Working with Center for Biologics Evaluation and Research

and

Suggestions for Successful Clinical Trials

Patricia Holobaugh

FDA Center for Biologics Evaluation and Research

Division of Inspections and Surveillance

Products Regulated by CBER

- Vaccines and Toxoids for immunization
- Allergenic extracts
- Somatic cell therapies
- Gene therapies
- In vitro diagnostics
- Devices
- Whole blood
- Blood components
- Blood derivatives
- Antitoxins, antivenoms, venoms
- Blood substitutes
- Tissues
- Xenotransplantation

History of Biologics Regulation

1901 – 10 children died from contracting tetanus from horse anti-diphtheria antitoxin

1902 – Biologics Control Act (later called Public Health Service Act)

- regulates sale of viruses, serums, toxins, analogous products
- authorized biologics regulations
- required licensing of manufacturers and establishments
- provided inspection authority

1903 – administered by Public Health Service Hygienic Laboratory

1906 – Food, Drug, and Cosmetic Act passed

1930 – PHS Hygienic Lab became NIH

1937 – NIH reorganized, Hygienic Lab became Division of Biologics Standardization

1972 – DBS transferred to FDA, became what is now called CBER

Unique Challenges for Biologics

- Must be processed under defined conditions/controls throughout production to consistently produce a safe, pure, and potent product and preclude the introduction of environmental contamination
- Cannot withstand heat sterilization – must be aseptically processed
- Stability is an issue – product may need frozen storage or preservatives. Shelf life may be limited.

Vaccines and Toxoids for immunization Allergenic extracts, Venoms

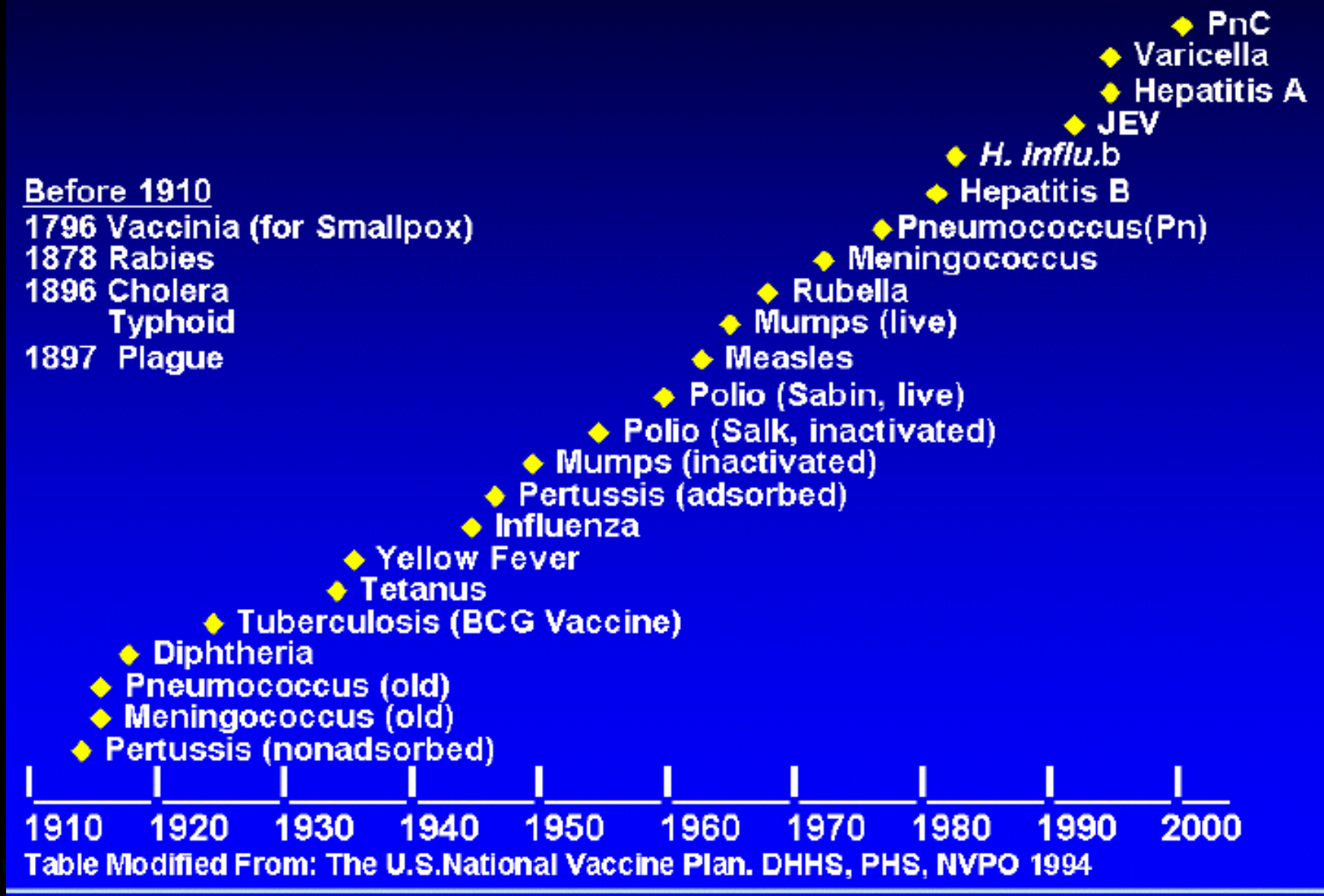
- These products are administered to millions of healthy people, including infants
- Safety is paramount
  - Safety for recipient
  - Safety for household contacts

