Regulatory Overview of Oncology Biologics Product Development from Bench to First-in-Man

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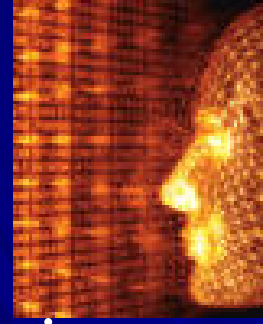
iSBTc 2008 Oncology Biologics Development Primer Feb 28-29, 2008

Overview



- Office of Cellular, Tissue, and Gene Therapies, CBER – Organization and Regulated products
- Office of Oncology Drug Product, CDER- Organization and Regulated products
- Bringing Novel Invention to Clinical Trial
  - Regulatory considerations for product
  - Regulatory pre-clinical considerations
  - Regulatory clinical considerations
- FDA-NCI collaboration
- Critical Path Opportunities

CBER Office of Cellular, Tissue, and Gene Therapies

Celia M.Witten, Ph.D., M.D., Director
Stephanie Simek, Ph.D. Deputy Director
Suzanne Epstein, Ph.D. Associate Director of Research
Richard McFarland, M.D., Ph.D., Associate Director of Policy

Division of Cellular and Gene Therapies

Raj Puri, M.D., Ph.D., Director
Kimberly Benton, Ph.D., Deputy Director

Division of Human Tissues

Ruth Solomon, M.D., Director

Division of Clinical Evaluation and Pharmacology/Toxicology

Ashok Batra, M.D., F.A.C.S., Director

Division of Cellular and Gene Therapies (DCGT)

Raj Puri, M.D., Ph.D., Division Director

Kimberly Benton, Ph.D., Deputy Director

Gene Therapies Branch
Daniel Takefman, Ph.D., Chief

Gene Transfer and Immunogenicity Branch
Andrew Byrnes, Ph.D., Chief*

Cell Therapies Branch
Keith Wonnacott, Ph.D., Chief

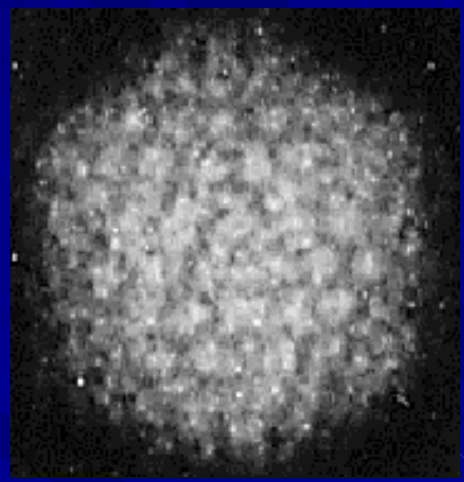
Tumor Vaccines and Biotechnology Branch
Raj Puri, M.D., Ph.D., Chief*

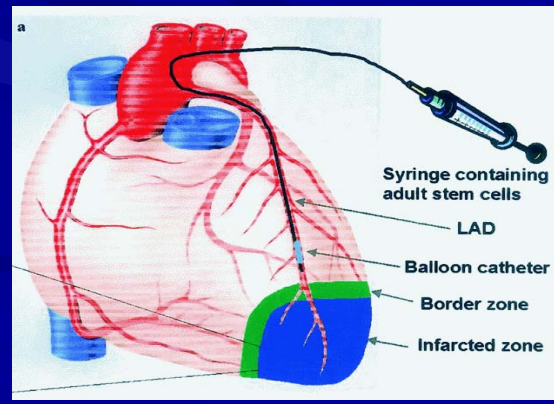
Cellular and Tissue Therapy Branch
Steven Bauer, Ph.D., Chief*

*Acting

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

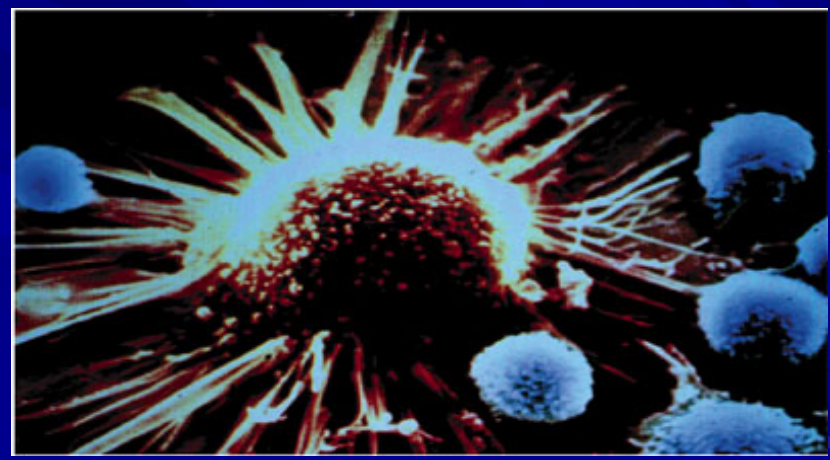
- Cellular Therapies
- Cancer Vaccines and Immunotherapy
- Gene Therapies
- Xenotransplantation Products
- Tissues and Tissue-Based Products
- Combination Products
- Devices Used for Cells and Tissues





