Regulation of Biologics in The United States:

From a Rich Tradition To A Challenging Future

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Presentation Overview

- History - A Rich Tradition
- History - CBER Update
- Current Approach to Regulation
- Challenging Future
- Scientific Research

History of Biological Products Regulation

1798 — Marine Hospital Service Original Public Health Agency

1800 — Smallpox Vaccination

1850 — Louis Pasteur (Rabies Vaccine)

1878 — Koch Isolated Anthrax Bacillus

1886 — Heat-Killed Vaccine

1887 — Public Service Lab Of Hygiene J. Kinyoun

1888 — Roux + Yersin (Diphtheria Toxin)

1890 — Antitoxins

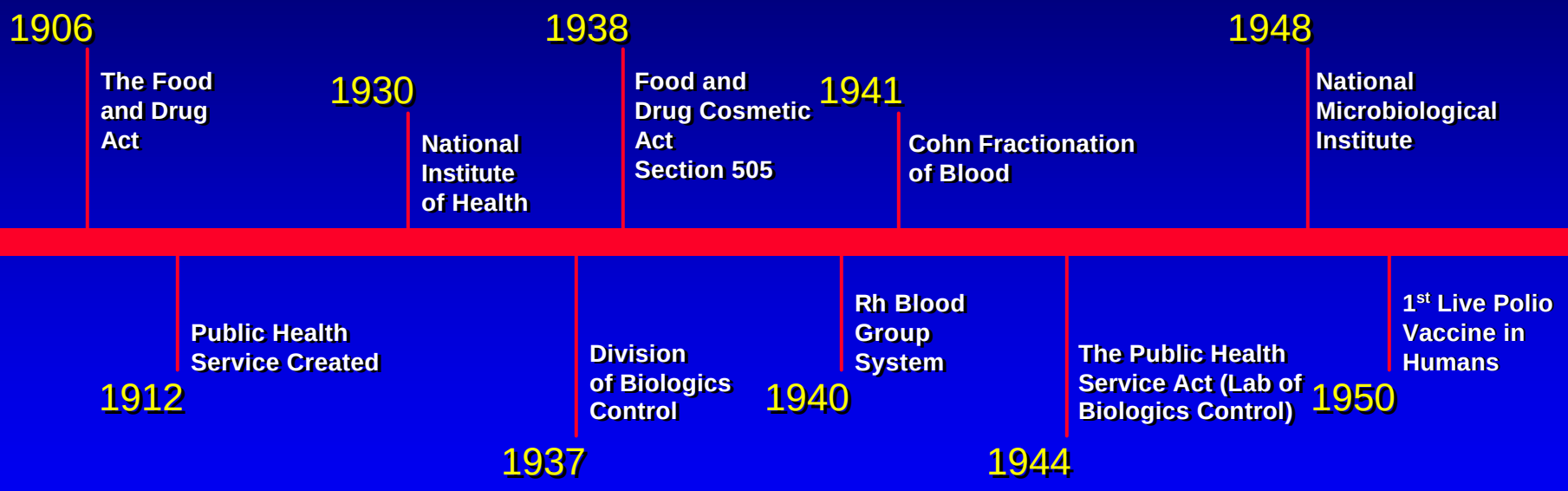
1894 — Public Health Labs Produce Diphtheria Antitoxin

1901 — 13 Children Died of Tetanus due to Contaminated Diphtheria Antitoxin

1902 — Biologics Control Act

100 YEARS 1902 2002 BIOLOGICS CONTROL ACT Commemorating 100 Years of Biologic Regulation

History of Biological Products Regulation (continued)



History of Biological Products Regulation (continued)

1955 — Cutter Polio Vaccine Incident

1962 — Kefauver-Harris Drug Amendment

1973 — New Provisions of PHS Act

1980's — Biotechnology Era

1988 — CBER Founded

1997 — FDAMA

2002 — MDUFA

1955 — Division of Biologics Standards (DBS) (NIH)

1972 — Division of Biologics Standards (NIH) to Food and Drug Administration (FDA) as Bureau of Biologics (BoB)

