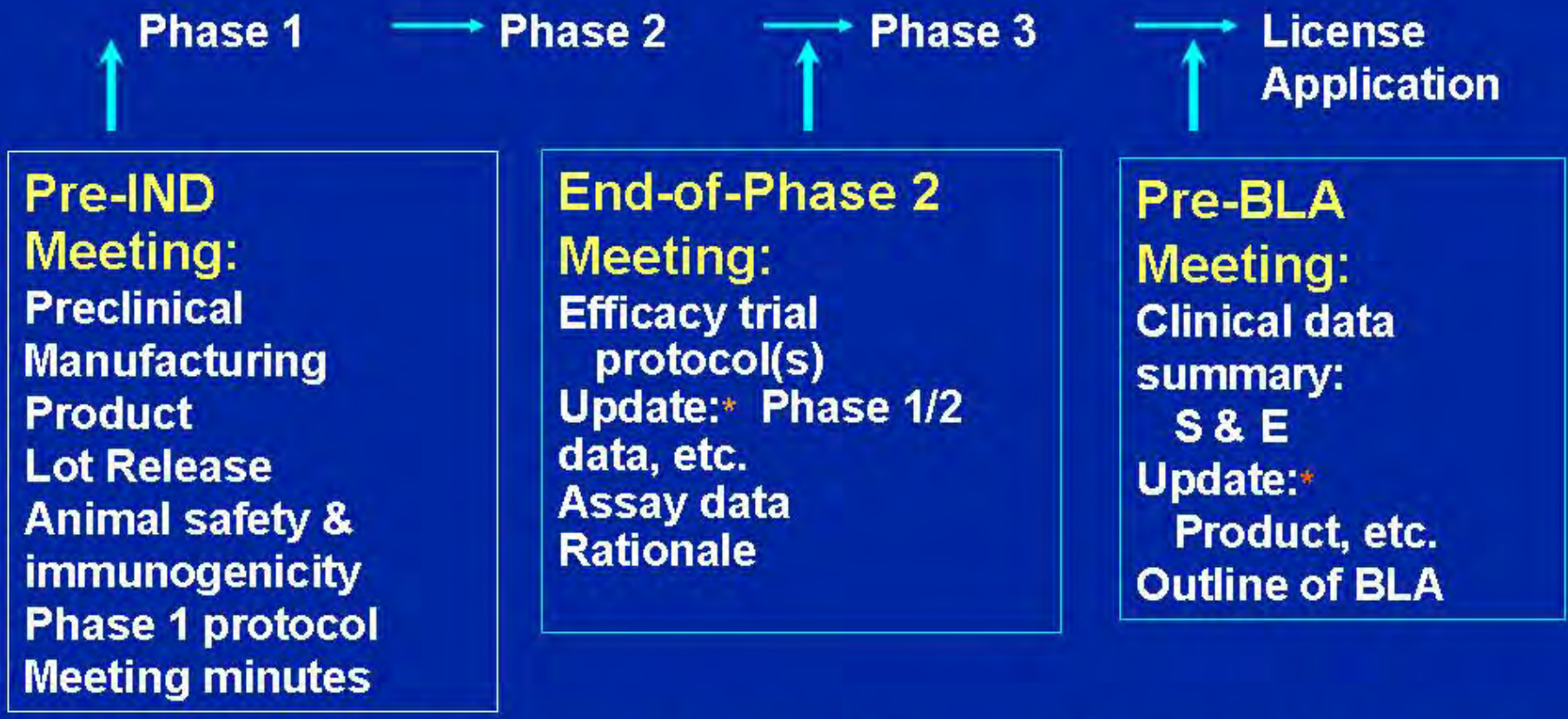
Vaccine IND Submissions: Common Pitfalls: Clinical

- **Protocol Issues:**
  - **Include subject diary card and case report form to document reactogenicity**
  - **Describe assays to evaluate immune response**
  - **Define clinical end point(s) & case definition**
  - **Describe statistical analyses & justify sample size**
  - **Inconsistencies**

