CBER 2007

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Outline

- CBER Overview
- Cellular, Tissue, and Gene Therapies
- Blood
- Vaccines

Vision for CBER

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

- **Protect and improve public and individual health in the US and, where feasible, globally**
- **Facilitate development, approval and access to safe and effective products and promising new technologies**
- **Strengthen CBER as a preeminent regulatory organization for biologics**

Products Regulated by CBER

- Vaccines (preventative and therapeutic)
- Blood, blood components and derivatives
- Allergenics
- Cell and Gene Therapies
- Tissues
- Xenotransplantation Products
- Related Devices (including certain IVDs)

CBER's Biological Products: Unique Issues/Needs for Science

- Made using or derived from living cells, tissues, or organisms:
  - *Inherent risks from product (e.g. live vaccine) and/or contamination*
  - *Risk from new and emerging threats (natural, man-made)*
- Complexity of manufacturing facilities/materials, processes and products
- Multiple mechanisms of action (not always predictable)
- Highest public concern for safety of critical products given to healthy individuals – vaccines (235 million),

  blood (30 million), tissues (>1 million)
- Unique roles in health care and national preparedness (pandemic, war/disaster, counterterrorism)
- Market incentives and, as a result, infrastructure, frequently weak for preventive measures and for emerging technologies and diseases
- New technologies important– high visibility/interest and complex risks

CBER Organization

- Immediate Office of Director
- Office of Blood Research and Review
- **Office of Cellular, Tissue and Gene Therapies**
- Office of Vaccines Research and Review
- Office of Compliance and Biologics Quality
- Office of Biostatistics and Epidemiology
- Office of Management
- Office of Communication, Training, and Manufacturer's Assistance

FDA Collaboration/Outreach

- Product specific confidential enquires during pre-IND (IDE), IND (IDE) process
- Standards activities
- Guidance documents
- Advisory Committees: BPAC, TSEAC, CTGTAC, Vaccines, and Allergenic Products
- Site Visit Program (RSVP)
- Workshops
- Interagency and other collaborations Critical Path Initiative

Enhancing Product Safety

- *Integrated approaches* to early detection, analysis, action and communication
- Using all available technology, including health care databases
- Risk assessment/management and communication training plus special unit for complex issues/modeling

Office of Cellular, Tissue, and Gene Therapy

- Tissue and tissue based products
- Cellular therapies
- Tumor vaccines
- Gene therapies
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues
- Anti-idiotype antibodies

Human Cells, Tissues, or Cellular or Tissue-Based Products (HCT/Ps)

Brief History of Tissue Regulation

- First tissue rule published in December 1993 in response to infectious disease concerns
- Legal Authority: Section 361 of Public Health Service (PHS) Act—prevent the introduction, transmission, or spread of communicable diseases
- Approach to regulation of Human Cells, Tissues, or Cellular or Tissue-Based Products (HCT/P)
  - Tiered risk-based approach
  - Broad scope of cells and tissues
  - Implemented through rulemaking

Tissue Rules
21CFR1271, Effective May 25, 2005

- Establishment Registration
- Donor Eligibility
- Good Tissue Practices

- Not a premarket review program

“HCT/Ps”—Definition

- Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient

What is Included?
Human Cells, Tissues and Cellular and Tissue-based Products (HCT/Ps)

- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves
- Dura mater
- Reproductive tissue
- Hematopoietic stem/progenitor cells
- Other cellular therapies
- Tissue/device and other combination therapies

Not Included

- Vascularized human organs
- Minimally manipulated bone marrow
- Xenografts
- Blood products
- Secreted or extracted products; e.g., human milk, collagen, cell factors
- Ancillary products used in manufacture
- *In vitro* diagnostic products
- Blood vessels recovered with organs for use in organ transplantation

