U.S. FOOD & DRUG ADMINISTRATION

Facilitating Expedited Development of Advanced Therapy Products

CASSS Cell & Gene Therapy Products:

Manufacturing, Quality and Regulatory Considerations

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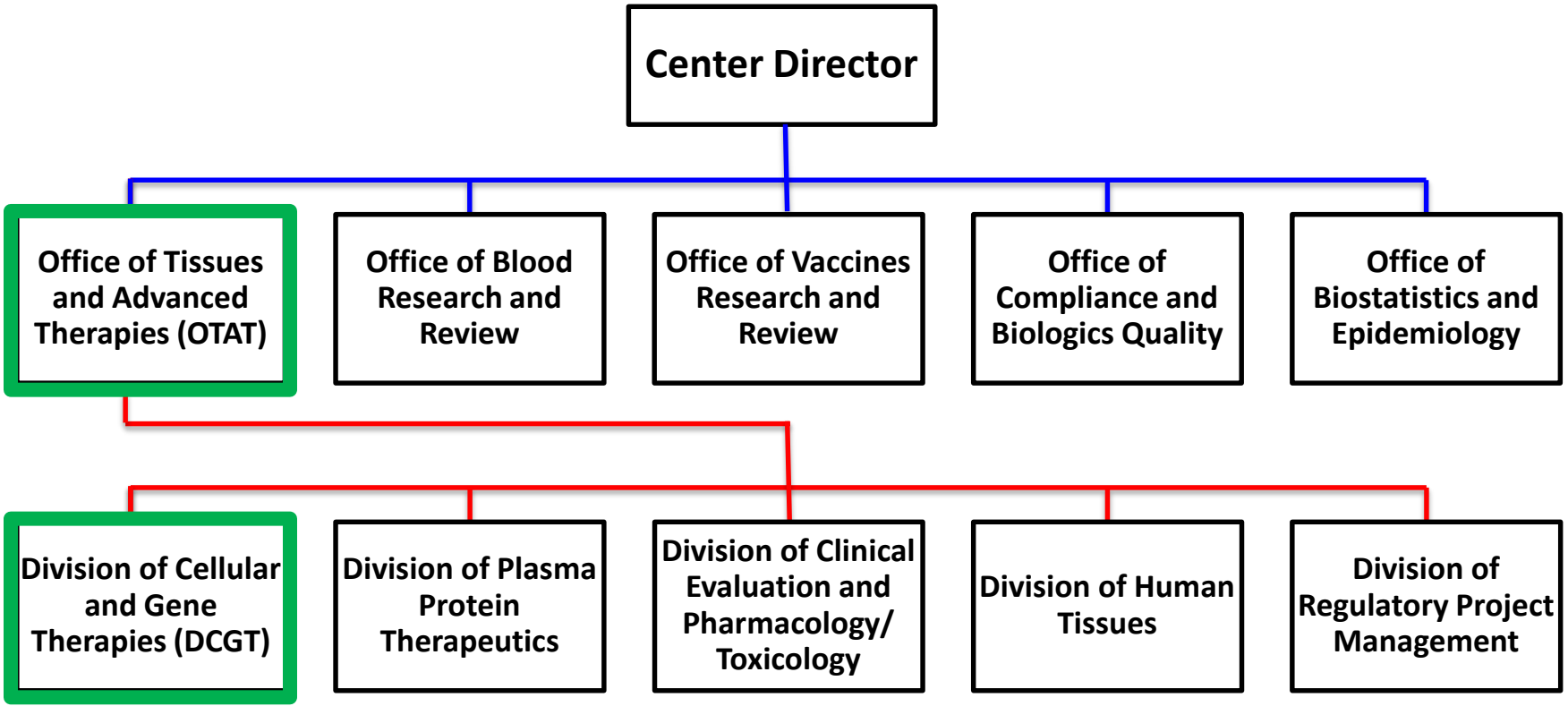
Steven S. Oh, Ph.D.
Deputy Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research, FDA