1982 — National Center for Drugs and Biologics

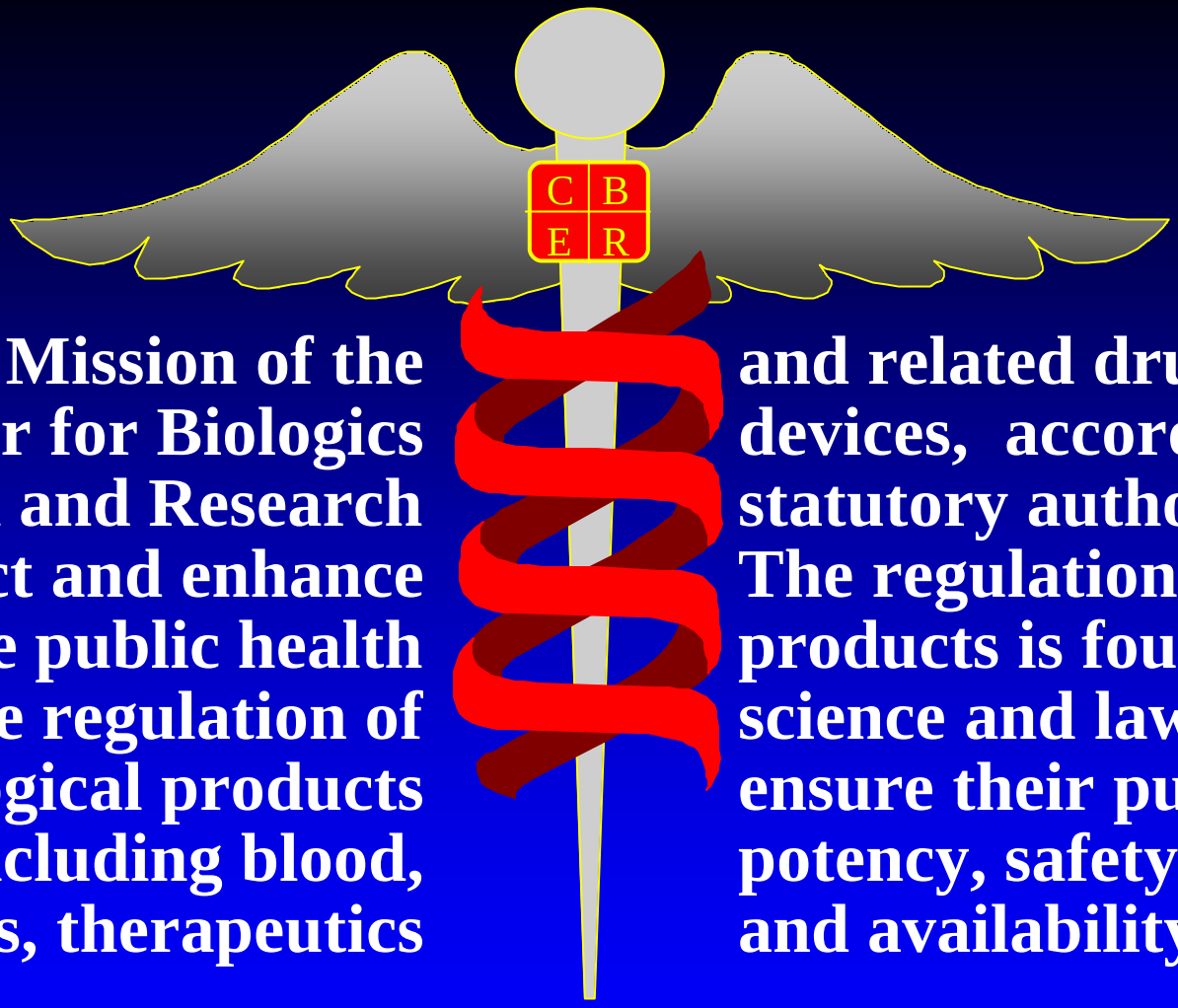
1992 — PDUFA 1, 2, 3

1997

2002

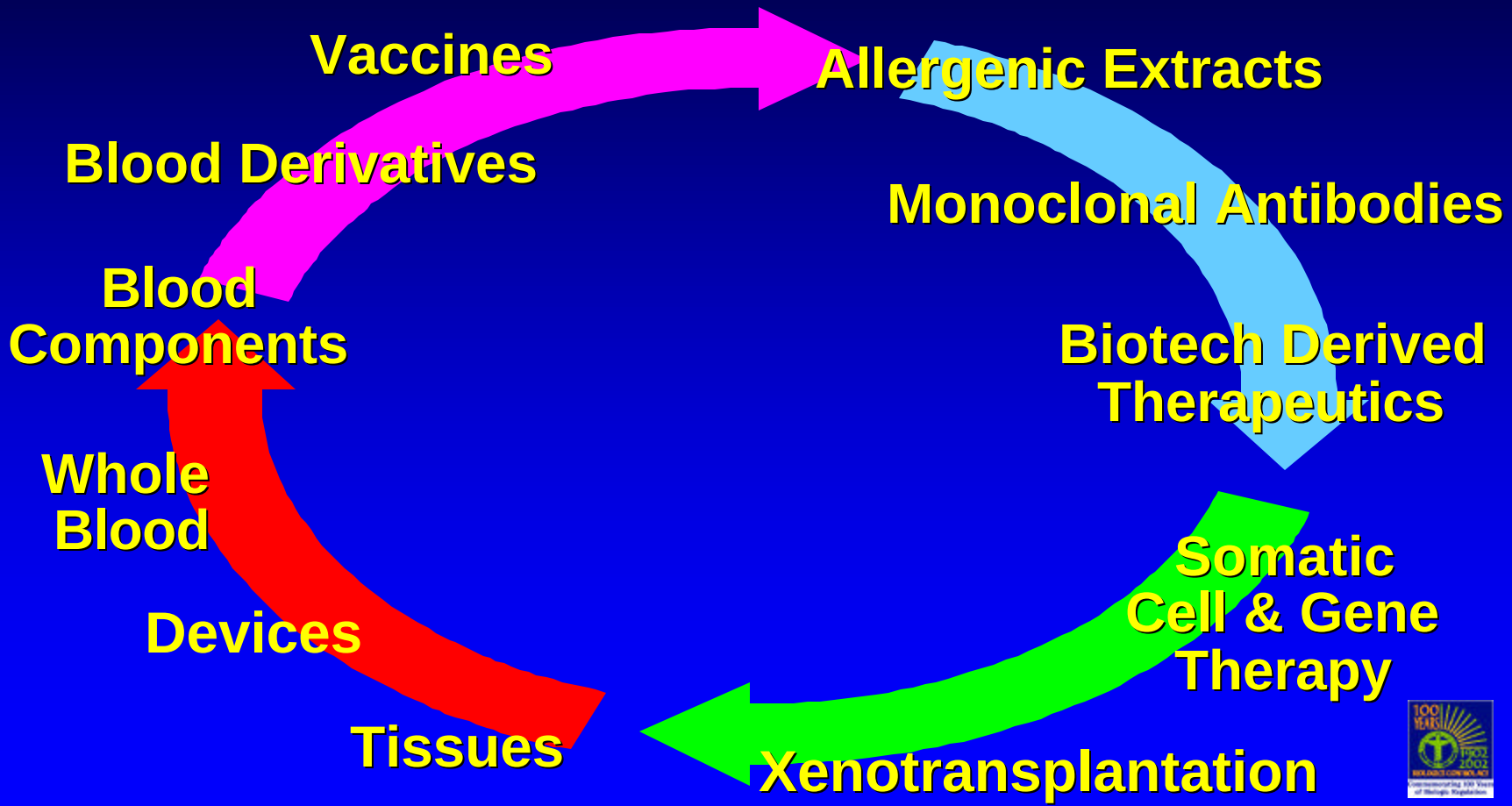
Historical Legacy

- Scientists regulated biologic products and are actively involved developing therapies
- Scientist conducted research on problems related to development, manufacture and testing of biologics
- Scientists conducted studies to assure safety, purity, and potency of biologic products, to improve existing products and develop new products.
- Emphasis on licensing/ inspection of manufacturing facilities
- Adverse public health events precipitate change/ regulation



The Mission of the Center for Biologics Evaluation and Research is to protect and enhance the public health through the regulation of biological products including blood, vaccines, therapeutics and related drugs and devices, according to statutory authorities. The regulation of these products is founded on science and law to ensure their purity, potency, safety, efficacy and availability.