Current Activities

- Human Tissue Task Force (HTTF)
  - recent release of report with recommendations
- MedSun Tissue and Cell Pilot Project
  - surveillance for tissue & cell transplant adverse events
  - >50 hospitals, >100 hospital personnel trained
- Transplantation Transmission Sentinel Network (TTSN)
  - Tissue and organ common donor ID, adverse event reporting
- Collaboration with HRSA
  - Advisory Committee on Organ Transplantation, policy issues
- PHS Advisory Committee on Blood Safety and Availability
  - Expansion of Charter, includes tissues and organs
  - Biovigilance focus
- International efforts (Eustite, DGSanco, WHO)

Workshop

- Public Workshop: Processing of Orthopedic, Cardiovascular, and Skin Allografts October 11-12, 2007
- http://www.fda.gov/cber/meetings/allog101107ag.htm

Guidance

- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products 2/27/07

Cellular Therapies

Cells: Examples of Indications/Sources

- Pancreatic islets for diabetes
- Stem and skeletal muscle progenitor cells for ischemic cardiac disease
- Hematopoietic reconstitution in treatment of malignancies
- Stem cells for metabolic storage diseases
- Stem cells for CNS indications (Parkinson's disease)
- Expanded autologous cartilage for joint repair

Cellular Therapies: Challenges

- Autologous/allogeneic
- Single (or small) lot
- Cell banks (limited size and cell passage)
- Characterization/biological activity
- Contaminating cells
- Adventitious agents
- Cell fate post transplant

Outreach and Collaboration with Cellular Therapy Community

Conferences and Workshops

- 7th Annual Somatic Cell Therapy Symposium. (September 26-28, 2007) Co-sponsored by ISCT, FDA, AABB
- Bringing Therapeutic Cancer Vaccines and Immunotherapy Through Development to Licensure. (February 8-9, 2007) Co-sponsored by NCI and FDA

Liaison & MOU Activities

- Cell Therapy Liaison Group
- Islet Cell Resource Consortium
- NINDS
- NIH Human Embryonic Stem Cell Task Force

Cellular Therapies: Recent Draft Guidances

- Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs) 7/23/07
- Draft Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage 7/6/07
- Draft Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies 1/16/07

Gene Therapy Characterization and Safety

Gene Therapies

- Transferred directly to the subject or ex vivo modified cells administered to subjects
- Gene Therapy Vectors
  - Plasmid
  - Adenovirus
  - Adeno-associated virus
  - Retrovirus & Lentivirus
  - Poxvirus
  - Herpesvirus
  - Bacteria

Special Considerations for Gene Therapy

- Vector Toxicity-inherent risk for some vectors
- Potential to permanently modify genome
  - Risk of uncontrolled transgene expression
  - Insertional Mutagenesis
  - Germline alteration-risk to future generations
- Potential to spread viral vectors from patient to the environment
  - Medical professionals
  - Household members
  - Public at large

Outreach, collaborations, scientific discussions

- NTP study to assess preclinical safety model for retroviral vector-mediated insertional tumorigenesis
- NIH Recombinant DNA Advisory Committee
- ICH Gene Therapy Discussion Group
- WHO Monitoring Group on Gene Transfer Medicinal Products