Vaccines
Toxoids for immunization
Allergenic extracts, Venoms

- Starting materials may have inherent bioburden:
  - Egg-based vaccines
  - Starting materials may be infectious until inactivated (bacteria and viruses)

- From beginning to end, the process may take a year

Progress in the Availability of Vaccines



Progress in Vaccines 2001-2006

- Quadrivalent human papillomavirus (types 6, 11, 16 7 18) rec. vaccine
- Zoster vaccine, Live
- Rotavirus vaccine, live oral, pentavalent

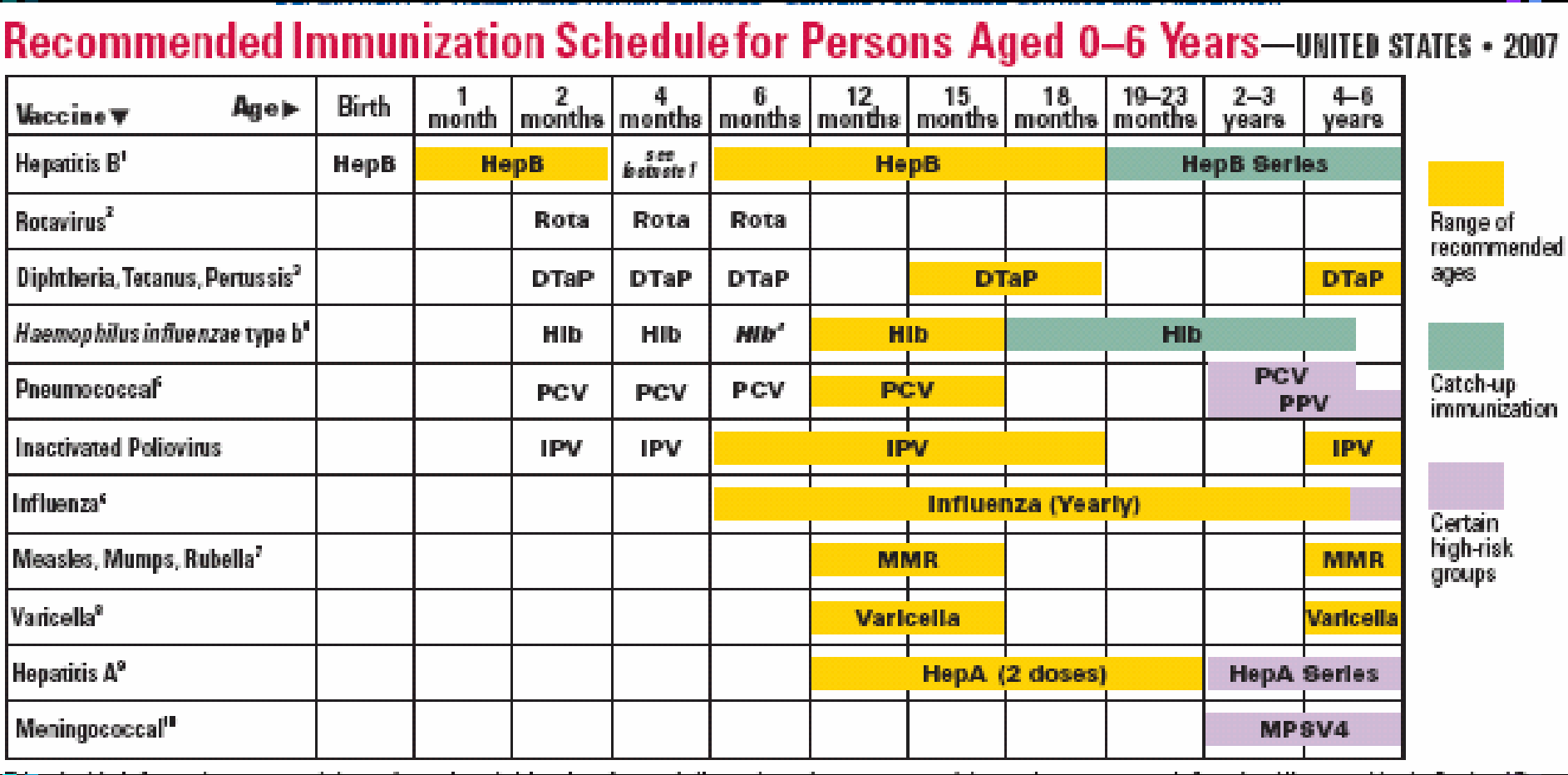
- Mening. polysaccharide diphtheria conj. vaccine
- Tetanus Toxoid, red. diphtheria toxoid & acell. pertussis vaccine (adsorbed)
- Influenza virus vaccine
- Measles, mumps, rubella & varicella virus vaccine live

- Tetanus & diphtheria toxoids (adult use)
- Influenza virus vaccine live, intranasal

- Diphtheria & tetanus toxoids & acell. pertussis vaccine adsorbed hepatitis B (rec.) & inactivated poliovirus vaccine combined
- Diphtheria & tetanus toxoids & acell. pertussis vaccine adsorbed

- Hepatitis A inactivated/Hepatitis B (recombinant) vaccine

http://www.cdc.gov/vaccines/recs/schedules/



Recommended Immunization Schedule for Persons Aged 0–6 Years—UNITED STATES • 2007

Vaccine ▼ Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB		see footnote 1	HepB				HepB Series		
Rotavirus[2]			Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP		DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	Hib[4]	Hib		Hib			
Pneumococcal[5]			PCV	PCV	PCV	PCV				PCV PPV	
Inactivated Poliovirus			IPV	IPV	IPV						IPV
Influenza[6]					Influenza (Yearly)						
Measles, Mumps, Rubella[7]						MMR					MMR
Varicella[8]						Varicella					Varicella
Hepatitis A[9]						HepA (2 doses)				HepA Series	
Meningococcal[10]										MPSV4	

Range of recommended ages

Catch-up immunization

Certain high-risk groups

http://www.cdc.gov/vaccines/recs/schedules/

Recommended Immunization Schedule for Persons Aged 7–18 Years—UNITED STATES • 2007

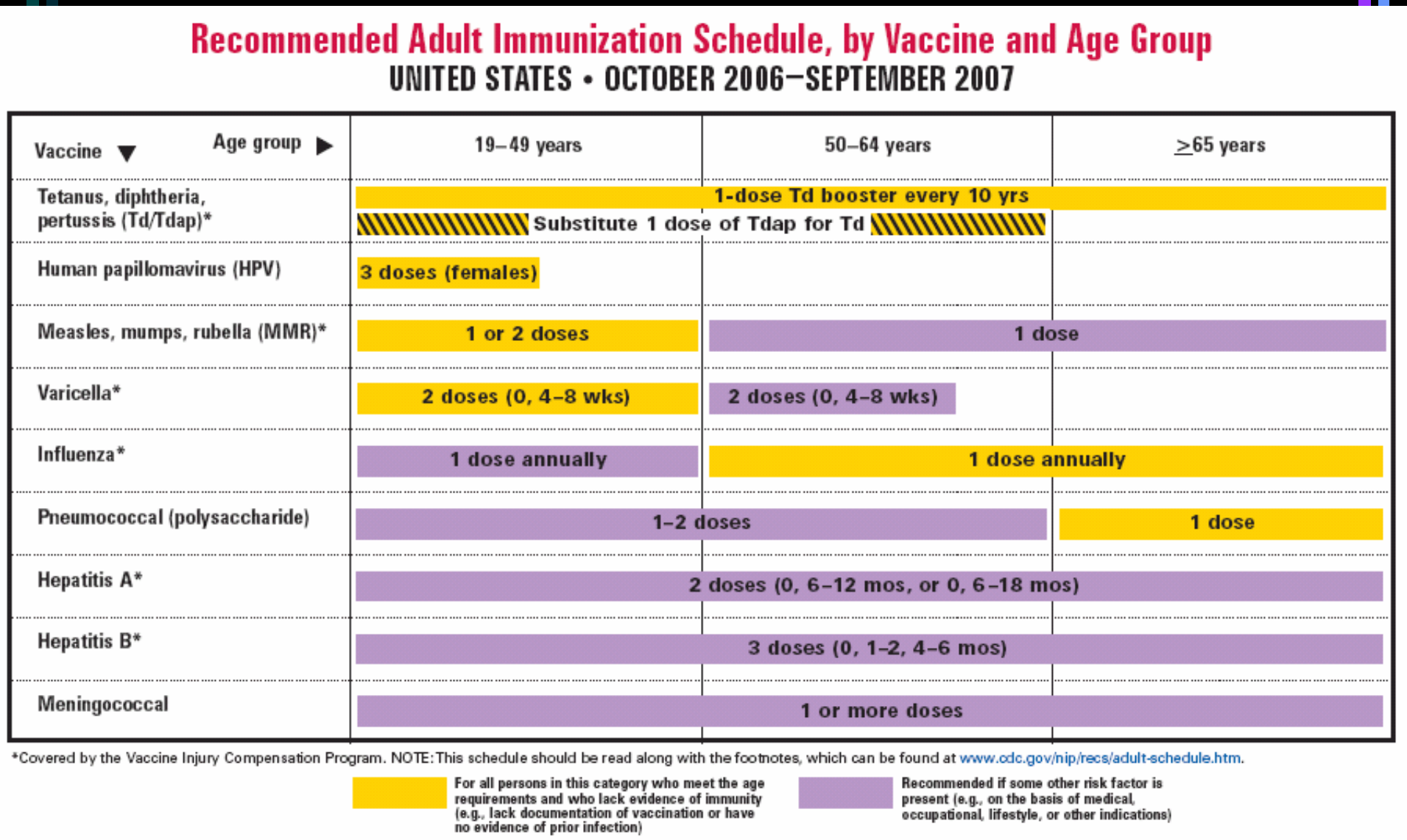
Vaccine ▼ / Age ▶	7–10 years	11–12 YEARS	13–14 years	15 years	16–18 years
Tetanus, Diphtheria, Pertussis[1]	see footnote 1	Tdap	Tdap		
Human Papillomavirus[2]	see footnote 2	HPV (3 doses)	HPV Series		
Meningococcal[3]	MPSV4	MCV4	MCV4	MCV4[3]	
Pneumococcal[4]	PPV				
Influenza[5]	Influenza (Yearly)				
Hepatitis A[6]	HepA Series				
Hepatitis B[7]	HepB Series				
Inactivated Poliovirus[8]	IPV Series				
Measles, Mumps, Rubella[9]	MMR Series				
Varicella[10]	Varicella Series				