OCTGT Cancer Vaccines and Immunotherapy Products

- Cells
  - E.g., dendritic cells, activated T lymphocytes (TIL, LAK), B cells, monocytes, cancer cells chemically modified or unmodified, *Ex vivo* gene modified cells ..
- Tumor cell lysates
- Proteins, peptides
  - Mixed with adjuvants
- Idiotypic and anti-idiotypic antibodies



OCTGT Gene Therapy Products

- **Vectors Expressing Transgenes**
  - Plasmid DNA vectors
  - Replication defective viral vectors
  - Attenuated bacterial vectors

- **Gene Modified Tumor vaccines**
  - Non-viral and viral vectors expressing immunogenic molecules (e.g. TAA, TCR ligands, co-stimulatory molecules)

OCTGT Gene Therapy Products contd..

- **Viral therapy (Oncolytic Virus) products**
  - Oncolytic viruses (OVs) - replication competent or attenuated viruses, e.g., adenoviruses, vaccinia, herpes simplex viruses, Newcastle disease virus (NDV)
  - OVs can be either naturally occurring or genetically modified, to achieve tumor-specific targeting and ‘bystander’ tumor cell killing, etc.

CDER Office of Oncology Drug Products

Richard Pazdur, M.D., Director
Karen Weiss, M.D. Deputy Director

Division of Drug Oncology Products
Robert Justice, M.D. , Director

Division of Medical Imaging and Hematology Products
R. Dwaine Reeves, M.D., Acting Director

Division of Biologic Oncology Products
Patricia Keegan, M.D., Director

Office of Biotechnology Products

Steven Kozlowski, M.D., Director

Division of Monoclonal Antibodies

Kathleen Clouse, Ph.D., Director

Division of Therapeutic Proteins

Amy Rosenberg, M.D., Director

Therapeutic Biological Products Evaluated by CDER

- Monoclonal antibodies for in vivo use.
- Proteins intended for therapeutic use, including
  - cytokines (e.g., interferons), enzymes (e.g., thrombolytics), and other novel proteins, except for those that are specifically assigned to CBER (e.g., vaccines and blood products).
  - Therapeutic proteins derived from plants, animals, or microorganisms, and recombinant versions of these products.

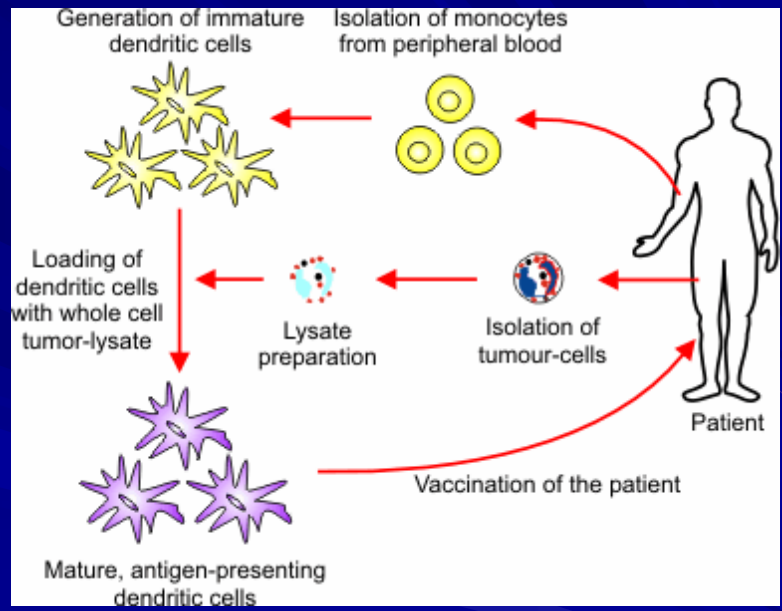
Therapeutic Biological Products Evaluated by CDER contd..

- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response).

- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo.

Cancer Therapy Products are Combined with other Biological Agents (e.g.,)

- Dendritic cells pulsed with tumor antigens, peptides, purified or recombinant proteins, cell lysates, nucleic acids or transduced with gene transfer vectors
- Cells cultured and expanded in growth factors or cytokines and administered as such or mixed with growth factors
- Tumor antigens or cells mixed with adjuvant (BCG, KLH, CPG, GM-CSF etc.) either injected separately or together
- Antibody, tumor antigen and adjuvant (anti-CTLA-4 Ab, peptide and montanide)



Collaboration between CBER, CDER and CDRH for oncology products

- Weekly meeting to discuss cross-FDA oncology related activities
- Discussion of inter-center review issues
- Monthly Executive Briefing on oncology activities
- Joint workshops and participation in interaction with stakeholders such as interaction with iSBTc, AACR, ASCO, AAI, International Biological Society (IABs), ASGT, ISCT, and others

Collaboration between CBER, CDER and CDRH for oncology products contd..

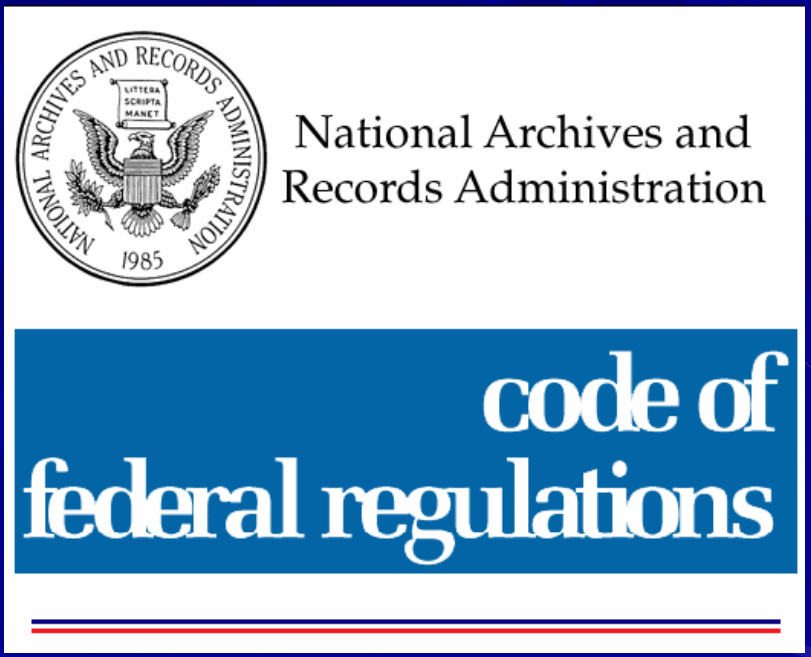
- Joint participation in FDA and NCI Inter-Agency Oncology Task Force (IOTF)
- Joint participation in policy and guidance document development (e.g., tumor specific guidances on end points)
- Supplementation of expertise to advisory committee discussions [Cell, Tissue and Gene Therapy Advisory Committee (CTGTAC), Oncology Drug Advisory Committee (ODAC) and device panels]
- Joint participation in FDA Critical Path Initiative to promote development of oncology products