Biological Products Regulated By CBER

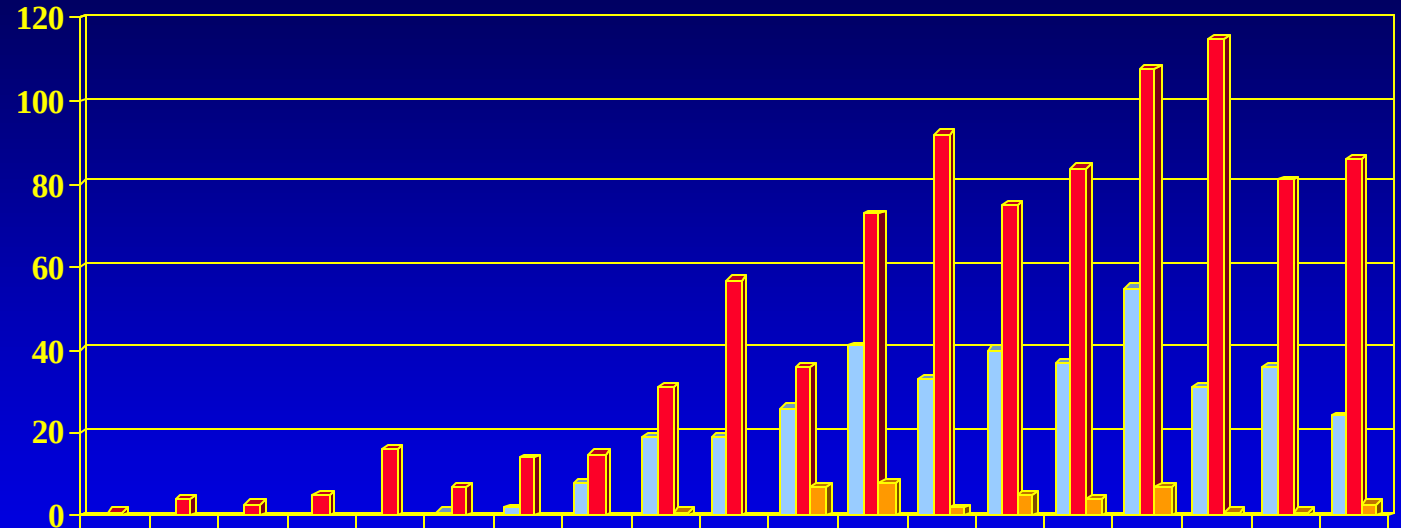


Office of Cellular, Tissue, and Gene Therapies (OCTGT)

- Increase in promise of, and resultant regulatory activities in, cellular and tissue-based products, gene therapies, xenotransplantation, unique associated reproduction
- Consolidation of products into one office
  - Increasing complexity of products
  - New scientific advances, unique safety issues
  - Need for creative clinical, regulatory and risk management approaches
  - Need for seamless and transparent coordination and communication

Gene Therapy, Somatic Cell Therapy, Xenotransplantation INDs/IDEs

Received FY 1984 - FY 2002



	FY84	FY85	FY86	FY87	FY88	FY89	FY90	FY91	FY92	FY93	FY94	FY95	FY96	FY97	FY98	FY99	FY00	FY01	FY02
GT INDs	0	0	0	0	0	1	2	8	19	19	26	41	33	40	37	55	31	36	24
SCT INDs/IDEs	1	4	3	5	16	7	14	15	31	57	36	73	92	75	84	108	115	81	86
Xeno INDs									1	0	7	8	2	5	4	7	1	1	3

Note: A total of 7 INDs were for Xeno and GT, and are included in the counts for both.

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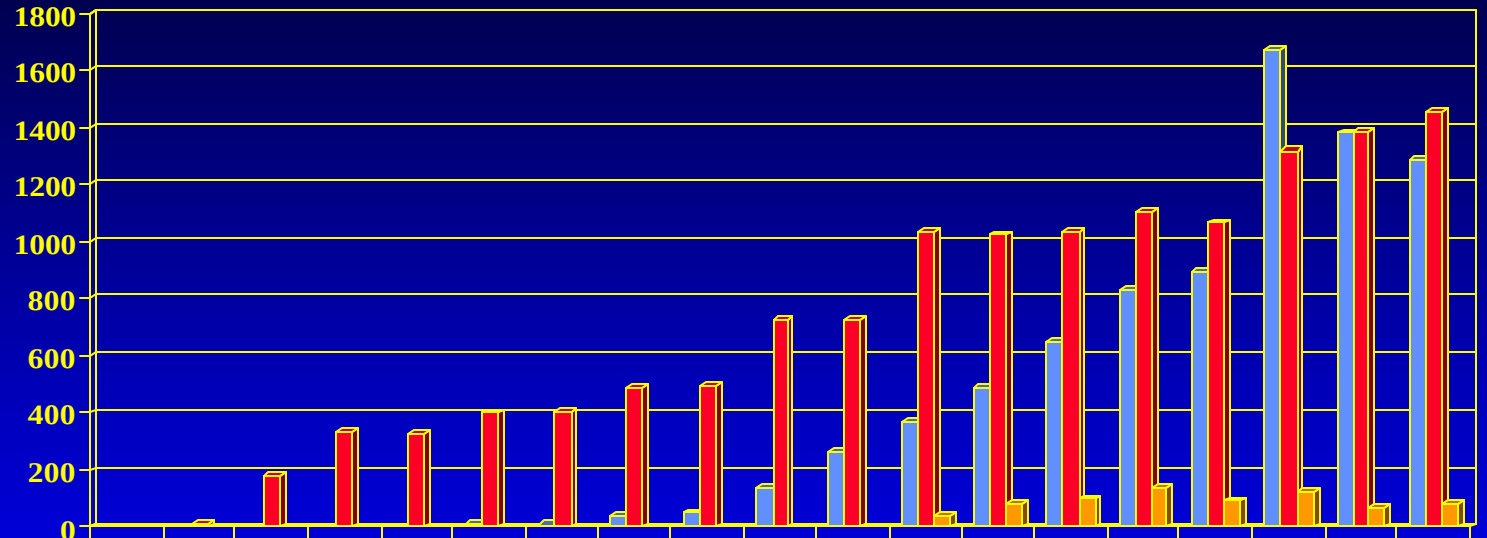
Gene Therapy, Somatic Cell Therapy, and Xenotransplantation IND/IDE Amendments

Received FY 1984 - FY 2002



	FY84	FY85	FY86	FY87	FY88	FY89	FY90	FY91	FY92	FY93	FY94	FY95	FY96	FY97	FY98	FY99	FY00	FY01	FY02
GT Amend's						13	12	40	54	137	268	369	488	650	834	892	1670	1378	1285
SCT Amend's	1	14	180	337	328	403	405	488	494	730	728	1033	1023	1036	1105	1068	1315	1386	1453
Xeno Amend's											3	43	82	103	139	96	124	68	82

Note: A total of 317Amendments were for INDs that are both Xeno and GT and are included in the counts for both..

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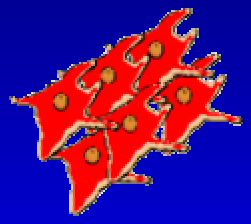
Biological – Medical Device Combination Products

Biological Products

Combination Products

Medical Devices



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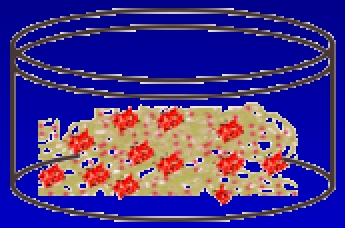
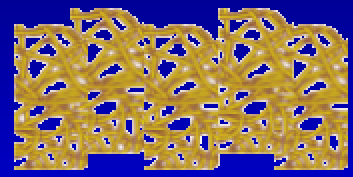
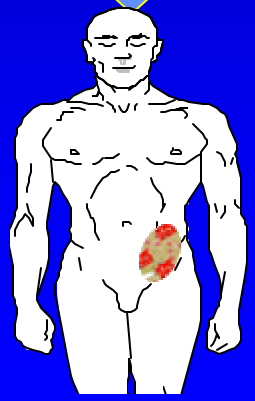
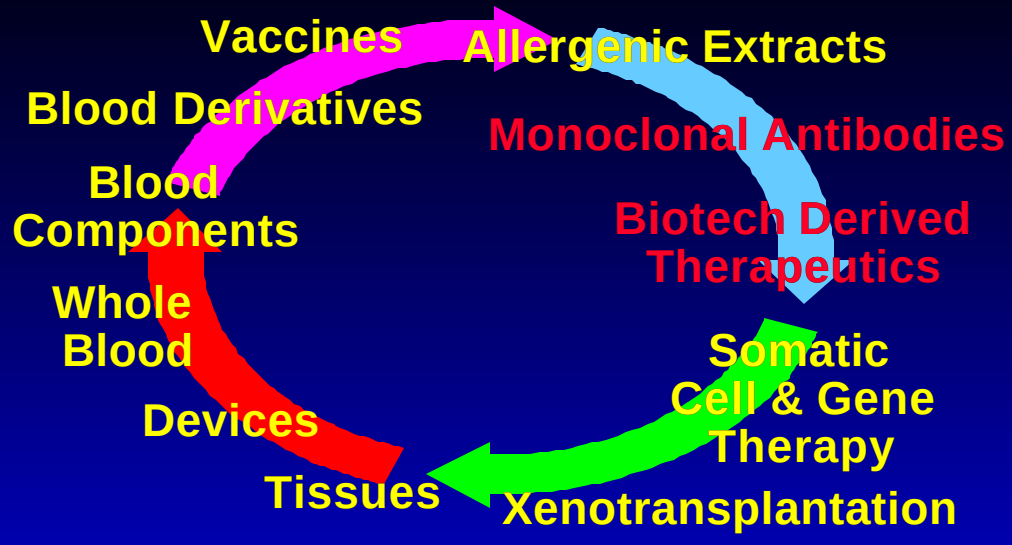








