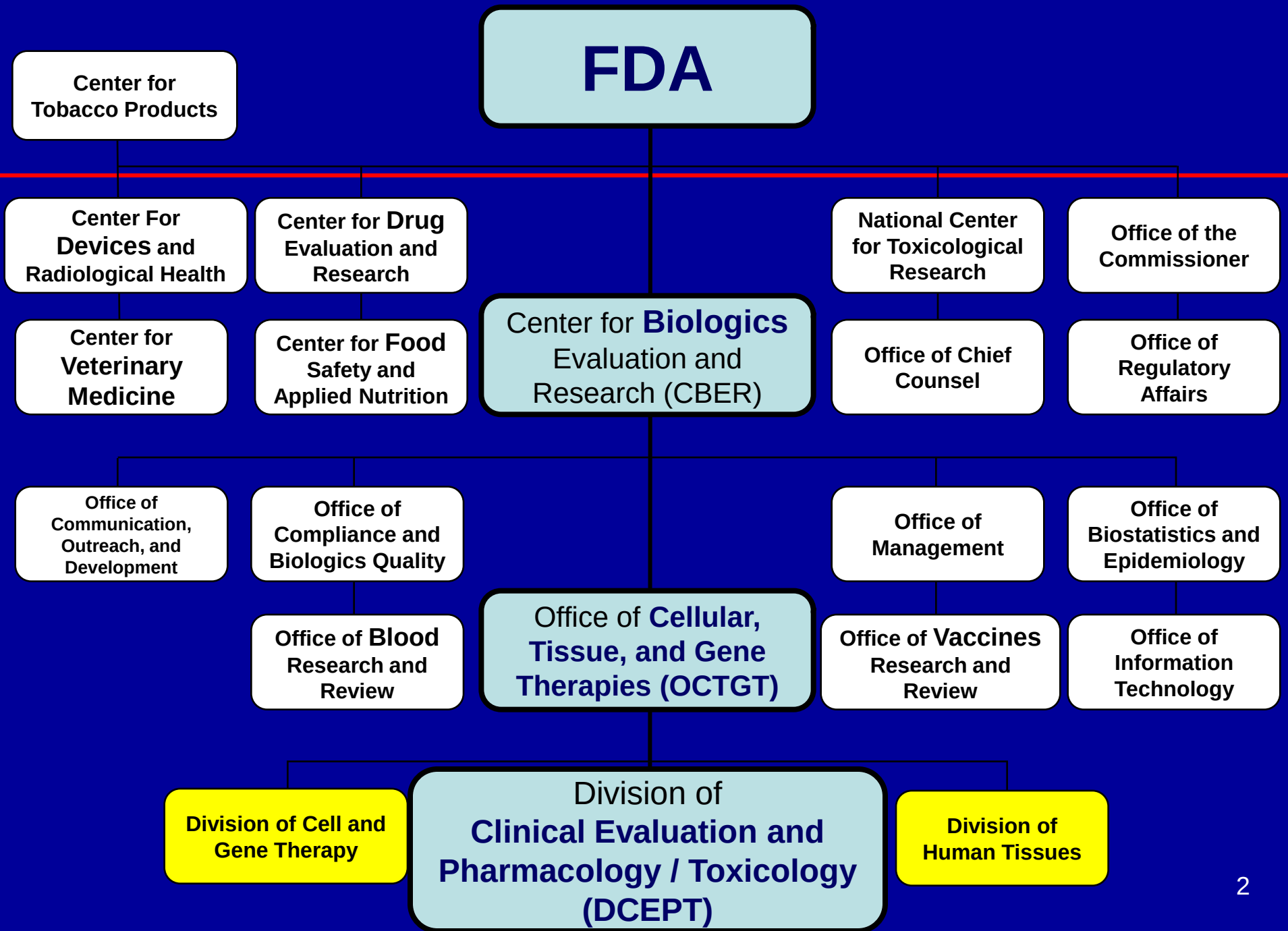
Clinical Trials of Cell Therapies for Parkinson's Disease

CIRM Webinar
November 14, 2013

Wilson W. Bryan, M.D.

Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Cellular, Tissue, and Gene Therapies
FDA / CBER / OCTGT / DCEPT


FDA
Center for Tobacco Products
Center For Devices and Radiological Health
Center for Drug Evaluation and Research
National Center for Toxicological Research
Office of the Commissioner
Center for Veterinary Medicine
Center for Food Safety and Applied Nutrition
Center for Biologics Evaluation and Research (CBER)
Office of Chief Counsel
Office of Regulatory Affairs
Office of Communication, Outreach, and Development
Office of Compliance and Biologics Quality
Office of Management
Office of Biostatistics and Epidemiology
Office of Blood Research and Review
Office of Cellular, Tissue, and Gene Therapies (OCTGT)
Office of Vaccines Research and Review
Office of Information Technology
Division of Cell and Gene Therapy
Division of Clinical Evaluation and Pharmacology / Toxicology (DCEPT)
Division of Human Tissues

CBER Office of Cellular, Tissue, and Gene Therapies

Celia M. Witten, Ph.D., M.D., *Director*

Stephanie Simek, Ph.D., *Deputy Director*

Division of Cellular and Gene Therapies

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

Kimberly Benton, Ph.D., *Deputy Director*

Division of Human Tissues

Capt. Ellen Lazarus, M.D., *Director*

Division of Clinical Evaluation and Pharmacology / Toxicology

Wilson Bryan, M.D., *Director*

Cell Therapies for Parkinson's Disease (PD)

- First-in-Human (FIH) Clinical Trials
  - Trial Design
  - Example: Product is a cell, or genetically-modified cell, for intra-cerebral administration
- Expedited Programs for Serious Conditions
  - Breakthrough Designation

FIH Clinical Trial

- Objectives
- Basic Design
- Study Population (Eligibility Criteria)
- Dose / administration
- Monitoring
- Endpoints

FIH Trial – Objectives to assess:

1) Safety
2) Tolerability
3) Dose-exploration
   a) Maximum Tolerated Dose (MTD)
   b) Maximum Feasible Dose
   c) Optimum Biologic Dose

FIH Trial – Objectives to assess:

4) Feasibility, including:
   a) Logistics
   b) Recruitment

5) Preliminary Efficacy –
   better to fail early than to fail late(?)

FIH Trial – Basic Design

- Proof-of-concept
  - From non-clinical studies (animal models)
  - Helps justify risks to subjects
  - Helps guide the clinical study design
- Cohorts
  - Sequential
  - Size

FIH Trial – Basic Design

- Controls
  - Improve assessments of safety and efficacy
  - Historical; no treatment; sham surgery; placebo
- Randomization (if concurrent control)
- Blinding (particularly if sham surgery or placebo control)

FIH Trial – Eligibility Criteria

- Criteria for diagnosis of PD
- Disease status
  - Patients with a prospect of direct benefit
  - Not well-controlled; disabled
  - Ability to provide informed consent
  - Informative with regard to safety (and possibly efficacy)
  - Concomitant medications stable

FIH Trials – Dose / Administration

- Dose
  - Starting dose based on pre-clinical experience with study agent, and on any clinical experience with related products
- Dose-escalation
  - Sequential cohorts
- Unilateral intra-cerebral administration

FIH Trials – Dose / Administration

- Specify administration procedure, e.g., volume of administration; rate of administration; devices / catheters (whether FDA-cleared or investigational)
- Training in administration procedure

FIH Trials – Dose / Administration

- Immunosuppression
  - Necessary or not?
  - If necessary, for what duration?
- Concomitant medications
  - Maintain constant dosing for study duration, if feasible
  - Document dose and regimen

FIH Trials - monitoring

- Long-term Follow-up
- Endpoints
  - Biochemical markers
  - Brain Imaging
  - Clinical outcomes (safety and efficacy

Cell Therapies for Parkinson's Disease (PD)

- First-in-Human (FIH) Clinical Trials
  - Trial Design
  - Example: Product is a cell, or genetically-modified cell, for intra-cerebral administration
- Expedited Programs for Serious Conditions
  - Breakthrough Designation

Expedited Programs

- Fast Track
- Accelerated Approval
- Priority Review
- Expanded Access ("compassionate use")
- Breakthrough Designation