Bringing Novel Invention to Clinical Trial

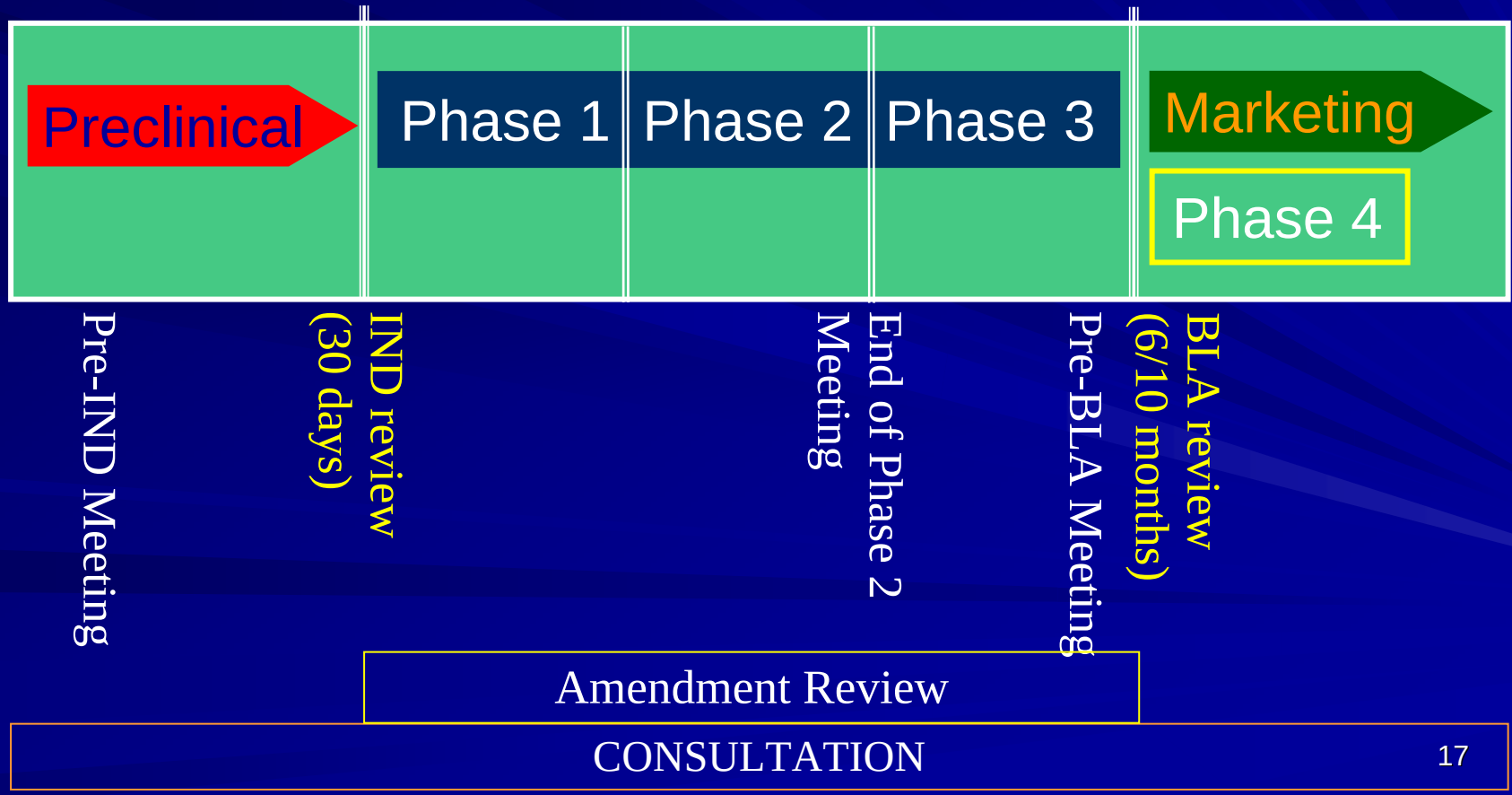
- Anytime you are conducting a clinical trial with an investigational drug or biologic – you need an IND

  21 CFR 312

- Investigational New Drug Application



Phases of Clinical Investigation



Pre-IND Meetings

- Sponsor may request a pre-IND meeting in writing
- Request should include:
  - Identification of specific issues to be addressed
  - Description of the product, pharm/tox studies and clinical protocol
  - Agenda/attendees list
- Meeting package due 30 days before meeting, including:
  - Manufacturing summary
  - Pre-clinical data
  - Clinical protocol
  - Issues to be discussed with specific questions

Investigational New Drug (IND)

- Investigational plan
- Investigator's instructions
- Study protocols
- Manufacturing information
- Pharmacology / Toxicology
- Environmental information
- Previous human experience

http://www.fda.gov/cber/ind/ind.htm

http://www.fda.gov/cber/ind/indpubs.htm

Team Approach to IND Review of OCTGT Products

- **Review Team**
  - Product
  - Clinical
  - Pharmacology-toxicology
  - Statistician
  - Project Manager
  - Supervisors from different divisions/branches
  - Consult/collaborative reviewers
- **Within 30 days (in effect or hold)**
  - Outstanding hold and non-hold issues conveyed by phone and detailed letter is issued.
  - Must satisfactorily address hold issues and submit for FDA review (30 days) prior to proceeding

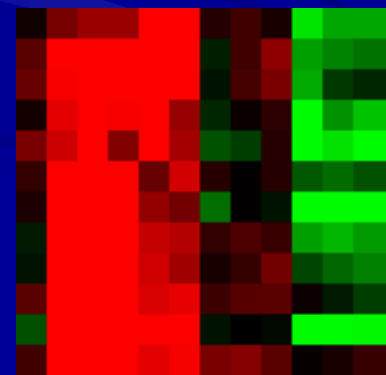
Regulatory Concerns Common to all Biologic Products