Outline

- CBER/OTAT & advanced therapies
- Expedited development of advanced therapy products
- CMC considerations for expedited development
- Interaction with CBER/OTAT & INTERACT program
- Conclusion

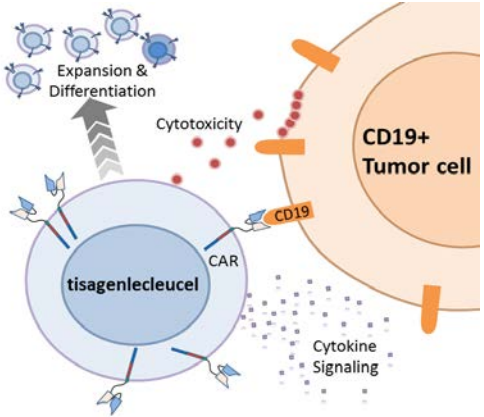
CBER/OTAT & advanced therapies

CBER organization for pre & post-market regulation



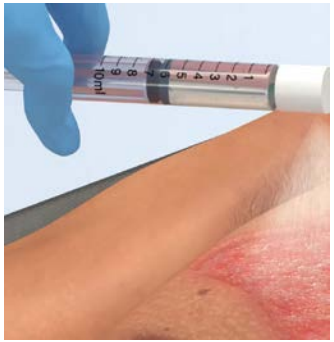
Gene therapy products

- **ZOLGENSMA (onasemnogene abeparvovec-xioi):** Adeno-associated virus vector-based gene therapy for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene
- **LUXTURNA (voretigene neparvovec):** Adeno-associated virus vector-based gene therapy for treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy
- **YESCARTA (axicabtagene ciloleucel):** CD19-directed genetically modified autologous T cell immunotherapy for treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL)
- **KYMRIAH (tisagenlecleucel):** CD19-directed genetically modified autologous T cell immunotherapy for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse; Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL)



Cell therapy products

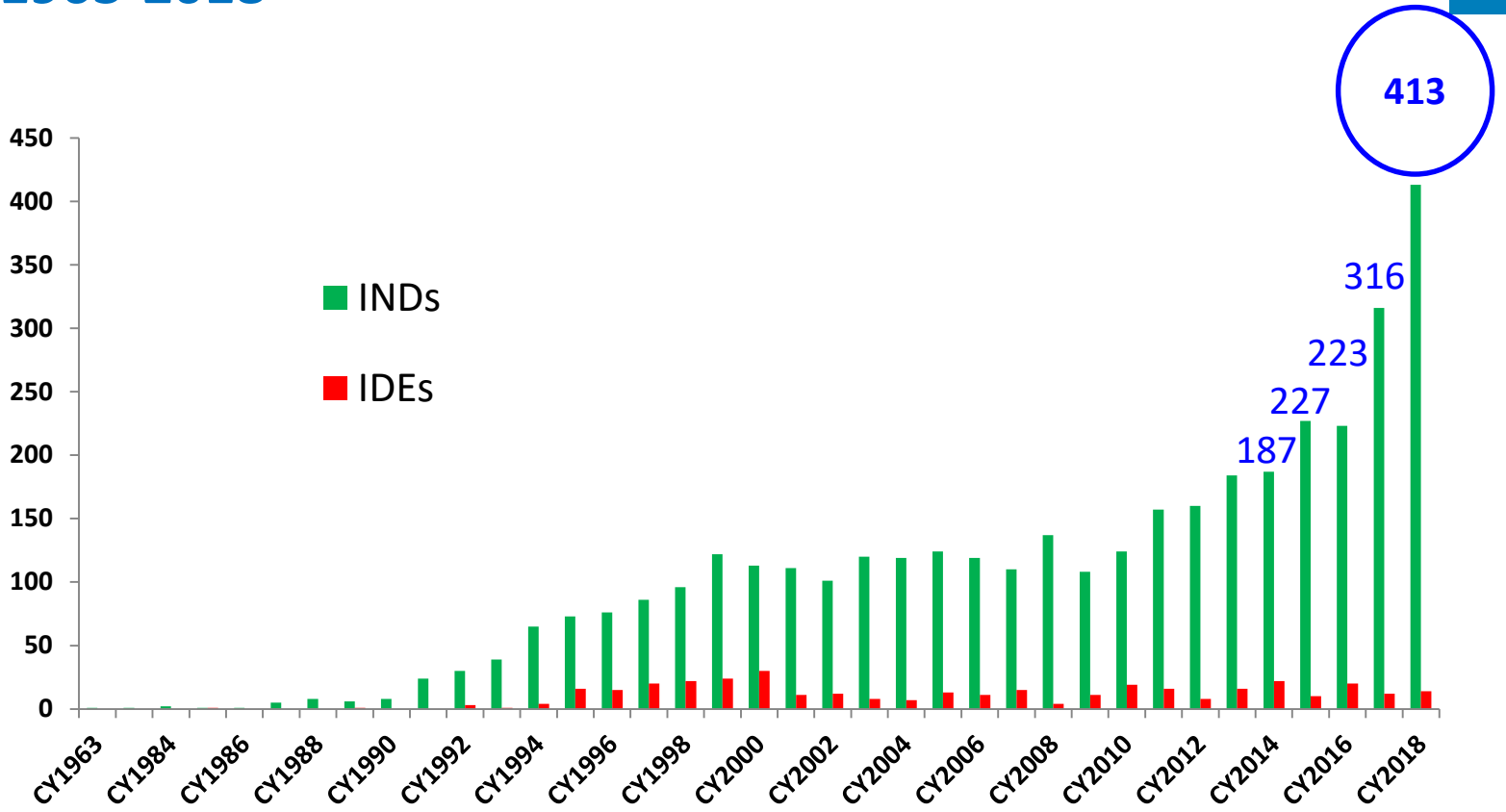
- **RECELL Autologous Cell Harvesting Device:** For treatment of acute thermal burn wounds in adult patients. Used at the patient's point-of-care to prepare autologous Regenerative Epidermal Suspension (RES™) for direct application to acute partial-thickness thermal burn wounds or application in combination with meshed autografting for acute full-thickness thermal burn wounds.



- **MACI (autologous cultured chondrocytes on a porcine collagen membrane):** Autologous cellularized scaffold product for repair of single or multiple symtomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults.
- **GINTUIT (allogeneic cultured keratinocytes and fibroblasts in bovine collagen):** For topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults.
- **PROVENGE (sipuleucel-T):** Autologous cellular immunotherapy for treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer

New INDs and IDEs Submitted to OTAT

CY 1963-2018



Expedited development of advanced therapy products

Expedited development of promising treatments

Expedited Programs

- Accelerated Approval (1992)
- Priority Review (1992)
- Fast Track (FT) (1997)
- Breakthrough Therapy (BT) (2012)
- Regenerative Medicine Advanced Therapy (RMAT) (2016)

FDA Guidance

Expedited Programs for Serious Conditions—Drugs and Biologics (2014)

Expedited Programs for Regenerative Medicine Therapies for Serious Conditions (2019)

Expedited Development Programs – *Criteria*

Accelerated Approval	Priority Review	Fast Track (FT)	Breakthrough Therapy (BT)	Regenerative Medicine Advanced Therapy (RMAT)
-**Serious condition** AND - **Meaningful advantage** over available therapies - Demonstrates an effect on either: a **surrogate endpoint or an intermediate clinical endpoint**	-**Serious condition** AND -Demonstrates potential to be a **significant improvement in safety or effectiveness**	-**Serious condition** AND -**Nonclinical or clinical data** demonstrate the **potential to address unmet medical need** Note: Information to demonstrate *potential* depends upon stage of development at which FT is requested	-**Serious condition** AND -**Preliminary clinical evidence** indicates that the drug may demonstrate **substantial improvement over available therapy** on one or more clinically significant endpoints	-**Serious condition** AND -It is a regenerative medicine therapy - **Preliminary clinical evidence** indicates that the drug **has the potential to address unmet medical needs** for such disease or condition