Range of recommended ages

Catch-up immunization

Certain high-risk groups

http://www.cdc.gov/vaccines/recs/schedules/



Probiotics

Probiotics – “Live microorganisms which when administered in adequate amounts confer a health benefit to the host”

“Guidelines for the Evaluation of Probiotics in Food” Report of the Food and Agriculture Organization of the United Nations and the World Health Organization, May 1, 2002

An example of a probiotic dietary supplement is yogurt with live cultures

When products are used as drugs and need an IND

If intended to "*diagnosis, cure, mitigation, treatment, or prevention of disease in man*" then it is a drug and requires an IND.

If the product is administered any way other than orally it is a drug and requires an IND.

Examples of Studies that Require an IND

Probiotics:

* used to treat or prevent diarrhea
* administered with a catheter

CLINICAL TRIALS

Deaths Prompt a Review of Experimental Probiotic Therapy

The high death rate in a Dutch clinical trial is raising concerns about the use of friendly bacteria, or probiotics, in some patients. Researchers announced last week that in a trial to prevent infections in patients with acute pancreatitis, significantly more patients in the treatment group died than did those in the placebo group. Dutch authorities are now investigating whether the trial design was appropriate and whether probiotics pose any general risks.

In a press conference on 23 January, researchers from Utrecht University in the Netherlands said that 24 patients in the study's treatment arm died after receiving a mix of benign bacteria by feeding tube, compared with nine patients receiving a placebo. That positive effect on the health of the gut, in part by stimulating the immune system and in part by outcompeting pathogenic bacteria. Strains used as probiotics are typically those that inhabit a healthy gut, such as lactobacilli or bifidobacteria. They have been used to treat a variety of conditions, including allergies and some inflammatory diseases. They are also marketed as a food additive. Two preliminary studies had suggested that probiotics could be beneficial for patients with pancreatitis.

In 2004, the Dutch Acute Pancreatitis Study Group proposed a double-blind trial that would test the use of probiotics in 200 patients. Acute pancreatitis is a sudden inflammation of the pancreas, often seen in patients with alcoholism. A frequent complication is acute infection of the pancreas,

Whole blood
Blood components
Blood derivatives
Antitoxins, antivenoms

- For transfusion
- For manufacturing (example – clotting factors)
- CBER regulates cell separation devices and blood collection containers
- CBER establishes standards for these product
- FDA inspects blood establishments every two years, or more often if there are problems.