- Safety, purity, potency, efficacy
- Oversight of both product and process
- Quality control of product and intermediates
- Reproducibility of lots

*Draft Gene Therapy Guidance document and Draft Somatic Cell Therapy Guidance documents. http://www.fda.gov/cber/genetherapy/gtpubs.htm

Cancer Vaccines and Immunotherapy: Product Quality I

- Identify appropriate targets of therapies
- Potency, identity and purity testing should provide meaningful information about the product prior to its release/use
- Appropriate tests and standards are critical
- Greater product knowledge (mechanism of action, characterization, etc) will aid in developing meaningful assays and/or novel approaches for product characterization – consider applying novel technologies

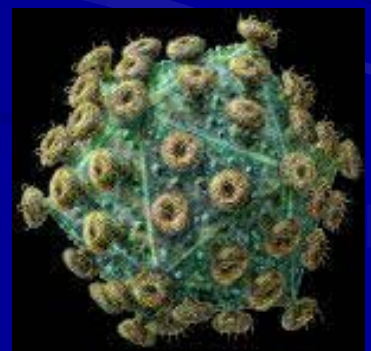


Cancer Vaccines and Immunotherapy: Product Quality II

- Patient-specific cellular product challenges: Potency
- Functional components within complex cell mixtures or lysates
  - Specificity of “target”
- Rapidly and accurately confirm sterility of cellular products with a very short shelf life
- Stability of cellular products
  - Effects of storage
- Consistency of cellular products
  - E.g., after process or facility change in manufacturing

Unique Regulatory Concerns: Gene Therapy

- Potential for rescue of replicating virus
- Potential for permanent alteration to somatic or germline DNA
  - Long-term toxicity
  - Risk of secondary cancer
- Potential for inappropriate immune response to vector components or transgene



Unique Regulatory Concerns for Gene Therapy Products: Oncolytic Virus

- Challenges in product characterization
  - Adventitious viral testing
  - Characterizing recombinants, presence of wild type virus
  - Selectivity
- In vivo replication in non-cancer cells
- Viral shedding
- Summary ICH workshop on oncolytic viruses and future ICH considerations paper
  - www.ICH.org, gene therapy discussion group

Key Goals of Preclinical Studies*

- Recommend initial safe starting dose and safe dose escalation scheme in humans
- Determine an acceptable risk/benefit ratio in humans
  - Identify potential target organ(s)
- Identify clinical parameters to monitor
- Identify “at risk” populations (patient eligibility criteria)
- Discern the mechanism of action
  - More accurate and more efficient clinical studies

*presentation

Unique Issues for Oncology Biologics Products

- Biodistribution/trafficking to nontarget tissues
- Aberrant immune response
- Insertional mutagenesis
- Enhanced tumorigenicity
- Long-term toxicity

Clinical Study Design: Early Phase Study Objectives

- Safety profile - safety of combinations*
- Optimal dose and schedule
- Define appropriate patient population
- Early evidence of activity/efficacy
- Biological/immunological markers
- Co-development of assay and therapeutics

*presentation

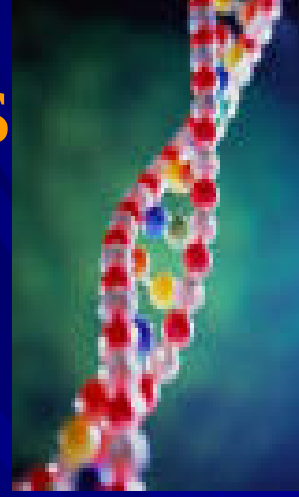
Unique Aspects of Early Phase Clinical Studies with Cancer Vaccines and IT Products

- Metabolism does not follow standard pharmacokinetics and/or pharmacodynamics
- Distinct product mechanism of action requires different trial design
  - Defining optimal biologic dose (OBD) rather than maximum tolerated dose (MTD)
  - Consideration of unique toxicity profiles and monitoring

Early Phase Clinical Investigations: Recommendations: Target Populations

- Consider enrolling patients with a single tumor histology in phase I trials
  - Safety, feasibility and optimal dose regimen
  - If promising - consider evaluating the product in later phase trials in patients with different tumor histology
- Patients with minimal residual disease
- Patients with metastatic disease