Guidance

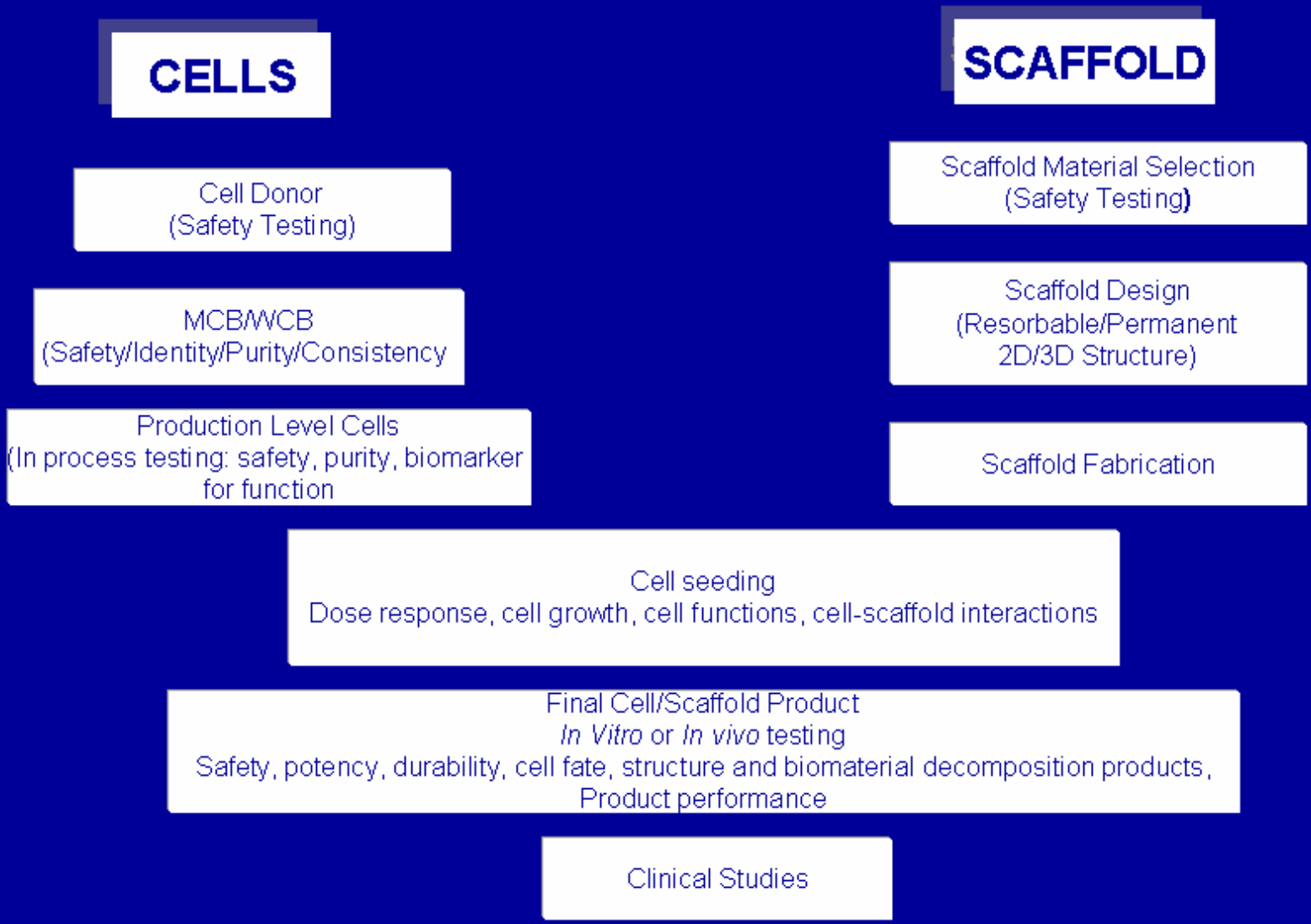
- Guidance for Industry: Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events 11/28/06
- Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors

Reference Materials

- **Retrovirus reference material**
- **Adenovirus reference material**
- **RNA spike-in controls**
- **Fluorescent standard solution**
- **Fluorescent microbead standard**

Cell-Scaffold Products

Cell Scaffold Products: Characterization and Safety



Regulation of Regenerative Medicine Products

- Guidances for Cellular, Gene Therapies, and Devices
- Leveraging existing guidances to support specific areas of tissue engineered medical products
  - CMC guidances for cellular products
  - General (CT and GT) preclinical guidances
  - Guidances for devices may be applicable to scaffolds
  - Many clinical guidances cross-cut product areas

CBER/CDRH Tissue Engineering Cross-Center Teams

- Facilitate intercenter co-operation and solutions of TE issues
- Provide a core resource of TE review expertise to CBER, CDRH, OCP
- Participate in development of regulatory policy and pathways
- Facilitate FDA participation in Standards Organizations
- Provide a strong, consistent FDA voice in outreach activities with academia, industry, other governmental programs
- Provide an educational resource for reviewers within CBER and CDRH

Collaboration and Outreach

- MATES/Strategic Plan
  - http://tissueengineering.gov/welcome-s.htm
- FDA/NIST Workshop: "In Vitro Analyses of Cell-Scaffold Products" December 6-7
- Liaison meeting with Tissue Engineering Regenerative Medicine Centers
- ASTM TEMPS

Upcoming FDA Public Workshops

- **Processing of Orthopedic, Cardiovascular, and Skin Allografts**
  - **October 11-12, 2007**
  - **NIH, Bethesda, MD**
  - **http://www.fda.gov/cber/meetings/allog101107.htm**
- **In Vitro Analyses of Cell/Scaffold Medical Products**
  - **December 6-7, 2007**
  - **NTSB Conference Center, Washington, DC**
  - **http://www.fda.gov/cber/meetings/invitro120607.htm**

Blood, Blood Components, Blood Derivatives, and Related Products Regulated by CBER

- Blood and plasma components
- Plasma derivatives
- Donor screening tests to prevent infections
- Blood grouping reagents to assure safe transfusion
- Devices used in collection, storage and processing
- Blood bank and related computer software
- HIV diagnostic tests

The Challenge for Blood Products

Enhance Product Safety, Purity and Potency

and

Avoid Product Shortages & Major Increased Costs

Protect and improve blood safety, efficacy and availability while working to prevent disruptions to the blood supply

- Newly formed CBER-wide Blood Safety Team to enhance timely & medically sound evaluation of epidemiological information, BPD reports, potential shortages, and other intelligence

Hot Topics Related to Blood and Tissue Safety

- Guidance on NAT for HIV-1 and HCV
- Donor testing for WNV: ID versus MP-NAT
  - Geographic/seasonal variations
- Donor testing for Chagas' Disease
  - T.Cruzi is transmissible by transfusion
  - T.Cruzi is endemic in portions of Mexico, Central America, and South America
  - Prevalence in US is due to immigration from endemic regions
  - Chronically infected donors are asymptomatic
- vCJD risk assessment for plasma derivatives
  - Risk communication on plasma-derived FVIII and FIX

Selected New Product Approvals

- Abbott Prism for detection of anti-HCV
- Procleix Ultrio Assay for HIV-1, HCV and HBV with fully automated TIGRIS system
- Ortho T. cruzi ELISA for donor screening
- Baxter CEPROTIN (protein C concentrate for deficiency)
- Cangene HBIG to prevent HBV after OLT
- Grifols and CSL Behring AHF/vWF products for surgical indications in VWD
- Novo Nordisk rFVIIa for surgical indications in acquired hemophilia
- Omrix fibrin sealant for hemostasis in vascular surgery
- CSL Behring Rho(D) for chronic ITP in Rho(D)+/non-splenectomized patients
- APTIMA HIV-1 RNA Qualitative Assay for HIV diagnosis

Blood Related Guidance Published in FY'07

- Biological Product Deviation Reporting for Blood and Plasma Establishments
- Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components
- Informed Consent Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs
- Guidance for Industry: Adequate and Appropriate Donor Screening Tests for Hepatitis B; Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Blood, Blood Components and Source Plasma Donations
- Draft Guidance for Industry: "Computer Crossmatch"

Continuing public dialogue to enhance product safety and availability

- Workshops 2006
  - Behavior-based deferrals in the NAT era, 3/06
  - Donor testing for malaria, 7/06
  - Molecular methods in immunohematology, 9/06
  - Immune Globulin Antibody Specificities and Potency, 4/07
- Workshops under development for 2007
  - Apheresis Licensure, 8/07
  - Regulation of BECS, 9/07
- Participation with other HHS components on IGIV availability

Current HHS Initiatives: Biovigilance

- Consistent with recommendations of the HHS Advisory Committee for Blood Safety and Availability, HHS has established an inter-agency working group on “biovigilance”
- The charge of the working group is to develop strategies to integrate and improve safety surveillance and novel event detection for transfusion and transplantation
  - The working group is developing a “gap analysis”
  - A principal goal is to clarify the respective roles of federal agencies and the private sector in “biovigilance”

Disaster Management and Preparedness

- AABB Interorganizational Disaster Task Force
  - Designated in ESF-8 of NRP for emergency blood supply coordination
  - Level 1 members convene by telephone conference within one hour of an event (including representatives from affected blood establishments)
    - Level 1 includes all major blood organizations, HHS, FDA, CDC, DOD
    - TF has been active in TOPOFF exercises, as well as proactive planning for large events (political conventions, superbowl, etc)
- AABB Pandemic Influenza Task Force
  - Proactive pandemic planning over past two years
  - Task Force has proposed FDA regulatory flexibility during pandemic-related shortages (Wide range of regulatory flexibilities proposed to FDA)
  - AABB has urged FDA to be transparent regarding its intentions so as to allow planning by the blood community

Safety Teams

- Integrated safety teams (e.g., epidemiologists, clinical/product reviewers, compliance/inspectional activities, communications) in all product areas to improve acquisition and utilization of safety information
  - Surveillance/follow-up on adverse event reports
  - Encompass entire product life cycle and all data relevant to safety, manufacturing and compliance
  - Active use of health care databases
  - Proactive: set research, policy & outreach agendas
  - Coordinate center response to emerging safety issues with other FDA Centers and HHS agencies, industry
- Tissue Safety Team and Blood Safety Team operational, Vaccine Safety Team in 07
- Cooperation with “biovigilance” initiative in HHS and “hemovigilance” initiative of AABB

Blood-Related Standards and Reference Materials

- Coagulation and other proteins (many collaborative with WHO, NIBSC, others):
  - Factor VIII, thrombin, α1-PI, IGIV and HBIG (anti-measles, polio, HBs), pre-kallikrein activator, anti-D, anti-A and anti-B hemagglutinins (w/ NIBSC, EDQM)
- Infectious agents
  - Nucleic acids: HIV-1 subtypes, HIV-2, HAV, HBV genotypes, HCV genotypes, B19, malaria
  - Antibodies: HTLV, anti-HBc, anti-HBs, monospecific anti-HCV,
- Blood group substances
- CBER Panels: WNV, HIV subtypes, Chagas

Global Harmonization and Collaboration: Examples

- **WHO Collaborating Center**
  - **Expert Committee for Biological Standards**
  - **Blood Regulators Network**
  - **Collaboration on Development of Biological Reference Preparations for High-risk Blood Safety-related *in vitro* Diagnostics**
  - **International Conference of Drug Regulatory Authorities**
- **WHO Global Collaboration for Blood Safety**
- **ICH, PIC-S, SoGAT, ISBT Working Party for TTIDs**
- **Council of Europe**
  - **EDQM**
- **Alliance of Blood Operators**

Vaccines

Recent Vaccine Approvals

- 2007
  - H5N1 (Sanofi Pasteur)
- 2006
  - Rotavirus Vaccine (Rota Tec)
  - Herpes Zoster Vaccine (Zostavax)
  - Human Papillomavirus Vaccine (Gardasil)
  - Influenza Trivalent Vaccine (FluLaval)

Major Vaccine Initiatives

- Pandemic influenza and emerging threat preparedness
- Enhancing Product Safety
- Manufacturing and Product quality activities
- Global Collaboration

Pandemic Influenza

- Build review and testing capacity—including for surge and new vaccine technologies (e.g. adjuvanted, recombinant, or cell-culture grown vaccines)
- Influenza virus strain and reagent preparation needed for vaccine manufacture and testing
- Improved assays for evaluating vaccine potency, immune responses, etc.
- Support DHHS planning and vaccine development activities—enhance emergency vaccine availability preparedness

Manufacturing and Product Quality Initiatives

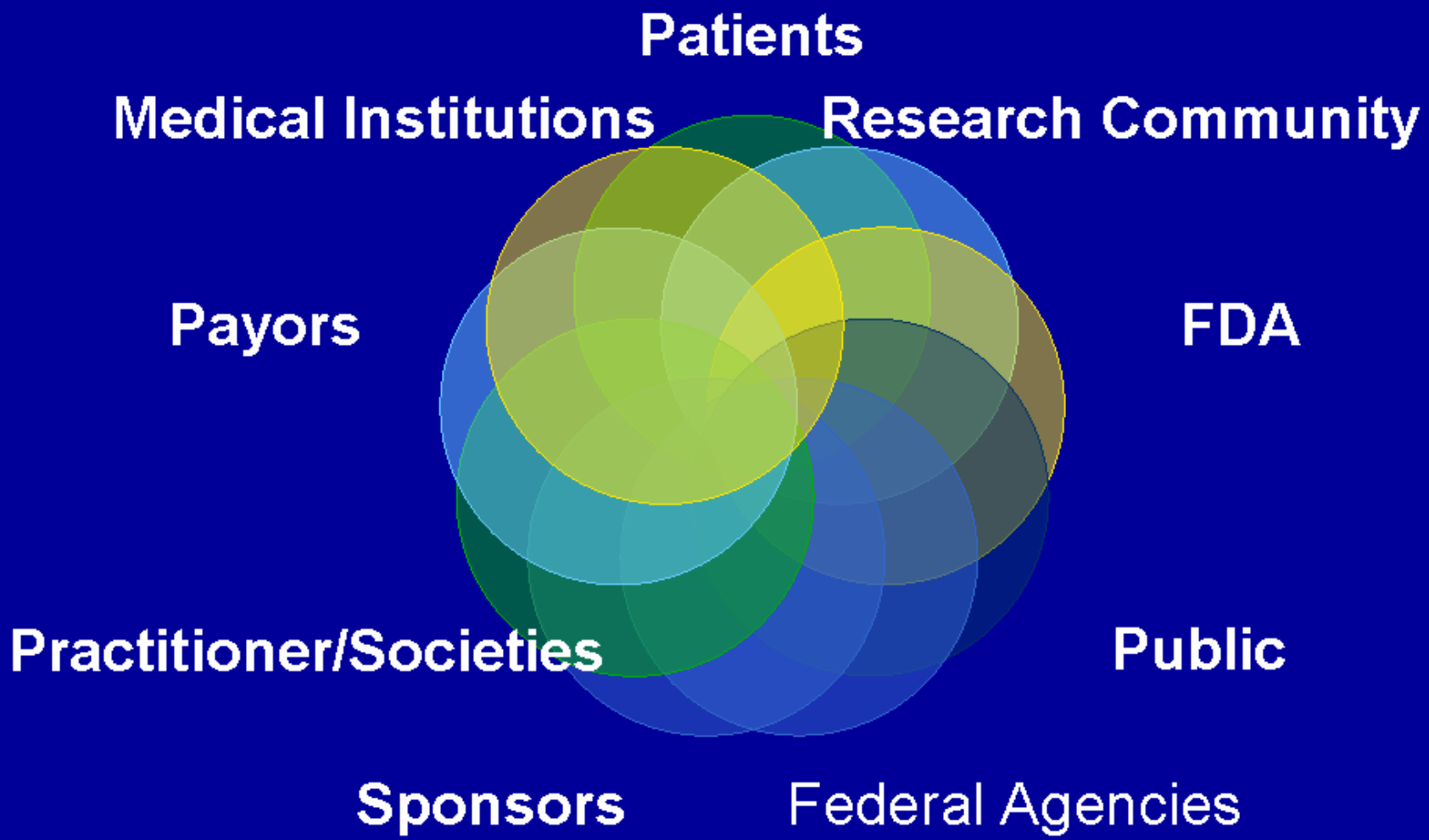
- New CBER laboratories in newly created Division of Product Quality
  - Quality environment for critical product testing and standards activities
  - Ongoing efforts toward ISO certification
- Research to modernize approaches
  - Develop/evaluate more rapid potency and other lot release and product characterization assays
  - Enhanced methods to measure immune responses

Global Collaboration

- Leadership role of FDA, together with WHO and Health Canada, in Pandemic Influenza Vaccine Regulators Initiative
  - Develop convergence on data needed to evaluate pandemic influenza vaccines
  - Regulators meetings held in 2006 and June 2007
- ECBS will be considering these draft guidelines later in 2007 to work toward finalization of document

Guidances

- Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines 5/31/07
- Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines 5/31/07
- Draft Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases 9/28/06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