CNN.com - Artificial blood tested on patients without consent - Feb. 20, 2004 - Microsoft Internet Explorer provided by CBER

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HEALTH

Artificial blood tested on patients without consent

Friday, February 20, 2004 Posted: 9:27 AM EST (1427 GMT)

CHICAGO, Illinois (AP) -- Paramedics are testing an experimental blood substitute on severely injured patients without their consent in an unusual study under way or proposed at 20 hospitals around the country.

The study was launched last month in Denver and follows similar research that was halted in 1998, when more than 20 patients died after getting a different experimental blood substitute.

PolyHeme blood substitute is made by extracting hemoglobin from red blood cells and can be used in patients with any blood type, according to its maker.

Done Internet

Somatic cell therapies
Gene therapies

Cell therapies are products composed of human or animal cells, or from physical parts of those cells.

Gene therapies introduce genetic material into the body to replace a defective or missing gene, or to treat or cure a disease medical condition.

Somatic cell therapies

Cell therapies are often confusing for those who wish to develop their ‘Good idea.’

When is an IND needed? Sometimes sponsors guess incorrectly.

IRBs are sometimes confused about when a cell therapy study requires an IND.

Call matt@cber.fda.gov 800-835-4709 301-827-1800

When is a Cell Therapy IND Needed?

An IND is needed when cells are more than minimally manipulated

- FDA defines “minimal manipulation" as processing that does not alter the relevant biological characteristics of cells or tissues 21CFR1271.3(f)

  (*ex vivo* propagation, expansion, or pharmacological treatment of cells would be considered more than minimal manipulation)
- Cord blood for non-homologous use

- Cord blood that is more than minimally manipulated
  - Ex vivo expansion

Xenotransplantation

Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs.

In vitro Diagnostics Devices

- Test kits used to screen donor blood, blood components and cellular products, and to diagnose, treat, and monitor persons with diseases (HIV, hepatitis, etc.)
  - Coming? An OTC HIV test kit that gives the result at home??
- Devices used in collection, processing, testing, manufacture, and administration of licensed blood, blood components, and cellular components. Includes 510k blood establishment computer software.

Tissues

Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P.

bone tendons corneas oocytes semen

skin dura mater heart valves ligaments

hematopoietic stem/progenitor cells derived from peripheral and cord blood

CBER does not regulate the transplantation of vascularized human organ transplants such as kidney, liver, heart, lung or pancreas.

Tissues

May 25, 2005 – Parts 1270 and 1271 regulations went into effect for human cell, tissue, and cellular and tissue-based products (HCT/Ps). Tissue establishments must:

* screen and test donors

* prepare and follow written procedures to prevent the spread of communicable disease – Current Good Tissue Practices

* maintain records.

* register with FDA.

~ 2000 registered tissue establishments

After two scandals/criminal actions, FDA inspected 153 tissue establishments that found no additional violative firms.

FDA's Office of Combination Products

Determines which Center will have jurisdiction

- drug-device
  - *drug-eluting stent*
- device-biologic
  - *orthopedic implants with growth factors*
  - *devices delivering blood components*
  - *bandages delivering wound healing factors*
- drug-biologic
  - *monoclonal antibody-radionuclide*

Many Biologic Products Transferred to CDER in 2003

Monoclonal antibodies for in vivo use, therapeutic cytokines and growth factors, and toxins for therapeutic indications

CBER continues to regulate these products when they are used solely as an ex vivo constituent in a manufacturing process or used solely as a reagent in the production of a product that is under CBER's jurisdiction.

CBER Reviews Many Types of Applications

- BLA – Biologics License Applications
- PMA – Premarket Approvals
- 510k
- NDA – New Drug Applications
- Sponsors should contact CBER's Office of Communications and Manufacturer's Assistance for help deciding which regulations apply

matt@cber.fda.gov 800-835-4709

Countering Bioterrorism

CBER plays an integral role under the President's Initiative on Countering Bioterrorism.

GOAL - Expeditious development and licensing of products to diagnose, treat, or prevent outbreaks from pathogens

Smallpox, anthrax, plague, botulism, tularemia, hemorrhagic fevers.

2004 Flu Vaccine – Lessons Learned

The Silver Lining

Problems with flu vaccine supply resulted in:

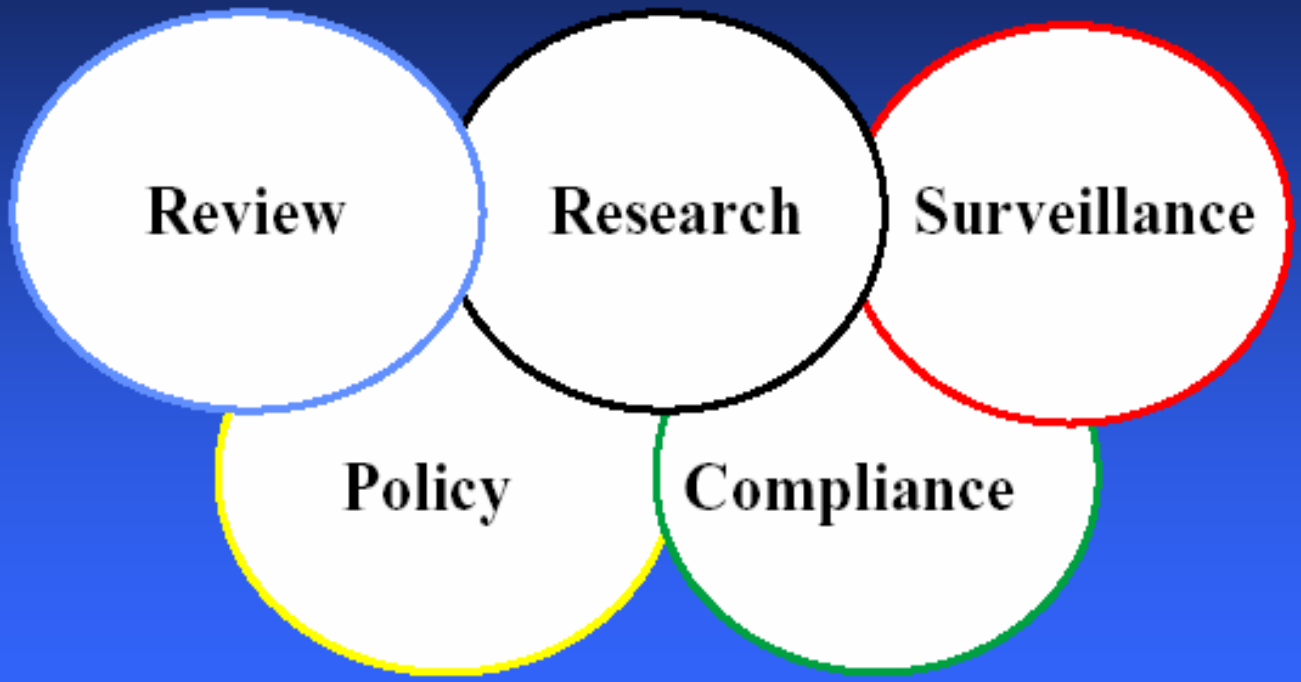
- A solid regulatory strategy to rapidly supply vaccine in case of an emergency
- Additional manufacturers seeking US approval
- Drawing of attention to importance of robust quality systems
- Highlighted the need to partner with our foreign regulatory counterparts

Meeting the Pandemic Flu Vaccine Challenge

- Increasing manufacturing diversity and capacity
- Developing needed pathways and regulatory processes to speed vaccine availability
  - Strain change, accelerated approvals on immunogenicity
- Assuring safety and public confidence
- Facilitating manufacturing and availability
- Considering pathways to prevent a pandemic
- Thinking and acting globally

CBER Regulation

Based on Sound Science, Law, and Public Health Impact



Surveillance of Product Safety

MedWatch

To report serious adverse events, product problems, or medication errors

- Voluntary for consumers and physicians
- Mandatory for drug/biologic manufacturers, distributors, and packers

Surveillance of Product Safety

Vaccine Adverse Event Reporting System (VAERS)

To report adverse events following vaccination.

- FDA and CDC
- Anyone can report to VAERS:
  - Health care providers, vaccine manufacturers, recipients or their parent/guardian, and state immunization programs.
  - www.vaers.org
- Not linked to Vaccine Injury Compensation Program

Surveillance of Product Safety

Biologic Product Deviation Reporting (BPD)

- Required for manufacturers of licensed biological products and for all manufacturers of blood and blood components.
- Must report errors and accidents that might affect safety, purity, or potency of a distributed product.
- Within 45 calendar days from date of discovery

Surveillance of Product Safety

Transfusion Related Fatalities and Donation Related Deaths

21 CFR 606.170 requires these to be reported. Initial notification may be by phone, fax, or email ASAP, followed by a written report within 7 days

CBER's Bioresearch Monitoring Branch

- Conduct pre-approval data audit inspections
- Investigate complaints
- Answer questions about Good Clinical Practices
- Help evaluate concerns about data integrity

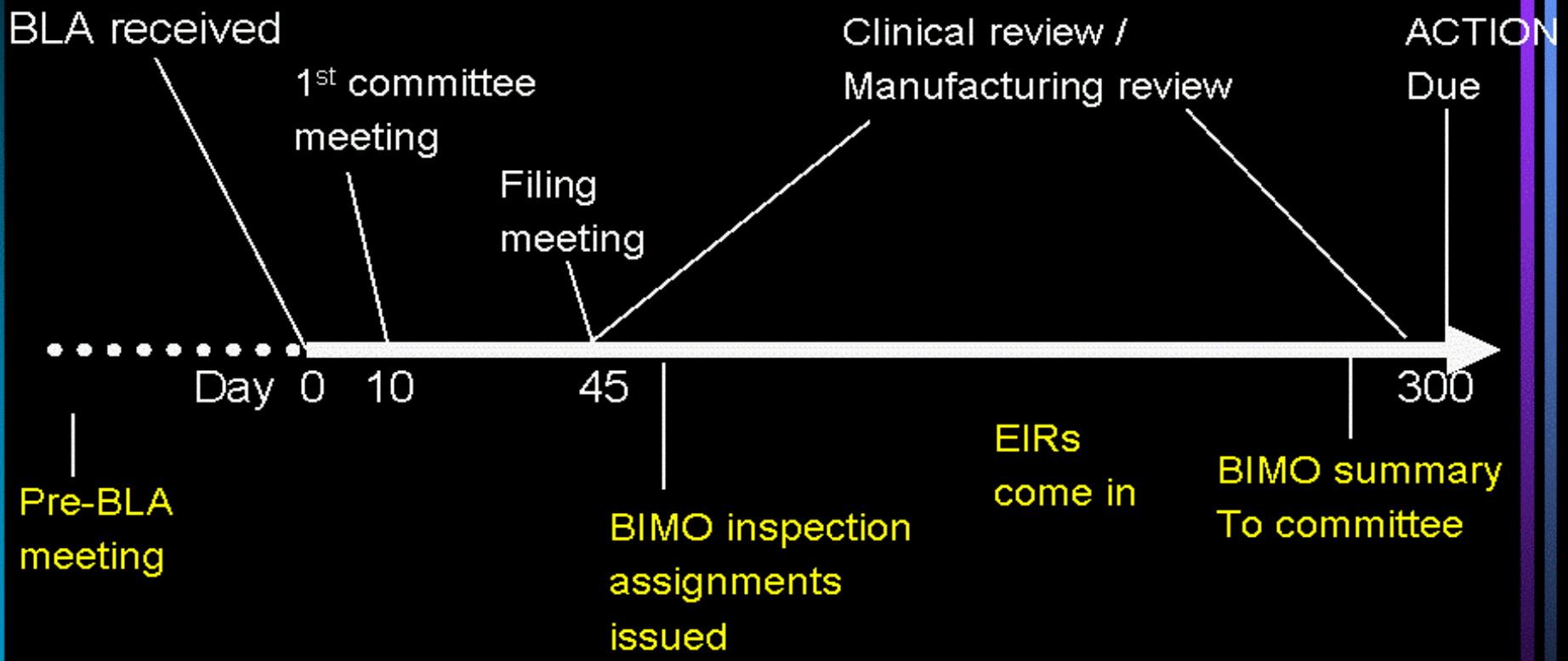
Clinical investigators

Sponsor/Monitor/CROs

IRBs

GLP/Nonclinical Labs

BIMO Milestones for Standard BLA



6-month Priority and PMA timeframes adjusted accordingly

CBER is assigning more inspections of ongoing studies under IND/IDE

"Real time" surveillance

- Cell therapies
- Gene transfer
- Vaccines
- Blood products
- Devices

Recent focus on studies enrolling pediatric subjects, and Flu

True or False???

Clinical investigator: “I’m only doing phase 1 and 2 studies – I’ll never be inspected by FDA.”

True or False???

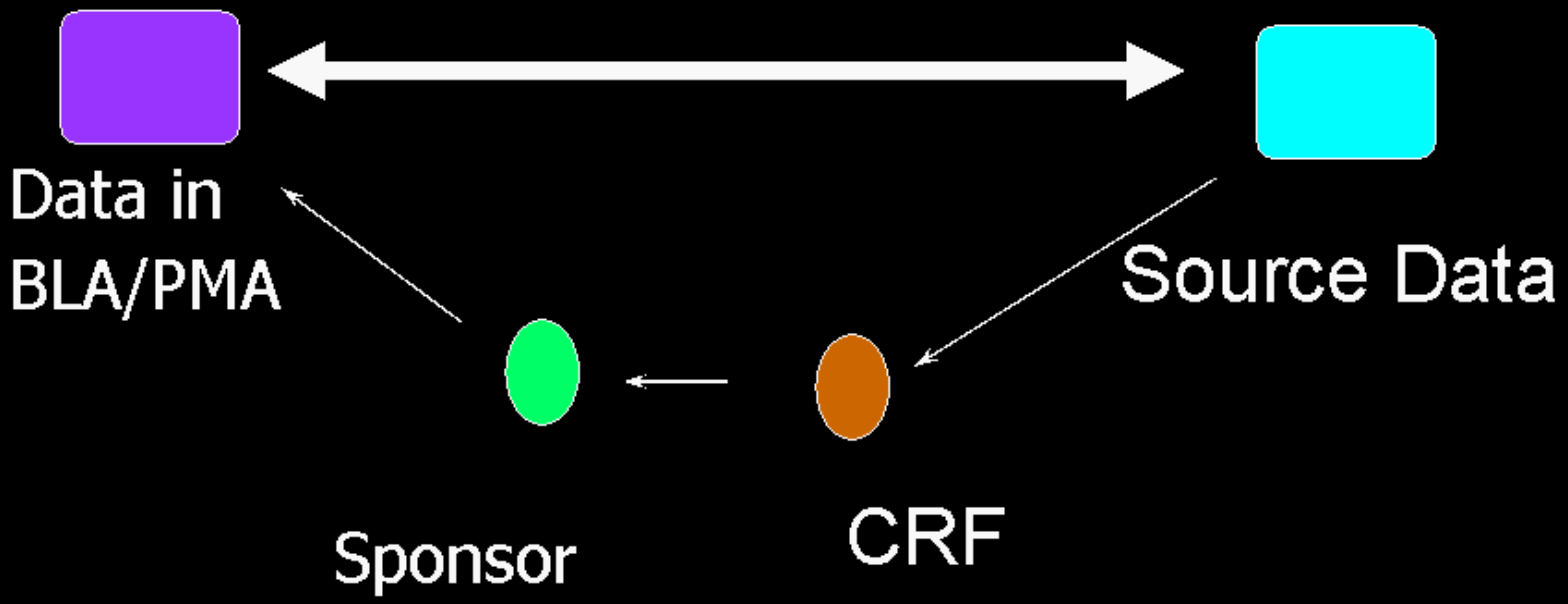
Clinical investigator: "I'm only doing phase 1 and 2 studies – I'll never be inspected by FDA."

FALSE

Clinical investigators of studies in all phases may (*and are*) inspected by FDA....

And ALL GCP regulations apply.

Comparison of Data in BLA / PMA to Source Data



CBER is expanding our inspections of clinical studies of blood *in vitro* diagnostics

Rapid kits to diagnose HIV in an individual

Diagnostic devices used to screen donated blood for blood supply

Preliminary findings:

- Higher rate of noncompliance by sites
- Lack of oversight by sponsors
- Lack of supervision by investigators
- Sponsors aren't checking on CRO activities

☹ Horror Stories ☹

Perform monitoring while critical activities are being performed.

We are hearing more reports of study staff lying about credentials and experience.

- ‘Nurse” with only high school degree
- Study coordinators fired from last 2 jobs for falsifying data

Are they now working with YOU???

Inappropriate delegation to subinvestigators

Investigator – individual who actually conducts an investigation (i.e., under whose immediate direction the drug is administered or dispensed to subjects.

**** How many miles (or states!) away ????

Sponsor must ensure that CI controls the study

***** BIG challenge for study coordinators and support staff

Suggestions to Prevent Noncompliance

- BEFORE -

- Understand what you are responsible for…

  …..And get training

- Document the delegation of duties

- Develop forms or checklists to make sure all screening tests and study visit activities are performed…*if not provided by the sponsor*

Suggestions to Prevent Noncompliance

- BEFORE -

- Develop a plan for organizing records
- Train study staff before the study starts….and train replacements when staff leave
- Don’t overextend to many concurrent projects
- Don’t take on satellite sites you cannot directly supervise

Suggestions to Prevent Noncompliance

- During -

- Track dates when reports are due to IRB and the sponsor
- Promptly report protocol violations to IRB and sponsor.
-
- Obtain written approval from the sponsor before you do something prohibited by the protocol

Suggestions to Prevent Noncompliance

- During -

- Verify that delegated duties are performed
- Work with monitors
- Correct small problems before they grow

Suggestions to Prevent Noncompliance

- *After* -

Organize the study records ---

- So non-study staff can find them
- To show what a good job you did
- To fulfill record retention requirements
- For possible FDA inspection

(years later - depending on the sponsor and phase of the research)

CBER is Here to Help You!!

www.fda.gov/cber

Email CBER :

Manufacturers: matt@cber.fda.gov

Consumers, health care professionals:

octma@cber.fda.gov

Phone: 800-835-4709 or 301-827-1800

CBER's Bioresearch Monitoring Branch

- Main phone 301-827-6221
- Branch Chief
  Pat Holobaugh 301-827-6347
  patricia.holobaugh@fda.hhs.gov
- FAX 301-827-6748