Expedited Development Programs – *Features*

Accelerated Approval	Priority Review	Fast Track (FT)	Breakthrough Therapy (BT)	RMAT
Approval based on surrogate or intermediate clinical endpoints* ✓ **Save valuable time** in the drug approval process. ✓ **Reduce waiting period to obtain clinically meaningful benefit.**	✓ **Short Review Clock** ✓ **FDA will Take action on an application within 6 months after filing** (compared to 10 months after filing under standard review).	**Frequent meetings** Frequent written communication Eligibility for *: ✓ **Accelerated Approval** ✓ **Priority Review** ✓ **Rolling Review** *if relevant criteria are met	**All of FT Features** **+** ✓ **Intensive guidance** on an efficient drug development program, beginning as early as Phase 1 ✓ Organizational commitment **involving senior managers**	**All of BT Features** **+** **Early discussion** of potential surrogate or intermediate clinical endpoint

BT Designations by product types and indications

Status as of May 31, 2019

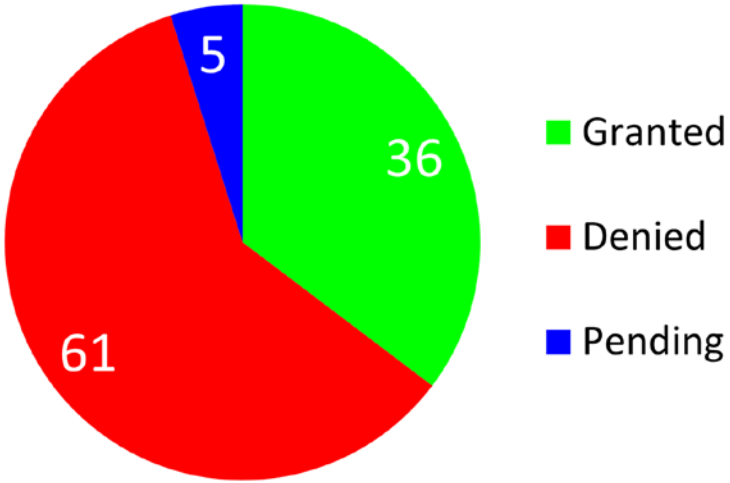
(Excluding withdrawn and pending requests)

Products	Requested	Granted
Gene Therapy	51	24
Cell Therapy	27	4
Others	21	4

Indications	Requests	Granted
Oncology (Solid Tumor)	36	7
Hematology (Malignant and Benign)	29	18
Non-Onco/Hema	34	7

RMAT designation requests

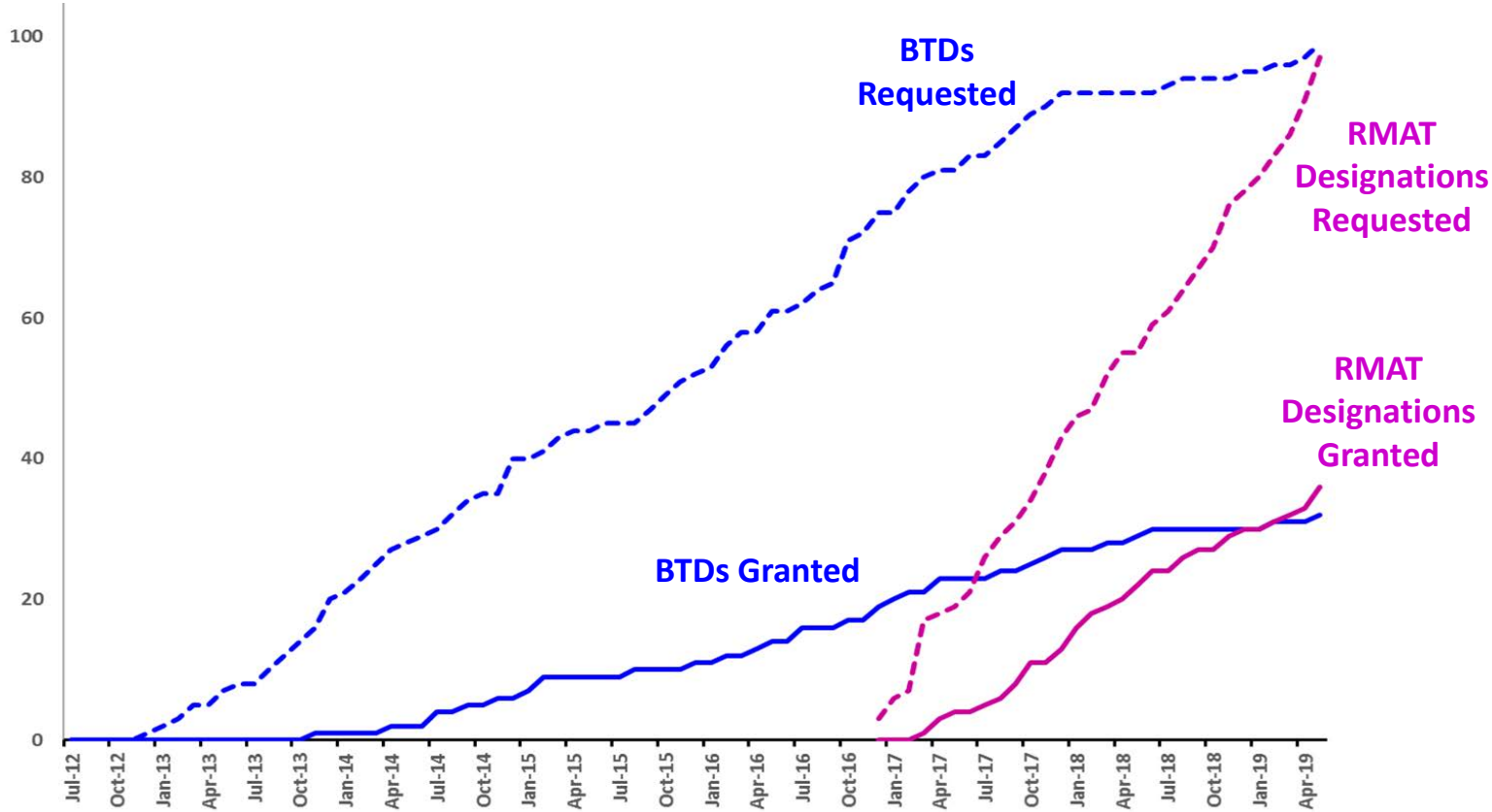
Status as of May 31, 2019



Analysis of denied RMAT requests

- Administrative Reasons
  - Inactive IND
  - No preliminary clinical evidence submitted
- CMC Reasons
  - Clinical data not based on same product
  - Not Qualified for RMAT product
- Insufficient Preliminary Clinical Evidence
  - Study design issues
  - Inconsistent results with regard to product activity

BT and RMAT Designation requests and granted
(cumulative through May 31, 2019)

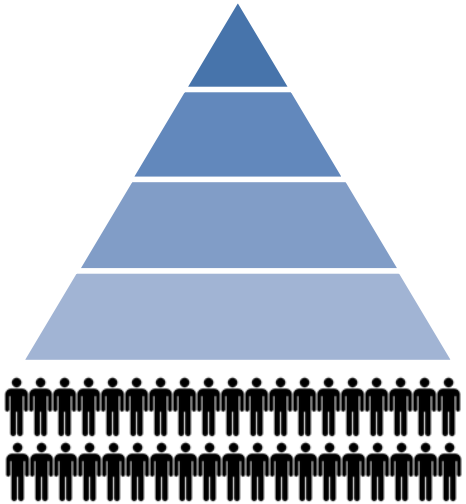


CMC considerations for expedited development

CGT Product manufacturing: a new paradigm

Conventional Drug/Biologic

1 product lot



Many patients

Raw materials

CGMPs

Advanced manufacturing

In process and lot release testing

Scale up/scale out

Comparability

Distribution

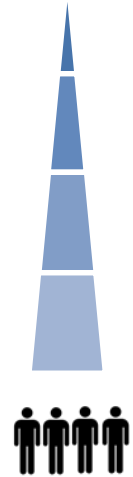
Impact of manufacturing failure

Cell & Gene Therapy Products

1 product lot

Personalized

1 product lot



Few patients

CGT Product: unique manufacturing challenges

- Limited product manufacturing experience prior to licensure (incomplete knowledge of Critical Process Parameters (CPP), limited lots made)
- CQAs not entirely understood due to limited characterization of drug product, drug substance, and in-process material
- Product variability arising from source materials
- Increased demand for qualified reagents and materials
- Assays not fully developed and qualified
- Limited time for testing due to limited material or short shelf-life
- Limited product stability data
- Reproducibility of replacement cell banks
- Complicated planning for advanced manufacturing, process automation, scale up / scale out
- Comparability studies in the absence of reliable reference standards and validated assays
- Direct impact of manufacturing failure on patient

CGT Product expedited development:
CMC expectations

- Clinical program advances rapidly for BT and RMAT products; timelines from early to late development may be compressed
- Accelerated clinical development should not change CMC and CGMP regulatory requirements and expectations
- Need to focus on all CMC and CGMP issues early if CGT Product received a BT or RMAT designation: e.g., CQA/CPP, assay & process development/validation, raw material qualification and supply chain, major manufacturing change
- Planning for commercial scale manufacturing including comparability studies (when needed) should be conducted early (Phase 1/2)
- **Aligning CMC with clinical development is crucial**

CGT Product expedited development:
CMC approach towards licensure

- **Essential goal:** Ensure the availability of a quality product that can be consistently produced at the time of approval
- **FDA may exercise some flexibility** *on the type and extent of manufacturing information* that is expected at the time of submission or approval for certain components to a certain degree. Case by case and dependent on:
  - Product characteristics
  - Seriousness of condition and unmet medical need
  - Manufacturing processes
  - Robustness of quality system
  - Strength of the risk-based quality assessment

- **Areas of potential flexibility**
  - Validation strategies, manufacturing scale-up/ scale-out strategies, use of post marketing commitments or post marketing requirements

CGT Product expedited development:
examples of CMC flexibility in BLA

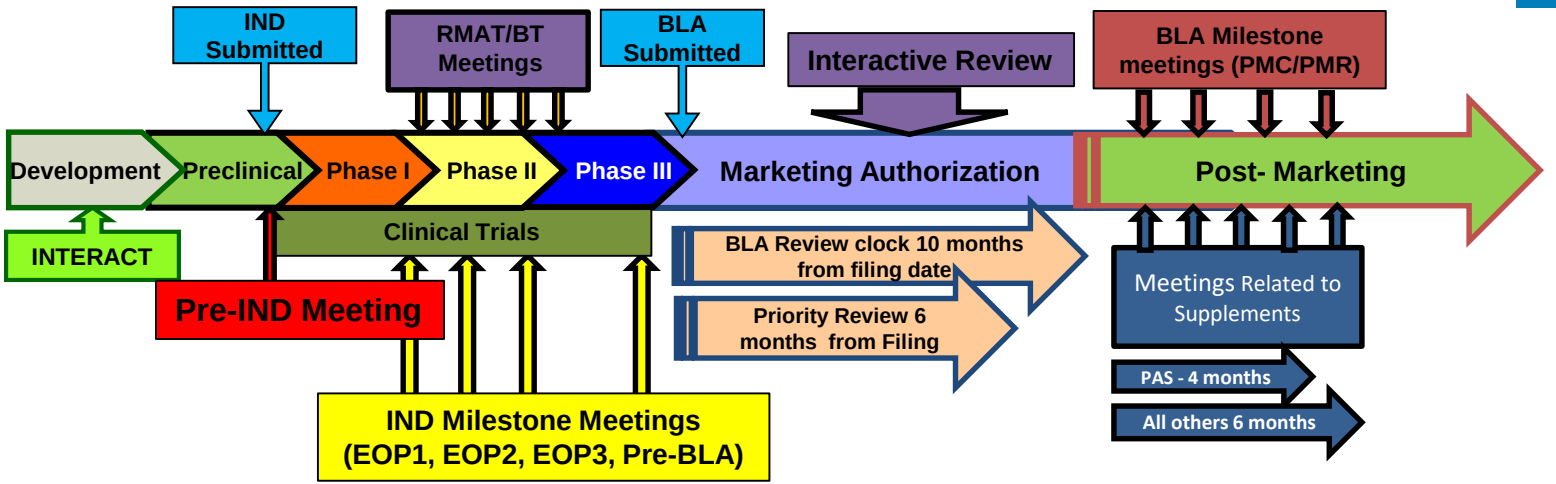
- **Concurrent release** of PPQ batches for distribution before completion of process validation
  - Might be applicable in rare cases, such as:
    Limited demand / limited manufacturing
    To alleviate short supply

- **Stability**
  - DS and DP Stability Protocols
  - Note: CGT Products are out of scope for ICH Q5C (Stability Testing of Biotechnological/Biological Products)
    Prior knowledge / supporting data may be relevant (example: frozen products)

- **Rolling BLA**
  - Submission of Module 3 as the last module in rolling submission