Early Phase Clinical Investigations Recommendations: Safety Monitoring



- Safety reporting requirements described in 21CFR312
- Safety monitoring should be guided by:
  - preclinical findings
  - features of the underlying disease
  - anticipated disease-product interactions
  - long term follow-up for applicable products

“Good Clinical Practice”

- International ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects

- Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected

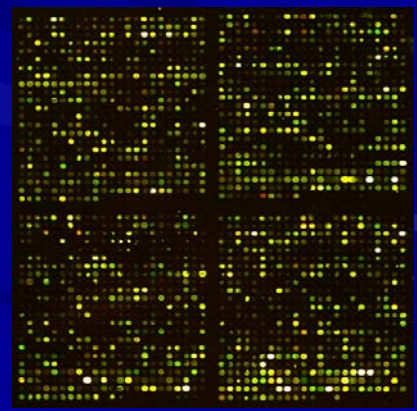
- ICH E6 GCP Guidance published 1997
  - http://www.fda.gov/cder/guidance/959fnl.pdf

Responsibilities of Investigators: Clinical trials of drugs and biologics

- Conduct study in accordance with protocol
- Personally supervise the investigations
- Informed consent of study participants
- Report adverse events
- Communicate with IRB
- Maintain adequate records

Facilitating 21st Century Medical Product Development: Collaboration with NCI

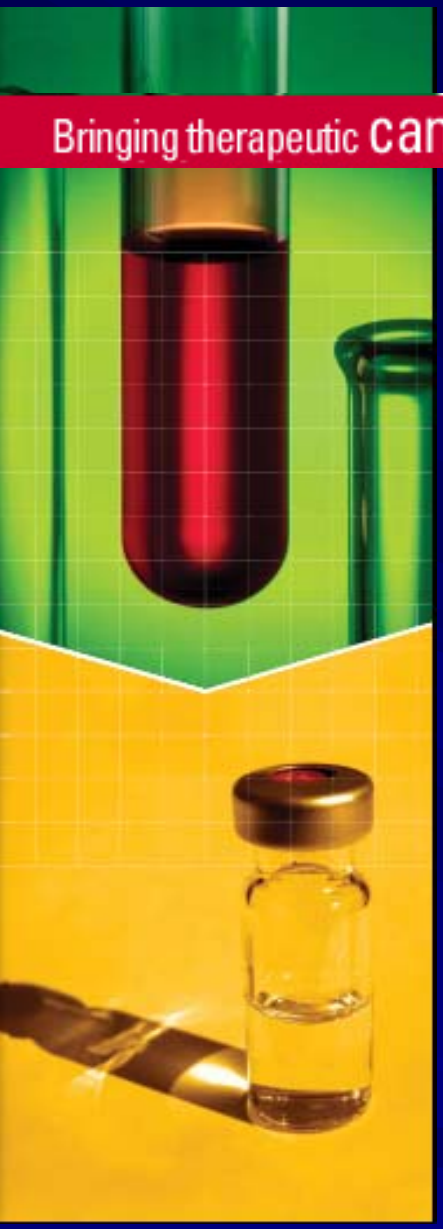
- Interagency Oncology Task Force (IOTF)
  - Facilitates interagency collaboration
  - Supports FDA/NCI joint fellowship training program
    - NCI supported training in cancer-related scientific research and regulatory review
    - http://iotftraining.nci.nih.gov/index.html
- Joint workshops
  - Examples to follow
- Scientific collaboration
  - Inter Agency Agreements (IAG)



Joint FDA/NCI Workshops

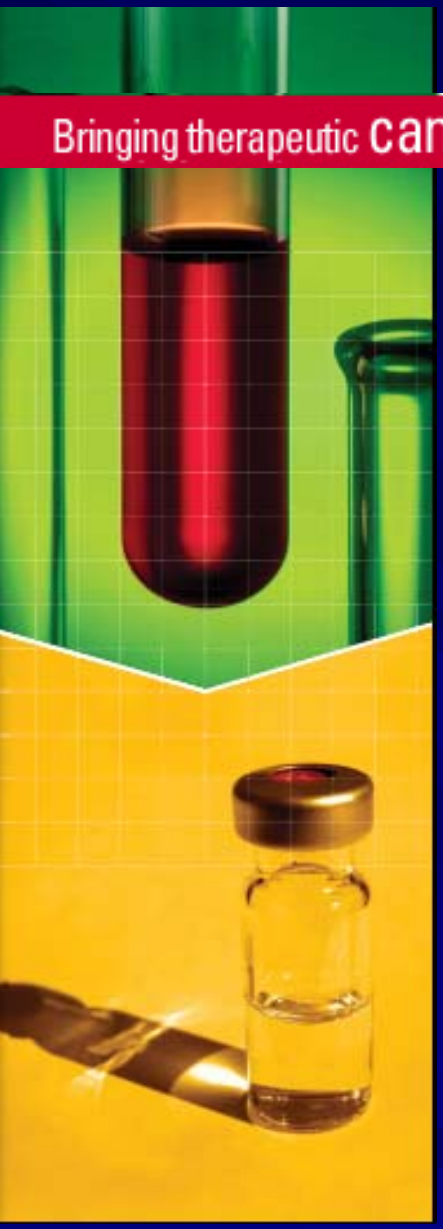
- Bringing Therapeutic Cancer Vaccines and Immunotherapy Through Development to Licensure
  - February 8-9, 2007 https://cms.palladianpartners.com/cms/1156354418/home.htm

- RAID Investigator Workshop 'Working with FDA: Biological Products and Clinical Development'
  - May 14, 2007
- Accelerating Anticancer Agent Development and Validation Workshop
  - June 20-22, 2007
- NCI Immunotherapy Agent Workshop -July 12, 2007
- Clinical Use of Biomarkers - October 29 – 30, 2007



FDA/NCI Co-Sponsored Workshop on Cancer Vaccines and Immunotherapy

- February 8-9, 2007
- Participation from AACR, AAI, CVC, IABs, iSBTc, BDA, Paul Ehrlich-Institute
- Agenda available
  - https://cms.palladianpartners.com/cms/1156354418/materials/agenda.htm
- Videocast available
  - http://videocast.nih.gov



A WORKSHOP SPOINSORED JOINTLY BY FDA AND NCI

Bringing therapeutic cancer vaccines and immunotherapies through development to licensure