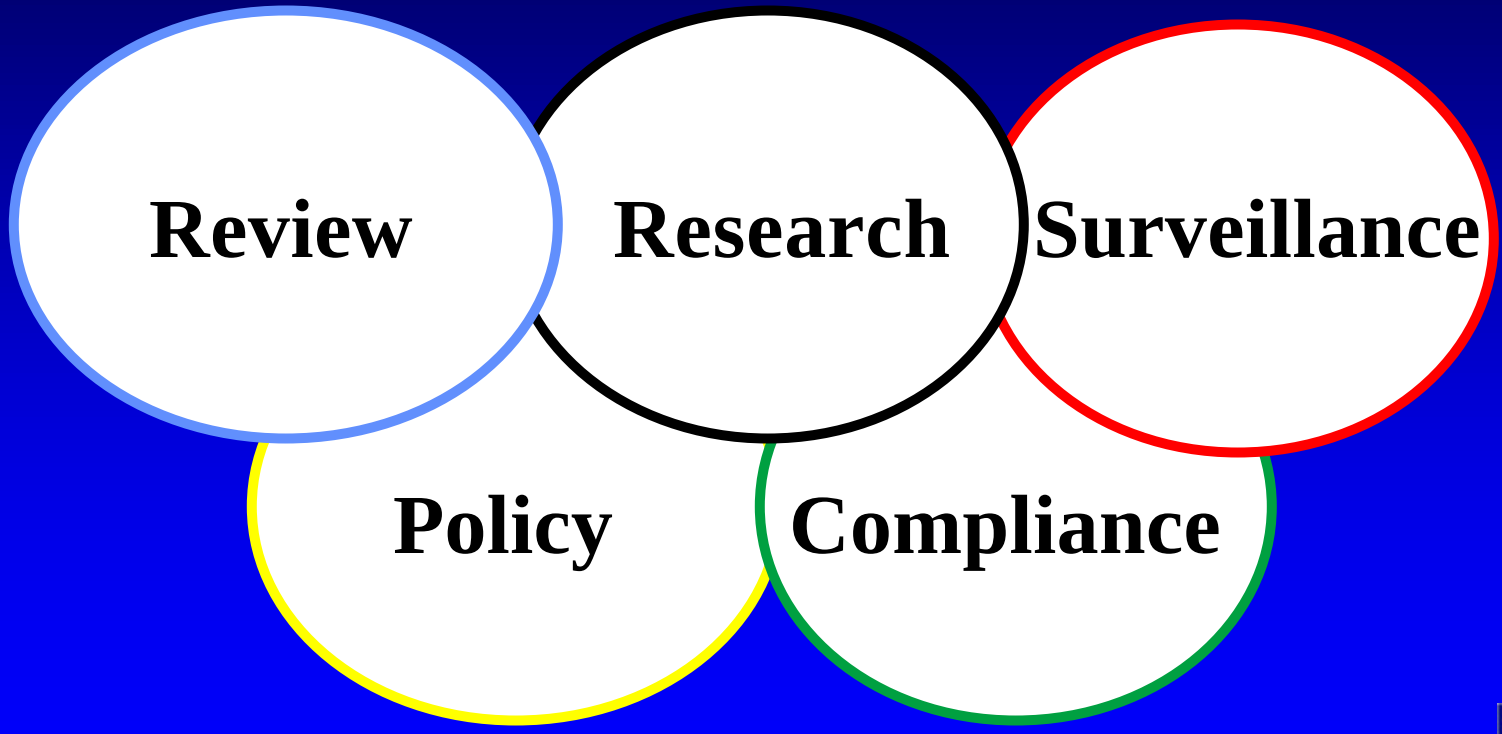
SOME PRODUCTS AT CBER

TODAY	TOMORROW
Monoclonal Antibodies	
Therapeutic Vaccines	Therapeutic Vaccines
rDNA Therapeutic Proteins	
Blood Derivatives and recombinant analogues	Blood Derivatives and recombinant analogues
Ancillary products	Ancillary products

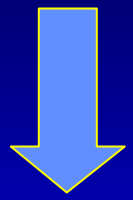
Current Approach To Regulation

Regulation of FDA Products

Based on Sound Science, Law, and Public Health Impact



FDA Policy Development



More focused
More specific

- Legislative Laws
- FDA Regulation - public rule making
- FDA Guidance - public notice and comment
  - Communicate CBER's current thinking on topic
  - Often provides acceptable approaches
  - However, alternate and acceptable approaches may also be used
  - *Option to submit draft guidance to FDA for consideration*

Policy Development

- Transparent Process & Opportunity to Comment
- Meetings
  - Public Hearings
  - FDA/ HHS Advisory Committees – focus specific products, specific concerns
  - Scientific Meetings/ Workshops – specific topic
- Scientific Research
- International component (e.g., ICH, WHO)
- Policy is revised as appropriate
  - Regulation and Rules – always open for comment

Product Development and Regulation

- GOAL: Balanced, flexible, responsive regulatory approach
  - Assure the safety and rights of subjects
  - Protect the public health
  - Not impede technological innovation & product development
- Influences
  - Available scientific knowledge, pre-clinical, clinical knowledge & experience
  - Crises/ tragic events
- Timing to develop policy, especially written policy
- **Appropriate Risk Assessment**