Clinical Holds

- **Grounds:**
  - **Phase 1:**
    - **Unreasonable & significant risk**
    - **Clinical investigators not qualified**
    - **Inadequate investigator's brochure**
    - **Insufficient information to assess risk**
  - **Phase 2/3:**
    - **Same reasons for Phase 1**
    - **Protocol design inadequate to meet objectives**

Recommended Meetings with FDA



IND =Investigational New Drug Application
BLA =Biologics License Application

*Shouldn't be a surprise (e.g., pivotal data not seen previously)

Meeting with FDA

- Type A meeting-
  - necessary for an otherwise stalled drug development program to proceed
  - Dispute resolution, clinical holds, special protocol assessment
  - Held within 30 days of receipt of written request

Meeting with FDA

- Type B meeting
  - Pre-IND meetings
  - Certain end of Phase 1 meetings
  - End of Phase 2/pre-Phase 3 meetings
  - Pre-BLA meetings
  - Held within 60 days of receipt of written request

Meeting with FDA

- Type C meeting
  - Any meeting other than Type A or B between FDA and sponsor or applicant regarding development & review of a product
  - Held within 75 days of receipt of written request

The Need for Facilitated Pathways

- Emerging and re-emerging diseases (e.g., SARS)
- Pandemic strains of influenza
- Vaccine shortages (e.g., PCV-7, influenza)
- New vaccines of local and global public health importance (e.g., TB, malaria, HIV, HPV, rotavirus)
- Bio-terrorism agents (e.g., smallpox, anthrax, plague)

Approaches to Facilitate Product Development and Licensure

- Early and frequent consultation between sponsor and FDA
- Fast Track (e.g., Gardasil)
- Priority Review (e.g., H5N1 influenza vaccine & Gardasil)
- Accelerated Approval (e.g., FluLaval & Fluarix)
- Animal Rule
- Project BioShield Act of 2004
- Careful attention to risk/benefit and risk management issues
- Collaboration with WHO & others

Fast Track Drug Development

- Designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs.
- Intended to meet the need of Section 112(b) of the Food and Drug Administration Modernization Act of 1997.

Fast Track Drug Development

- Incorporates an end of Phase I meeting
- Allows for a priority review of the BLA; allows for a “rolling” review of the BLA
- Allows for an accelerated approval of the product

Priority Review

- 6 Month review of the entire BLA
- The review clock will not begin until the applicant has informed FDA that a complete BLA has been submitted
- Allows for a “rolling” review, i.e., review by segments of the application (CMC, statistical, clinical, etc)
- The pneumococcal conjugate vaccine, Prevnar, is an example of a vaccine that was given a priority review.

Accelerated Approval

- Approval based on a determination that the effect of a surrogate endpoint is reasonably likely to predict clinical benefit (21 CFR 314.510 & 601.41)
- Post-licensure studies required
- There may be problems obtaining subsequent controlled clinical data

Correlate of Protection

- A predictor of vaccine efficacy based on a particular type and quantity of immune response associated with protection from disease or infection.
- Allows an assessment of protection for an immunized individual.
- Correlate of protection useful for interpreting immune response data, e.g., “bridging studies” for change in manufacturing, populations, dosing.
- However, identification of correlate not a requirement for licensure (e.g., acellular pertusis, typhoid, tuberculosis [BCG])

Biologics License Application (BLA)

- Clinical Safety and Efficacy Data
  - BioResearch Monitoring Inspection
- Manufacturing
  - 21 CFR 600 (Biologics) & 21 CFR 210-211 (GMP)
  - Process and Quality Control
  - Consistency
  - Lot Release
- Facility(ies)
  - Pre-Approval Inspection
- Product Stability Data – Expiry Dating
- Labeling
- FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) Discussion

CBER International Activities

CBER International Activities

- WHO/PAHO Collaborating Center for Biological Standardization
- Cooperative relationships with Foreign Regulatory Agencies
- Non-Governmental Organizations
- International Conference on Harmonisation (ICH)
- Scientific Collaborations

WHO/PAHO

- As a Collaborating Center, CBER (OVRR and other Offices)
  - Provides scientific expertise in the development of WHO written requirements/recommendations (expert committees & working groups)
  - Participates in collaborative laboratory studies for establishing WHO biological reference preparations
  - Undertakes research & testing for improving the standardization & control of biological products used in humans
  - Provides training and inspection programs
  - Influenza vaccines

Foreign Regulatory Agency Cooperation

- Confidentiality commitments and cooperation agreements with strategic counterpart agencies
  - EMEA
  - PEI
  - Health Canada
  - Others
- Activities
  - Info shared on range of issues of joint interest: inspectional, investigational, licensure, post-marketing surveillance, etc.
  - Dialogue on scientific policy development

Non-Governmental Organizations

- Global Alliance for Vaccines and Immunization (GAVI)
  - Private Foundations, Government, WHO, Industry
- Bill and Melinda Gates Foundation

Research Collaborations

- **Institutional, e.g., Indo-US Vaccine Action Program**
  - **addressing vaccine needs in India (US lead = NIH)**
- **Individual research projects with foreign collaborators**

CBER Role - ICH

- CBER has seat at ICH Steering Committee
- CBER staff active in ICH working groups
- Although product scope of ICH guidelines are not explicitly for all CBER products, they are used when relevant, e.g. vaccines

CBER Role in International Vaccine Community

- FDAMA supports international harmonization
- Recognition of global context of the vaccine industry

CBER Position

- Global engagement is desirable
  - Passive role (accept decisions of the international community)
  - Active role (participate in the development of international standards and policies)
- CBER has chosen to participate actively
  - Has the appropriate expertise
  - Can help to develop science-based policies

CBER Position (2)

- **Harmonization efforts are many and varied – ranging from contributing to technical/science-based guidance documents, participating in WHO activities promoting improvements in NRAs, training, etc.**

Summary

- Licensed vaccines must be:
  - Safe and effective
  - Manufactured consistently under cGMP
  - Vaccine testing encompasses:
    - Product characterization
    - In process, lot release, and stability
- FDA facilitates development, licensure, and availability of new vaccines through development of
  - New Guidance
  - New assays and standards to evaluate safety, potency, quality
  - An integrated vaccine safety team and close collaboration with CDC and other partners

Summary

- However, sponsors must do their part
  - Propose well-designed non-clinical and clinical testing strategies
- Ongoing communication with FDA is critical
- Global collaboration with WHO and others to encourage international convergence and more efficient product development through development of scientific and regulatory standards for safety, effectiveness, and product quality

Available Resources

- FDA guidance documents, Federal Register notices, FDA regulations
- International Conference on Harmonisation (ICH) documents (U.S., E.U. and Japan)
- WHO Guidelines on Nonclinical Evaluation of Vaccines (recognized by CBER and EU)
- WHO Guidelines on Clinical Evaluation of Vaccines (recognized by CBER and EU)
- Sutkowski EM, Gruber MF: Regulatory Considerations in the Nonclinical Safety Assessment of Adjuvanted Preventive Vaccines. Immunopotentiators in Modern Vaccines, 2006, Academic Press

Available Resources

- Baylor NW, Midthun K: Regulation & Testing of Vaccines. Vaccines, 4th ed., 2004, WB Saunders
- Finn TM, Egan W: Vaccine Additives and Manufacturing Residuals in United States-Licensed Vaccines. Vaccines, 4th ed., 2004, WB Saunders
- Shapiro SZ: The HIV/AIDS Vaccine Researchers' Orientation to the Process of Preparing a U.S. FDA Application …Preparing for Your Pre-IND Meeting. 2002, *Vaccine* 20:1261-80
- Chandler D, McVittie L, Novak J: IND Submissions for Vaccines. Vaccines: From Concept to Clinic, 1999, CRC Press

Available Resources

- Intro to the regulatory process for investigators http://www.nihtraining.com/fdaTraining/index.html
- Web: www.fda.gov/cber/vaccine/vacpubs.htm
- www.fda.gov/cder/guidance/index.htm
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