Fast Track, Accelerated Approval, and Priority Review

- These terms apply to licensure or to the licensure process for drugs and biologics

- Fast Track: process designed to facilitate the development, and expedite the review of drugs to treat serious diseases and fill an unmet medical need; available at any stage of development prior to submission of license application

Fast Track, Accelerated Approval, and Priority Review

- **Accelerated Approval: allows earlier approval of drugs or biologics that treat serious diseases, and that fill an unmet medical need based on a surrogate endpoint. A confirmatory trial is needed.**

- **Priority Review: Two-tiered system of review times**
  - **Standard Review: ten-month time frame**
  - **Priority Review: six-month time frame. Designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists**

Expedited Programs

A serious disease or condition is defined … as:

"a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. … the morbidity need not be irreversible if it is persistent or recurrent.

Expedited Programs

Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”

from FDA Draft Guidance for Industry:
Expedited Programs for Serious Conditions

Expanding Access to Investigational Drugs

- Use of an investigational drug outside of a clinical trial, for the sole purpose of treating a patient or patients with a serious or life-threatening disease who have no acceptable medical options

- Levels of expanded access are based on the number of patients to be treated and how much is already known about the drug:
  - Individual or intermediate size group access
  - Treatment IND

Food and Drug Administration Safety and Innovation Act (FDASIA)

- Signed into law July 9, 2012
- Fourth reauthorization of the Prescription Drug User Fee Act (PDUFA)
- Sec 902- Breakthrough Therapies

Breakthrough Therapy

A drug that is intended to treat a serious condition **AND** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies

Breakthrough Therapy

- All Fast Track designation features, plus
  - Intensive guidance on efficient drug development, beginning as early as Phase 1
  - Organizational commitment involving senior managers

Draft Guidances

- **Expedited Programs for Serious Conditions – Drugs and Biologics (June 2013)**
- **Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2012)**
- **Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (July 2013)**

OCTGT Contact Information

Wilson.Bryan@fda.hhs.gov

Regulatory Questions:

Contact the Regulatory Management Staff in OCTGT at CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov or by calling (301) 827-6536

OCTGT Learn Webinar Series:

http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

Public Access to CBER

CBER website:
http://www.fda.gov/BiologicsBloodVaccines/default.htm
Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)
Email: ocod@fda.hhs.gov
Phone: 301-827-3821

Manufacturers Assistance & Technical Training Branch (MATTB)
Email: industry.biologics@fda.gov
Phone: 301-827-4081

Follow us on Twitter
https://www.twitter.com/fdacber

Acknowledgements

Yao-Yao Zhu, MD, PhD

Theresa Chen, PhD

Acknowledgements – Division of Clinical Evaluation and Pharmacology / Toxicology

Pharmacology / Toxicology Branch	General Medicine Branch	Oncology Branch
Mercedes Serabian**, MS	Ilan Irony**, MD	Ke Liu**, MD, PhD
Pakwai Au, PhD	Changting Haudenschild*, MD	Peter Bross*, MD
Alex Bailey, PhD	Bruce Schneider*, MD	Bindu George*, MD
Theresa Chen, PhD	Mark Borigini, MD	Kristin Baird, MD
Shamsul Hoque, PhD	John Hyde, PhD, MD	Chaohong Fan, MD, PhD
Ying Huang, PhD	Agnes Lim, MD	Sadhana Kaul, MD
Wei Liang, PhD	Steve Winitsky, MD	Robert Le, MD, PhD
Jinhua Lu, PhD	Rachel Witten, MD	Lydia Martynec, MD
Allen Wensky, PhD	Lei Xu, MD, PhD	Maura O'Leary, MD
Yongjie Zhou, PhD, MD	Michael Yao, MD	Kevin Shannon, MD
	Yao-Yao Zhu, MD, PhD	

** Branch Chief; * Team Leader

OCTGT Contact Information

Wilson.Bryan@fda.hhs.gov

Regulatory Questions:

Contact the Regulatory Management Staff in OCTGT at CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov or by calling (301) 827-6536

OCTGT Learn Webinar Series:

http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm