



Perspectives on Rare Diseases and Gene Therapies

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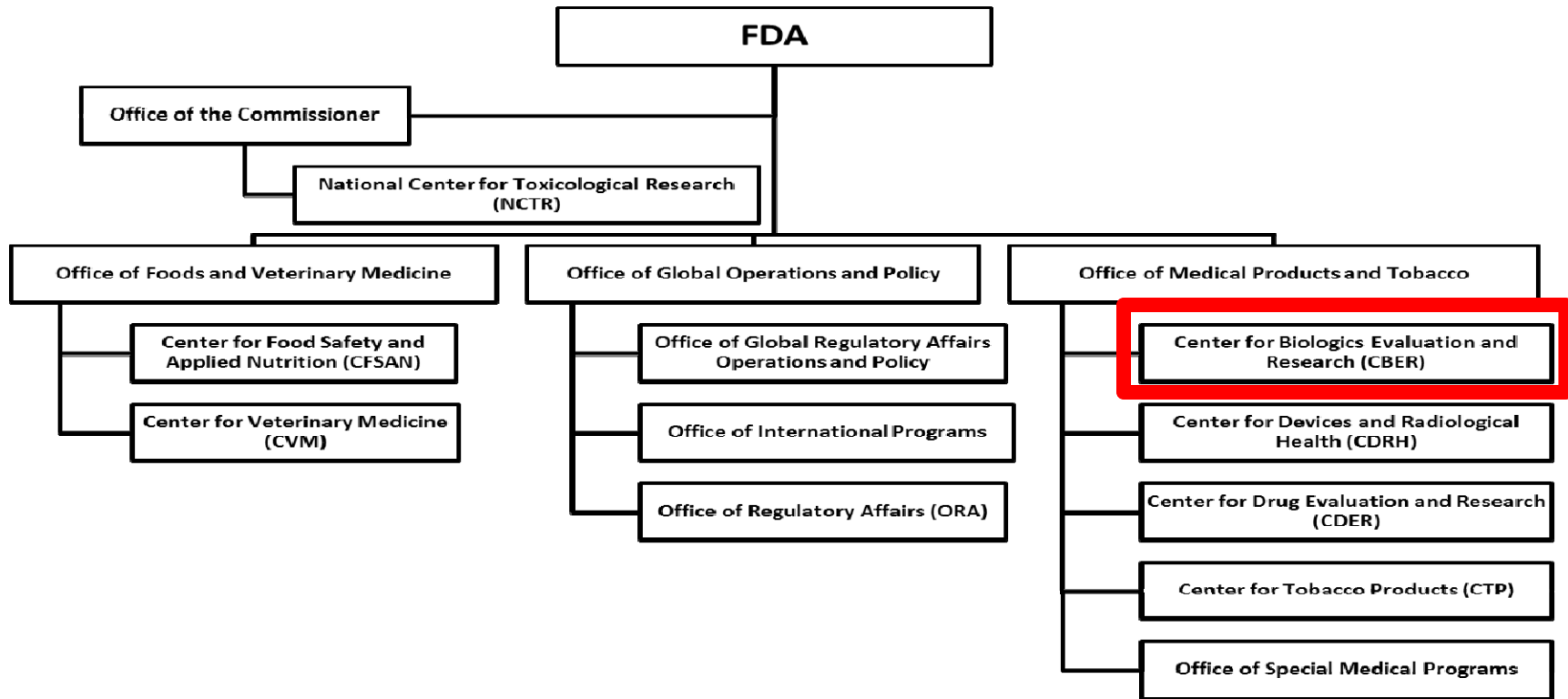
FDA/CBER/OTAT



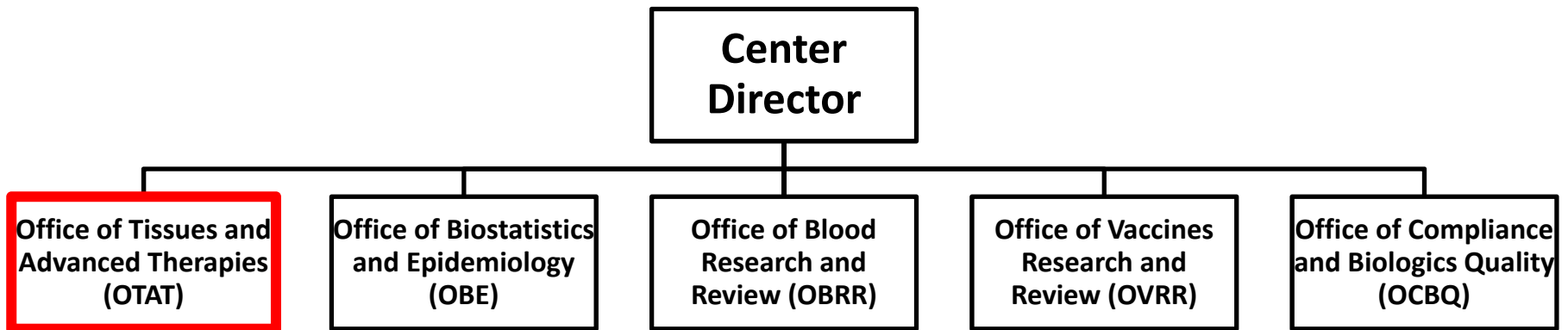
Outline

- FDA Office of Tissues and Advanced Therapies
- Brief overview of Orphan Drugs
- Gene Therapies for Rare Diseases

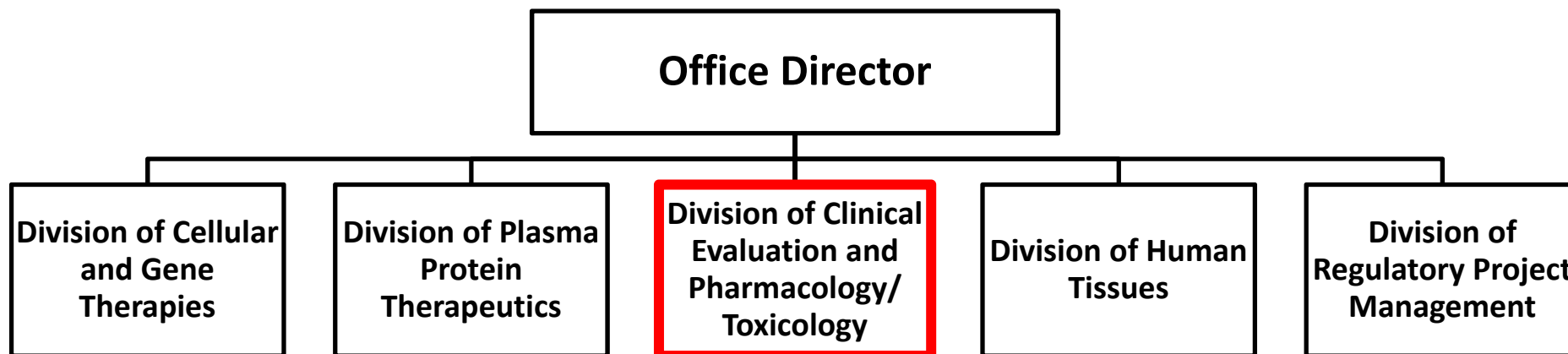
US Food and Drug Administration



Center for Biologics Evaluation and Research (CBER)



Office of Tissues and Advanced Therapies (OTAT)



Diversity of OTAT-Regulated Products

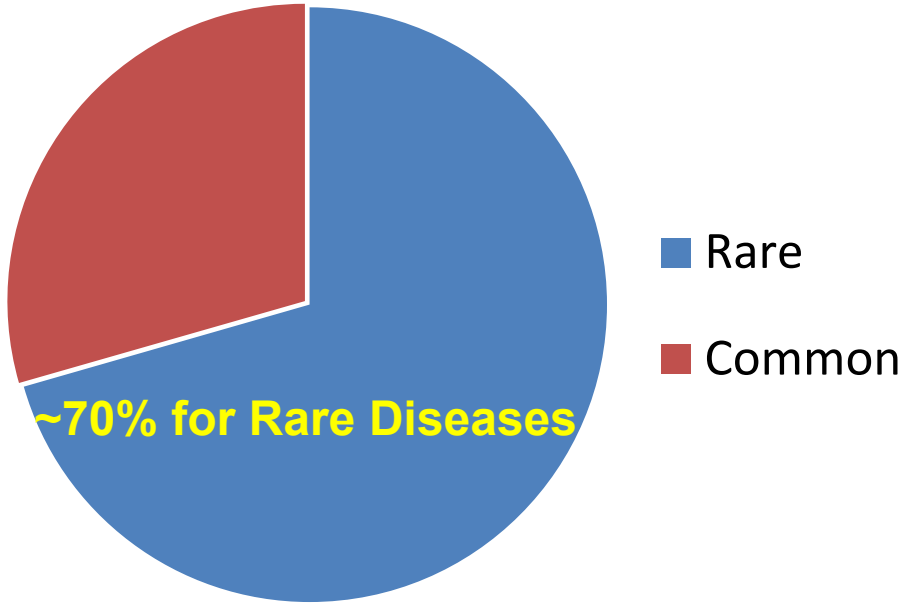


- **Stem cells/stem cell-derived**
 - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
 - Perinatal (e.g., placental, umbilical cord blood)
 - Fetal (e.g., neural)
 - Embryonic
 - Induced pluripotent stem cells (iPSCs)
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Gene therapies**
 - Ex vivo genetically modified cells
 - Non-viral vectors (e.g., plasmids)
 - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
 - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
 - Microbial vectors (e.g., Listeria, Salmonella)
- **Xenotransplantation**
- **Blood products**
 - Coagulation factors
 - Fibrin sealants
 - Fibrinogen
 - Thrombin
 - Plasminogen
 - Immune globulins
 - Anti-toxins
 - Snake venom antisera
- **Devices and combination products**
 - Engineered tissues/organs
 - Selection devices for the manufacture or delivery of cells
- **Tissues**





OTAT Cellular and Gene Therapies Investigational New Drug Applications





Rare Diseases – The Challenges

- Approximately 7,000 rare diseases – only ~ 250 - 300 with treatments
- 25- 30 million Americans or 10% of the US population
- Approximately 50-75% of rare diseases begin in childhood
- 30% of children with rare disease will not live to see their 5th birthday
- Rare diseases responsible for 35% of deaths in first year of life
- High phenotypic variability within individual disorders

An example: dystrophic epidermolysis bullosa



Source: Photo courtesy of
Jackson's Family
<https://www.flickr.com/photos/fdaphotos/5471543751>

Prevalence: ~700 cases in the US



Finding treatments and cures for rare diseases

- Specific endpoints, outcome measures, tools, instruments and biomarkers usually lacking
 - Natural history often poorly defined
 - Clearly defined clinical endpoints, or surrogate endpoints, not established
- Datasets (efficacy and safety) will almost always be small
 - Often limited by what is feasible



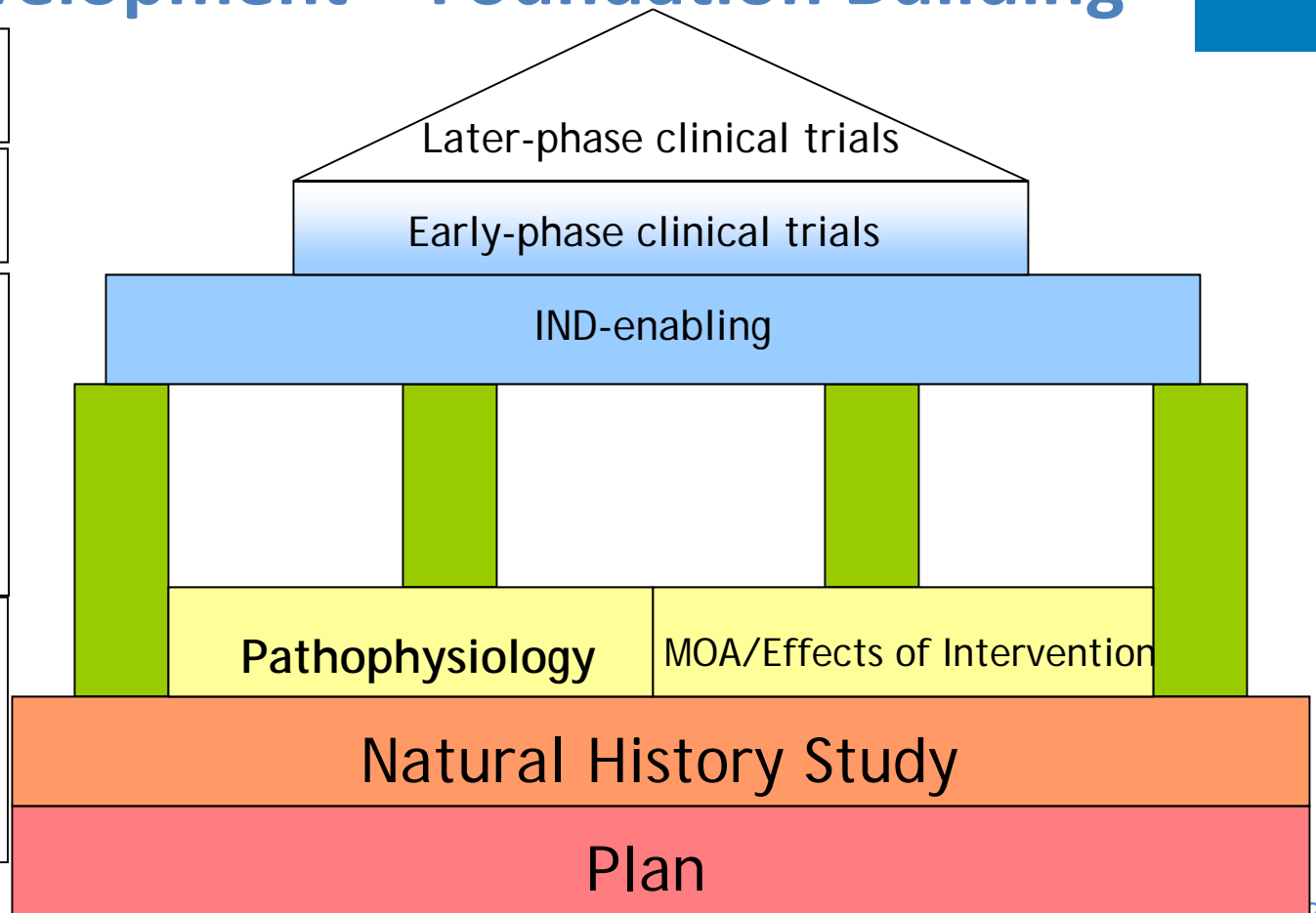
Orphan Drug Act

- The Orphan Drug Act (1983) defines a rare disease as a disorder or condition that affects less than 200,000 persons in the United States.
- The Orphan Drug Act provides incentives to make developing drugs for rare diseases financially viable. Incentives include:
 - protocol assistance;
 - tax credits equal to 50 percent of the qualified clinical testing expenses;
 - waiver of Prescription Drug User Fee Act marketing application fee;
 - orphan product development grants;
 - seven-year marketing exclusivity once the drug is approved by FDA.
- New incentive (2012): Rare pediatric priority review voucher

Drug Development – Foundation Building



- Efficacy trial design
 - Target population
-
- Pilot efficacy
 - Safety
-
- Non-clinical P/T
 - Population
 - Toxicities
 - Dose exploration
 - Biomarker/outcomes exploration
-
- Biomarker and outcomes development
 - Assays/testing
 - Diagnostics
 - Animal models





Begin with the end in mind

- The goal: an approved treatment or cure, commercially available and accessible
- Target Product Profile: imagine the final product prescribing information:
 - Which patients will receive this product?
 - What route of administration?
 - What outcomes will be affected?
 - What studies do I need?
- Plan, plan, plan...

Traditional Clinical Development

Phase 1 objectives

- Safety, tolerability, maximum tolerated dose, pharmacokinetics (if feasible), and activity / efficacy
- Guide dosing and monitoring of subsequent Phase 2 studies

Phase 2 objectives

- Determine dose, route, regimen, population, endpoints, and estimated magnitude of effect
- Guide design of subsequent confirmatory (Phase 3) studies

Phase 3 objectives

- Evidence of effectiveness and safety to support a marketing application (e.g., Biologics License Application (BLA))



Realistic Clinical Development in Rare Diseases

- Typically, Phase 1 and 2 are combined
- Often, a single Phase 3 trial with adaptive design features
- Critical Importance of Natural History (NH) Studies and Data



Natural History Studies

- The NH of rare diseases is often poorly described.
- FDA advises sponsors to evaluate the depth and quality of existing NH knowledge early.
- FDA does not require that NH studies be conducted.
- When knowledge about the disease is insufficient to guide clinical development, a well-designed NH study may help in designing an efficient drug development program.



Natural History Studies

Knowledge about the NH can inform important aspects of drug development:

- Defining the disease population:
 - Assessing the full range of disease manifestations
 - Identifying important disease subtypes
- Understanding and implementation of critical elements of clinical trials:
 - Clinical study design and study duration
 - Biomarker development and choice of endpoints
 - Subpopulations: preferably for the wide spectrum of phenotypes
 - Dose selection
 - Early recognition of safety signals



NH Studies – Historical Controls

- Historically controlled studies have been used in clinical development programs for rare diseases. However, historical controls may be unsuitable for adequate and well-controlled studies in many circumstances.
- In general, historically controlled studies are credible only when the observed effect is large in comparison to variability in disease course.