Gene Therapy Experience

- Increase in subject protection
  - Increased transparency on GT clinical studies
  - Investigator disclosure
  - Increased monitoring of clinical trials
- Described in IND “cGMP information”
  - An adequate QA/ QC program for manufacture of clinical gene therapy products
  - Description of segregation and cleaning procedures to prevent cross-contamination from production of multiple GT vectors in the same facility

Cells and Tissues

- Some Human Cells and Tissues and Cellular/ Tissue-Based Products – regulated by a fragmented approach
- Examples
  - musculoskeletal tissue
  - ocular tissue
  - cellular therapies
  - hematopoeitic stem cells
  - reproductive tissue
  - combination tissue/device; tissue/drug
  - human heart valves
  - dura mater

"New" FDA Approach to Regulation of Cells and Tissues - Tissue Rule (February 1997)

Objective

- Provide a unified, comprehensive regulatory framework
- Provide greater flexibility and innovation in this field of medicine
- Increased predictability of regulatory requirements
- Provide a tiered regulatory approach with the level of regulation proportional to the degree of risk

Five Areas of Regulatory Concern

- Preventing transmission of communicable disease
- Safe processing and handling
- Clinical safety and effectiveness, where appropriate
- Promotional claims
- Monitoring of industry

Product Characteristics

- Autologous vs. allogeneic
- Viable vs. nonviable
- Banked vs. unbanked
- Homologous vs. non-homologous function
- Minimal vs. more than minimal manipulation
- Structural vs. systemic function
- Combination tissue/device or tissue/drug

"Banked" Human Cells/Tissues Intended For Transplantation

- Tissue recovered, processed, stored, or distributed by methods not intended to change tissue function or characteristics
- Minimally manipulated, homologous use, metabolic tissue for self or close blood relative, or for reproductive use
  - Examples: bone, muscle, cornea, reproductive tissue, heart valves, dura mater and hematopoietic stem cells – (if minimally manipulated)
- Regulated only under communicable disease provisions of PHS Act ("361 Products")
  - Comply with Tissue Rule (Registration, GTP's, Donor Suitability)
  - Premarket approval not required, no submission

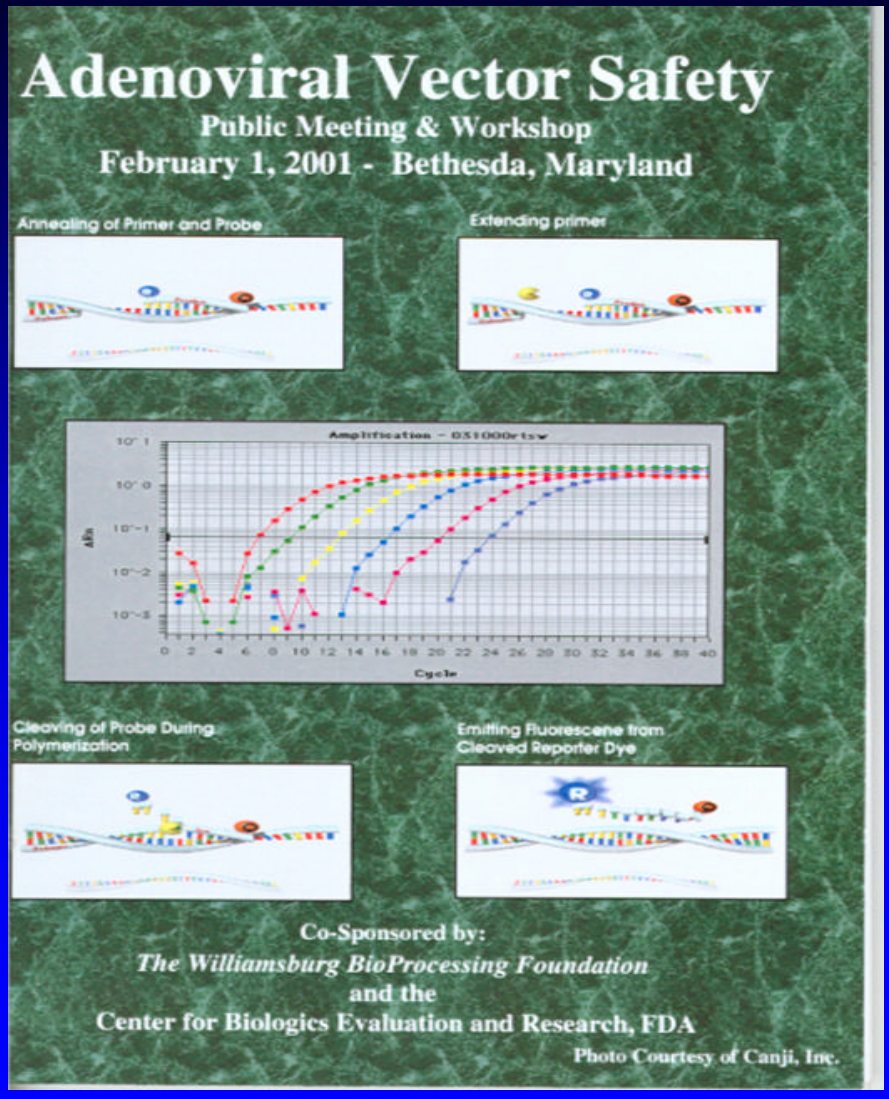
Cells & Tissues Regulated as Biologics or Devices

- The cells or tissues are:
  - Expanded, activated, genetically modified or encapsulated Non-normal/ Non-homologous use (ex: skeletal muscle in heart)
  - Clinical effect is systemic or dependent upon the metabolic activity of the cells for its primary function (e.g., pancreatic islets, hepatocytes, neurons)
  - Combined with another drug, device or biologic
- Regulated under more stringent safety and efficacy provisions of PHS Act (351) and FD&C Act (regulated as Biologic or Device)
  - Comply with Tissue Rule (Registration, GTP's, Donor Suitability)
  - Premarket review required – controlled clinical trials needed to demonstrate safety and efficacy.

Standards Development "Leveraging"

- Standards Organizations
  - Non governmental organizations (NGO)
  - Serve as facilitators to develop standards
- Identify Standard to be Developed
  - Participation by interested parties
  - Transparent Process
  - Agreement on "standard" reached by consensus
- Option for FDA to participate in development of standards
- Option for FDA to adopt standards

Adenovirus Vector Reference Material



Development of Adenovirus Vector Reference Material

- Issue – Determination of infectious particle/ dose of Adenoviral gene vector
- Workshop – participation by interested parties including industry & regulators
- Development of requirements for reference material – specified by FDA
- Open Bid for services to develop & test material
- Reference material manufactured and released
- Transparency of process and results
- *Reference: www.WilBio.com*

Challenges

CBER's Public Health Challenges

- Vaccine Safety and Availability
- Blood Safety and Availability
- Emerging Infectious Diseases
- Gene Therapy
- Xenotransplantation
- Human Tissues and Cell Products
- Counter-Bioterrorism
- New Technologies

Emerging New Technologies- Biomedical Research and Technology

- Proteomics
- Genomics
- Mass Spectroscopy
- Nuclear Magnetic Resonance Spectroscopy
- Plasma Resonance Spectroscopy
- PCR methods, e.g. MAPREC, TAQ-MAN

Application

- Product Quality
  - Complex Biological Product Characterization
  - Release Testing
  - Manufacturing process monitoring
  - Adventitious Agent Detection and Quantitation
  - Transitioning from Animal/Human Testing to Analytical, In Vitro, or Biochemical Testing
- Biological Assessments
  - Mechanisms of Immunity or Immunomodulation
  - Biological Responses
  - Mechanisms of Disease Pathogenesis
  - Mechanisms of Product Toxicity

The Future Challenges of New Technologies

- Quantitation
- Validation
- Robustness
- Standards
- Imagination and creativity in their application

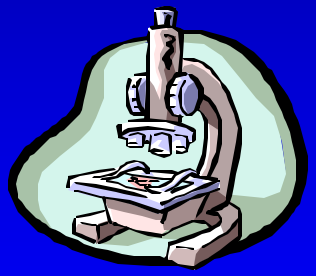
Scientific Research

Shepherding Safe and Effective Products

Regulatory Research

FDA

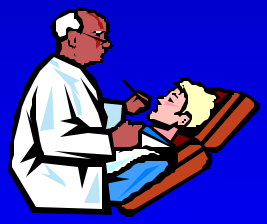
Bench



Translational Research

NIH
Academia
Industry

Bedside



Pharmaceutical Research

Industry

Marketplace

APPLIED
BASIC

SAFETY & QUALITY

Functions of CBER Research

- Encourages industry-wide adoption of new technologies
- Facilitates development of industry-wide standards and methods
- Contributes to improving existing products and developing new products
- Aids in recruiting and retaining excellent scientists

Other Approaches To Research
"Leveraging"

- Collaborative Research
  - CBER – NIH
  - CBER – Industry
- Pharmaceutical Quality Research Institute (Traditional Pharmaceuticals)
  - consortium of participants provide funding to research a specific issues
  - typically impacting on a regulatory issue potential for reduction in regulatory burden

CBER Available Documents

- On-line
  - –www.fda.gov/cber/publications.htm
- Outside US: 301-827-3844
- Email -Manufacturers assistance: MATT@CBER.FDA.GOV
- CBER Voice Information System at:
  - 1-800-835-4709 or 301-827-1800