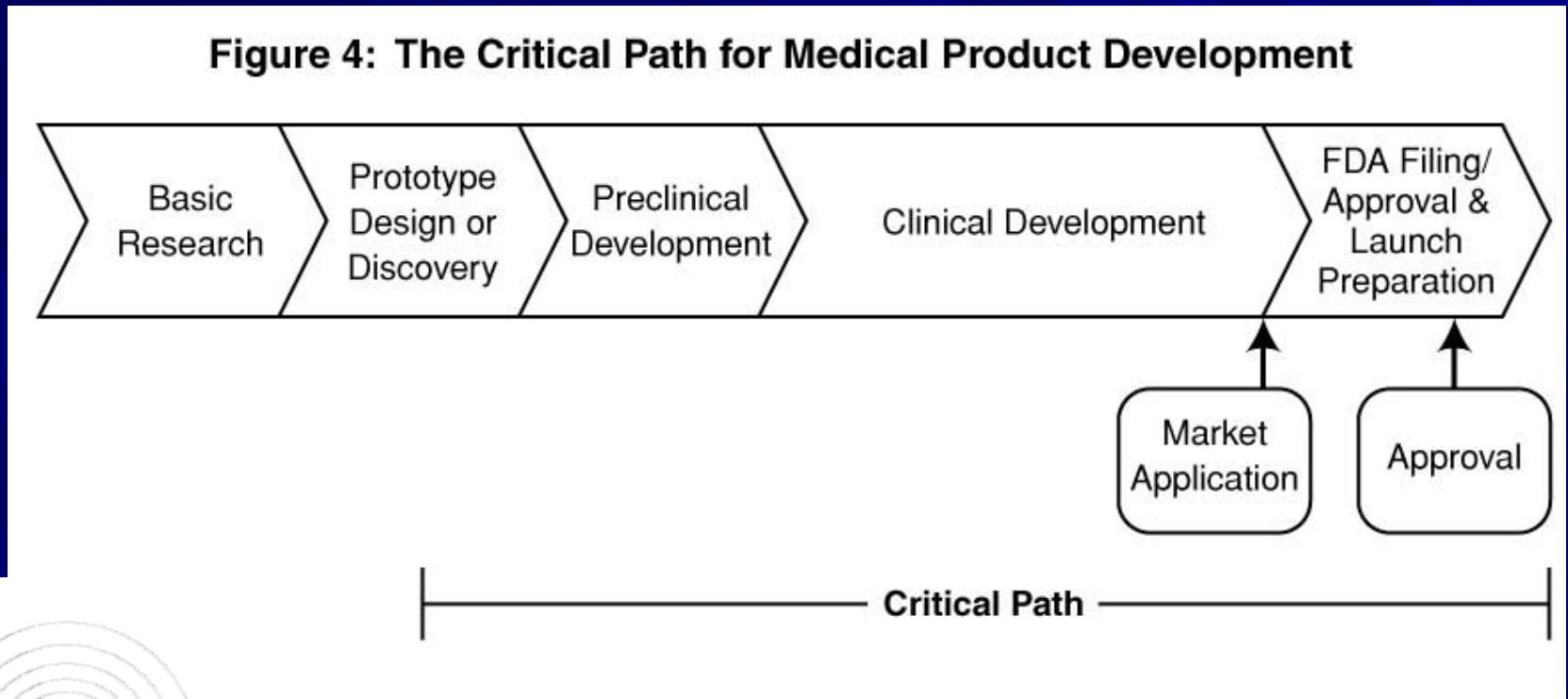
Content of workshop

- Unique regulatory aspects of developing cancer vaccines and immunotherapies
  - Early and late phase clinical trial design
  - Preclinical testing
  - Manufacturing controls

Outcomes of the workshop

- Greater dialogue among participants on the opportunities and challenges for these products
- Better understanding of guidance that is needed from FDA to facilitate development of these products

FDA Critical Path Initiative



Innovation
Stagnation

Challenge and Opportunity on the Critical Path to New Medical Products

FDA

www.fda.gov/oc/initiatives/criticalpath.htm

CBER/FDA's Unique Research

- **Problem solving vs. discovery**
- Performed by Researcher-Reviewers
  - Hundreds of applications (IND and BLA) have been *directly* supported by CBER research and expertise
- Driven by FDA's "big picture" perspective
- Not NIH research – may be done with NIH
- Critical Path tackles public health issues
  - product class challenges
- Collaborates to access needed expertise

http://www.fda.gov/oc/initiatives/criticalpath/

Critical Path Research Opportunities

- Tumor antigens as biomarkers of disease and product quality
- Immune monitoring e.g., effector cell and other assays in cancer vaccine clinical trials
- Monitoring regulatory cells in response to cancer vaccines and other cancer therapy products
- Identifying tracking of adoptively transferred cells (e.g., T cells) and their persistence
- Imaging methods for immune monitoring and tumor persistence (e.g., FDG PET)

Collaboration Opportunities to Improve Cancer Therapies: Biomarkers

- **FDA, NCI, and CMS Collaboration***
  - **Oncology Biomarker Qualification Initiative (OCBI)**
    http://www.fda.gov/bbs/topics/news/2006/NEW01316.html

- **The Biomarkers Consortium**
  - Joint venture FNIH-NIH-FDA-Academia-Industry
    www.biomarkerconsortium.org

Advancing Medical Science

– As a public-private research partnership of the Foundation for the National Institutes of Health (FNIH), The Biomarkers Consortium endeavors to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics. Biomarkers are molecular, biological, or physical characteristics that indicate a specific, underlying physiologic state to identify risk for disease, to make a diagnosis, and to guide treatment.

*presentation

Summary

- Oncology products are diverse and rapidly evolving, thus require new regulatory paradigms
- Sponsors are encouraged to refer to:
  - Guidance documents and educate themselves
  - Communicate with FDA staff
  - Start solving the problems early: plan ahead
  - Keep good records
- FDA staff facilitates development of, approval of, and access to safe and effective medical products
- FDA staff also performs Critical Path research: fill gaps, deal with scientific challenges, figure out what is important and communicate results publicly

Points of Contact: OCTGT

- Regulatory Project Manager: Teresita Mercado (Teresita.mercado@fda.hhs.gov)
- Manufacturing Issues: Division of Cellular & Gene Therapies
  - Gene Therapy Review Branch
    - Dan Takefman (daniel.takefman@fda.hhs.gov)
  - Cell Therapy Review Branch
    - Keith Wonnacott (keith.wonnacott@fda.hhs.gov)
- Clinical and Pharm-Tox: Division of Clinical Evaluation and Pharm-Tox (DCEPT)
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Thank you

- We are in the midst of new advances in targeted therapy, immunotherapy, cancer vaccines, gene therapy and combination therapy leading to development of safe and effective new cancer medicines for the 21st century

- New technologies need expert, innovative & interactive science, new models, standards and assays

- We see a positive future with exciting science and great opportunity for everyone.