Types of NH Studies

- Published medical literature review
- Retrospective chart review: a starting place for NH design
- Prospective cross-sectional: helps design the prospective longitudinal
- Prospective longitudinal
- NH knowledge is produced by a knowledge development program
 - May have multiple stages, evolving protocol, learn/ confirm
- Buy-in from stakeholders, mainly patients

Where NH fits in developing therapies



- Ideally:
 - Rare disease NH is well characterized prior to identification of promising therapies
 - NH independent of particular therapies
- Today's reality:
 - Genomic advances define new biomarkers and diseases
 - NH is developed in the context of a specific drug
 - Biomarker exploration and validation of surrogates along a specific drug development program

Regulatory Requirements



- Approval of all drugs – for both rare and common conditions – must be based on substantial evidence of effectiveness and evidence of safety.
- “Substantial evidence” is defined as: “evidence consisting of **adequate and well-controlled investigations**... on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use...”
- Certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases. For rare disease drugs, relying on one such trial with supporting evidence is not unusual, but the adequacy of this approach for any given drug must be considered in the context of the disease, the population, the properties of the drug, and the magnitude of the clinical trial results

Regulatory Requirements



- FDA “exercise[s] its scientific judgment” in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs. This flexibility extends from early phases of development to design of adequate and well-controlled studies needed to show safety and effectiveness to support marketing approval.

21 CFR 314.105

- FDA has a solid record of appropriately applying regulatory flexibility



Application of flexible clinical programs

CDER New Molecular Entity approvals 1/1/2008 – 9/25/2015

Flexible Clinical Programs	Rare Approvals	Non-rare Approvals
Use of ≥ 1 flexible approach	81% (73 / 90)	36% (64 / 177)

- Flexible clinical programs are defined as approval supported by other than 2 AWC Studies and / or use of a novel endpoint
- In contrast to Traditional Development, defined as ≥ 2 AWC using endpoints with prior precedents

Modified from Dr. John Jenkins presentation to NORD Summit 2016



Regulation of Gene Therapy

- Traditionally, the domain of academic medicine
- Recent increase in interest by large pharmaceutical companies
- To get this right from the beginning: get buy-in from rare disease patient network, harmonized advice from different regulatory authorities, plan for global trials for a reasonable enrollment rate: collaborate!!

Gene Therapy

Challenges



- Manufacturing and delivery of the product: patient access
- One dose can have prolonged or permanent effect: subject with rare disease cannot try multiple products and/or can try only few different doses
- Immunogenicity to vector (e.g., AAV capsid), transgene or the protein expressed can also be prolonged or permanent



Gene Therapy

Challenges (Continued)

- Tweaking the product to improve it is very common during development: comparability issues
- Dose exploration is limited by cost and manufacturing capability
- Often delivery through invasive methods: intra-cerebral, intracardiac

Gene Therapy

Product Development Considerations



- Traditional phases (e.g., Phase 1, 2, 3) are commonly blended into early phases versus late phases (more like learning and confirming)
- Prolonged or permanent effect: a subject in early phase can be followed for years and contribute good long-term efficacy and safety data
- Compared to small molecular drugs or therapeutic proteins, more critical to have early randomized controlled trials, even in first-in-human trials
- EMA Guideline on Clinical Trials in Small Populations – Choice of Control Groups (2006): “Every effort should be made to randomise patients from the beginning of the therapeutic testing phase... In cases where there is no existing treatment, even in life-threatening diseases, the use of placebo as a comparator should be considered. Where a placebo control may not be possible, an appropriate control group may be ‘best standard of care’”
- Develop delivery devices concomitant with the gene therapy, not after

Gene Therapy

Safety Considerations



- Compared to small molecule drugs, less experience with pharmacokinetics, and relatively low concern with drug-drug interaction, drug metabolism, QTc prolongation
- Novel safety concerns: insertional mutagenesis, greater oncogenic potential, viral vector shedding
- Concerns about new gene editing techniques: lack of specificity to target genes, effect on germline?
- These safety assessments leave much more uncertainty when evaluated in a small study population in a trial of a rare disease

FDA Oversight/Collaboration



- Collaboration:
 - Rare disease groups and advocacy organizations
 - NIH National Center for Advancing Translational Sciences
 - International Rare Disease Research Consortium
 - Other regulatory agencies: regularly scheduled cluster meetings or teleconferences
- FDA patient engagement: special government employees, patient-focused drug development meetings
- Clinical reviewer training and awareness

FDA Oversight/Collaboration



- New grants from Office of Orphan Products to NH studies and selected intervention studies
- Coordination and consultation among FDA centers: drugs, biologics and devices and the Office of Health and Constituent Affairs
- Seeking expert opinion from outside FDA: special government employees, patients and advisory committees
- Drug Development Tools (Biomarkers and Clinical Outcome Assessments) Qualification Program

Contact Information



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OCTGT Learn Webinar Series:

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

CBER website: www.fda.gov/BiologicsBloodVaccines/default.htm

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