Interaction with CBER/OTAT & INTERACT program

Opportunities for interaction with CBER/OTAT

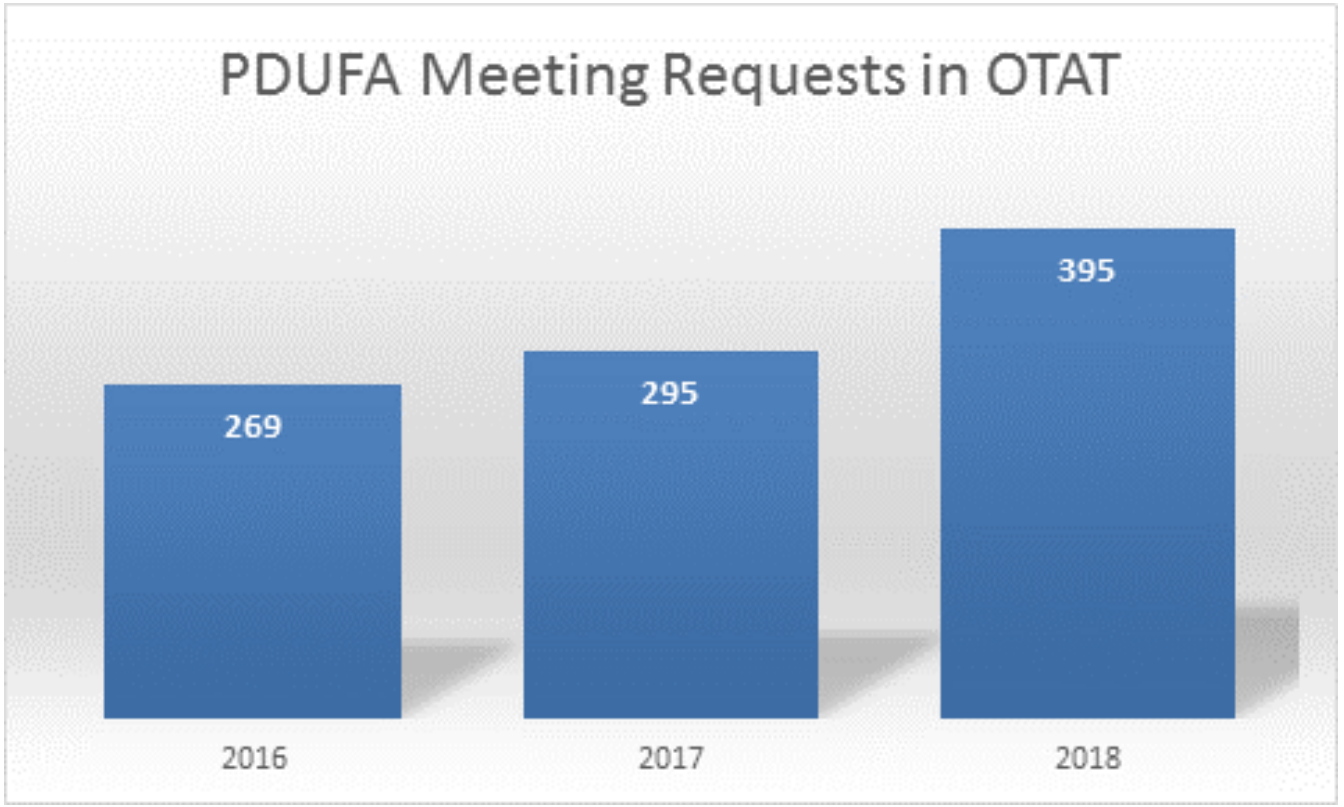


- Novel products & rapid timelines: Increased need for feedback from FDA during CMC development
- Communication is especially useful throughout the product lifecycle for:
  - Topics that lack published guidance
  - Special circumstances
- Provide advice to specific queries (face-to-face, teleconference, or written response)
- Written minutes for formal meetings

INTERACT program in CBER

- **INitial Targeted Engagement for Regulatory Advice on CBER producTs**
  *(previously known as **pre-pre-IND** interactions)*
  https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm
- **Goal:** To obtain preliminary informal consultation at an early stage of a product development; also for innovative investigational products that use complex or novel manufacturing technologies, innovative devices, or cutting-edge testing methodologies
- **Purpose**
  - A mechanism for early communication with CBER/OTAT
  - Not intended to take the place of a pre-IND meeting for products that are further along the development pathway
  - Informal, nonbinding advice from FDA regarding CMC, pharm/tox, and clinical aspects of the development program

Meeting Requests received by OTAT



Conclusion

Summary

- CGT Products require a new manufacturing paradigm and have many unique CMC challenges
- BT and RMAT designations provide numerous benefits towards a rapid clinical development of a novel therapy for serious or life-threatening conditions
- Due to significantly compressed timeline for clinical development under expedited programs, however, focusing on CMC development early and aligning it with the accelerated clinical program is crucial
- Invest enough resources in product characterization (including identification of CQAs) and assay development during early stages of the expedited program
- FDA may exercise some flexibility on the type and extent of manufacturing information in certain areas towards CGT Product license application; however, case-by-case per product
- Novel CGT Products and rapid timelines may require increased need for CMC feedback from FDA; interaction opportunities are available throughout the product lifecycle
- INTERACT is a new CBER program for obtaining informal, nonbinding advice before pre-IND; particularly suitable when using complex or novel manufacturing technologies or cutting-edge testing methodologies

Contact information

- **Steven S. Oh, PhD**
  Email: steven.oh@fda.hhs.gov
- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190
  Email: OTATRPMS@fda.hhs.gov and
  Lori.Tull@fda.hhs.gov

FDA Headquarters

- **OTAT Learn Webinar Series:**
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm

  Phone: 1-800-835-4709 or 240-402-8010

- **Consumer Affairs Branch**: ocod@fda.hhs.gov
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