FDA Regulatory Perspective: What has Changed and What is Missing to Move Single Agents into Clinical Trials

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National Academies Workshop,
Addressing Resistance in the Development
of Cancer Immune Modulator Therapeutics
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Disclosures

- My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.
- I have no financial relationships to disclose.

Outline

- FDA Regulation of Cell and Gene Therapy Products
- Risk-Benefit Considerations of Cellular and GT products
- Specific Examples (approved and investigational)
- Special Pediatric Considerations
- Summary

OTAT-Regulated Products

- **Gene therapies (GT)**
  - 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)
- **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)

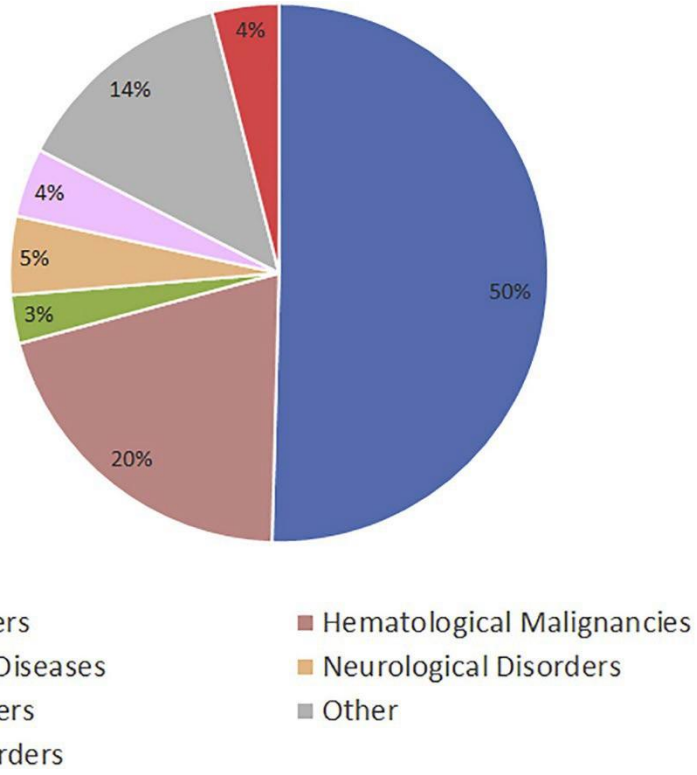
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Immune globulins
  - Anti-toxins
  - Anti Venin antisera for scorpions, snakes, and spiders
- **Combination products**
  - Engineered tissues/organs
- **Certain Devices**
- **Tissues ~~(~~Human and Xeno transplant~~)~~**

Cellular Immunotherapies for Cancer

- Majority (~70%) of CBER OTAT INDs are for anticancer indications
- First approved product was Sipuleucel-T (Provenge) 2010 for prostate cancer
  - Autologous cell therapy product, (not a gene therapy)
  - Tracking, manufacture, shipping present complex logistical challenges
  - Competing products limited commercial success
- Cell Transfer Therapy with Tumor Infiltrating Lymphocytes – (NCI)*
  - Identify, expand, and infuse mutation-reactive T-cells following lymphodepletion
  - Melanoma 50% ORR (N=226)*
  - Some patients with epithelial cancers experience clinical benefit (complete responses)
- "Engineered" T cells – vector insertion of transgene
  - Autologous, Allogeneic

*Rosenberg et. al., Clin.Cancer Res. 2021

Majority of IND Applications are in Solid Cancers and Hematological Malignancies

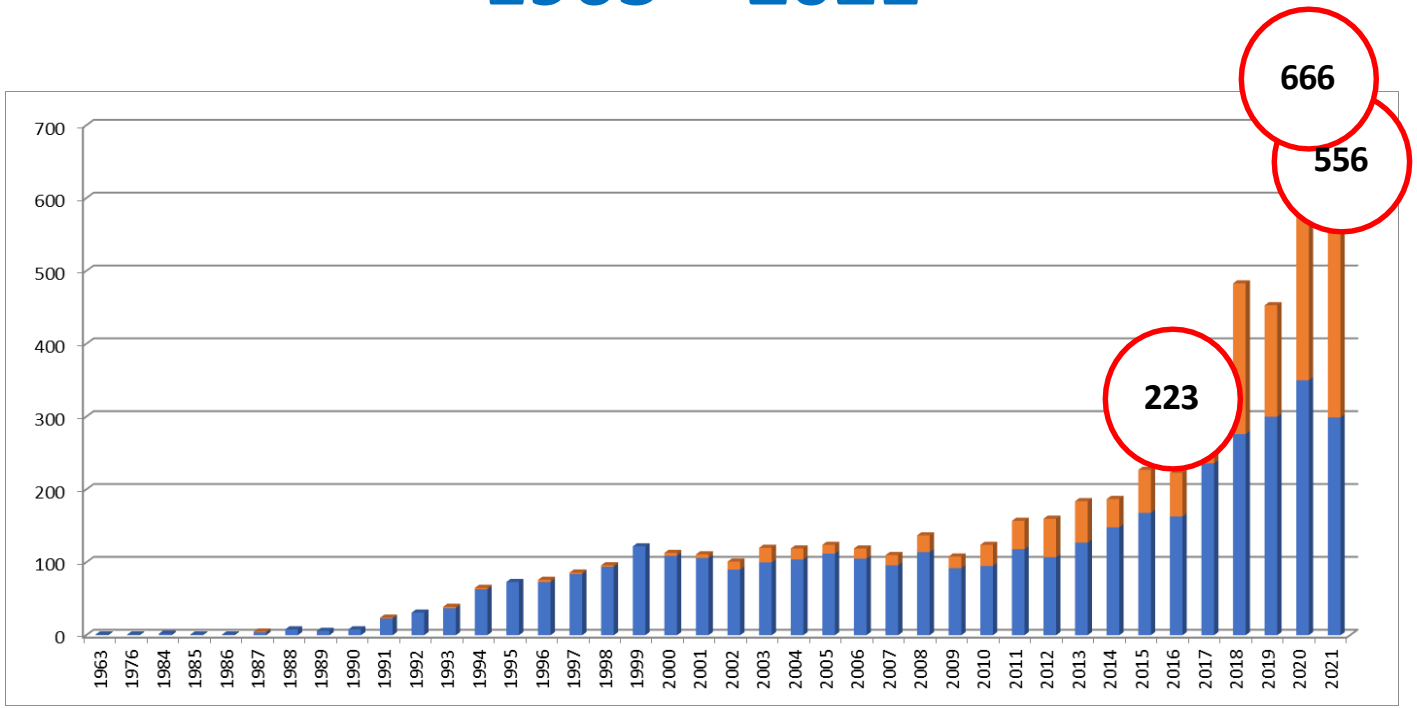


Lapteva L et al. Mol Therapy 2020;19:387-397

OTAT INDS

(i.e., Research and Expanded Access (EA))

1963 – 2021



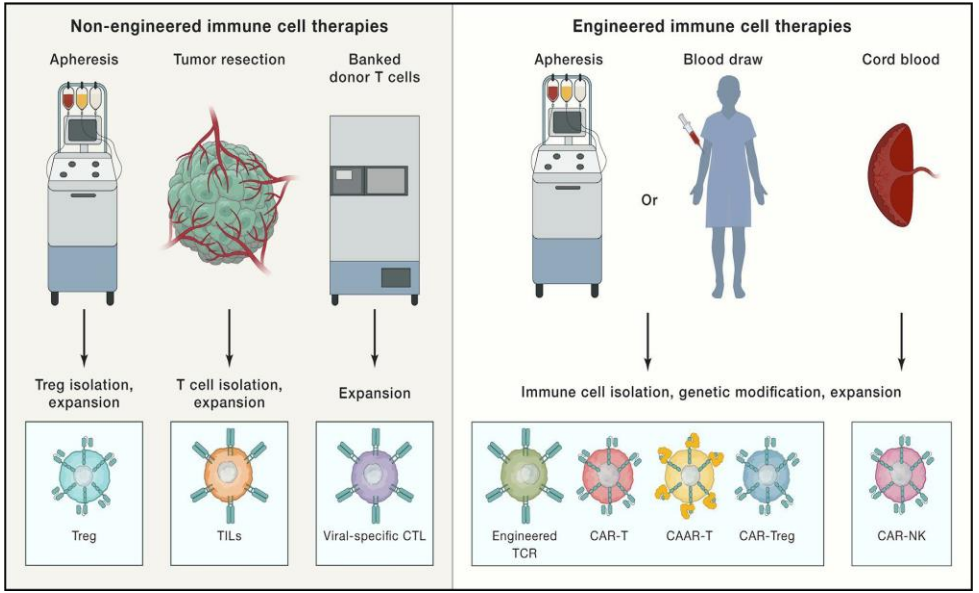
Cellular Immunotherapies for Cancer

Non-engineered cells

- Dendritic cells
- Tumor infiltrating lymphocytes (TILs)

Engineered cells

- Engineered T cell receptor (TCR)
- Chimeric antigen receptor (CAR) T cells
- Chimeric autoantibody receptor (CAAR) T cells
- CAR-regulatory T cells (CAR-Treg)
- CAR-expressing Natural Killer cells (CAR-NK)



Weber EW et al. Cell 2020;181:46-47

Engineered T cells for treatment of Cancer

- CARTs have demonstrated high response rates in refractory hematologic malignancies
  - Chronic Lymphocytic Leukemia – ORR 40-60% *
  - Acute Lymphoblastic leukemia 60 – 80% CR/Cri
  - Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL) 30-60% CR
  - Relapsed or Refractory Follicular Lymphoma 60% CR
  - Relapsed or Refractory Mantle Cell Lymphoma – 60% CR
  - Relapsed/Refractory Multiple Myeloma 70% ORR (B-cell maturation antigen)
- Results in solid tumors have been less compelling
  - Focus has been on Engineered T cell receptor (TCR) products directed against tumor specific antigens: MAGE, NYESO, PSMA, Claudin, etc.

Response rates from package inserts,
*Maus, et. al., Semin Oncol. 2017

Optimizing Benefit Risk in order to Move Single Agents into Clinical Trials

- Single arm studies should generally focus on
  - Relapsed/Refractory to available therapies
  - Potential for Accelerated Approval based on response
  - Contribution of effects a challenge for combinatorial studies
- Specific targets may require a companion diagnostic (CDx) assay
  - Antigenic targets (CDRH)
  - HLA restrictions (CBER OBRR)
- CDx Assays may require a Study Risk Evaluation (protocol-specific) assessing
  - Are subjects forgoing standard of care?
- Significant Risk devices require investigational device exemptions (IDE)

What is a companion diagnostic (CDx)?

A companion diagnostic is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product.

Companion diagnostics can:

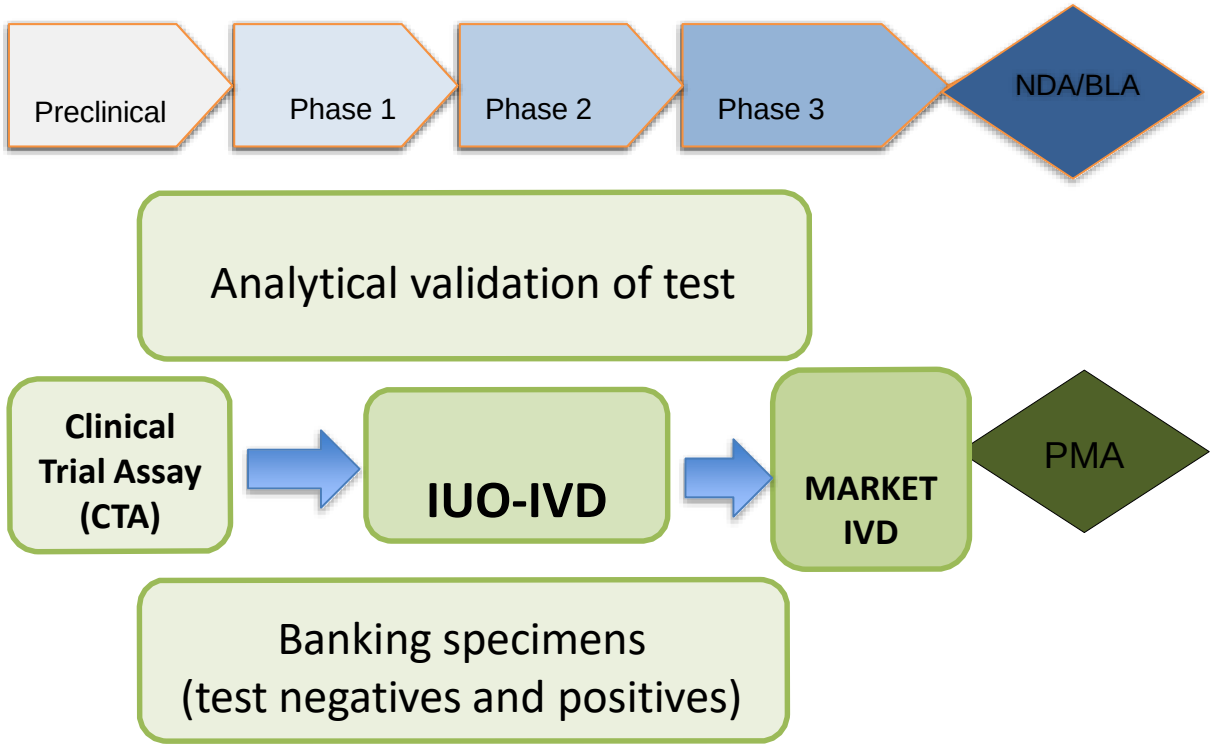
- Identify patients who are most likely to benefit from a particular therapeutic product;
- Identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- Monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

If the diagnostic test is inaccurate, then the treatment decision based on that test may not be optimal.

See FDA Draft Guidance for Industry: Principles for Codevelopment of an In Vitro Companion Diagnostic 3 Device with a Therapeutic Product (2016)

Co-development – Idealized scenario

PLAN EARLY!

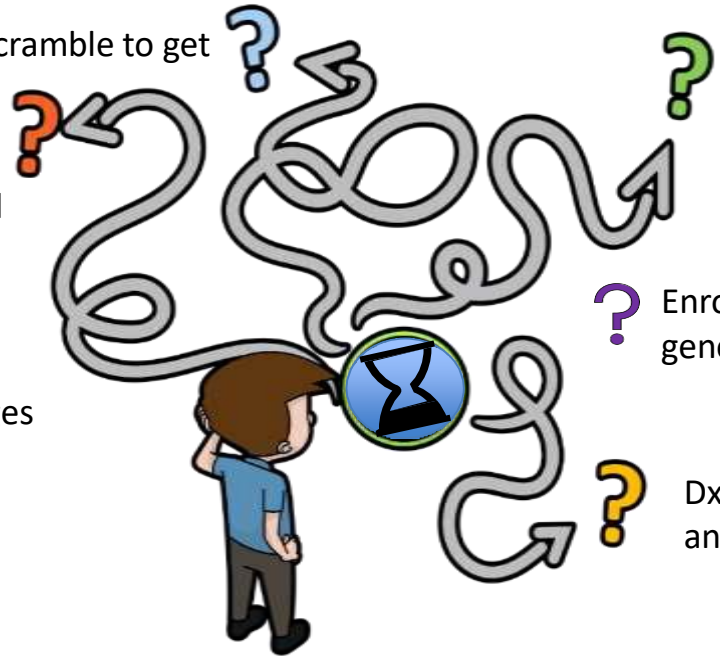


More realistic scenario:
Need to bridge a CDx to clinical trial assay(s)

Early phase data
used to support the Rx - Scramble to get specimens

Post-hoc, retrospective analyses points to a better cut-off or safety concerns

Variety of LDTs used to enroll patients; Absence of screen negatives



Enrollment leads to variety of unexpected genetic variants

Mid-trial test changes

Dx brought in late – inability to meet anticipated timelines

How do I determine if I have an SR investigational device?

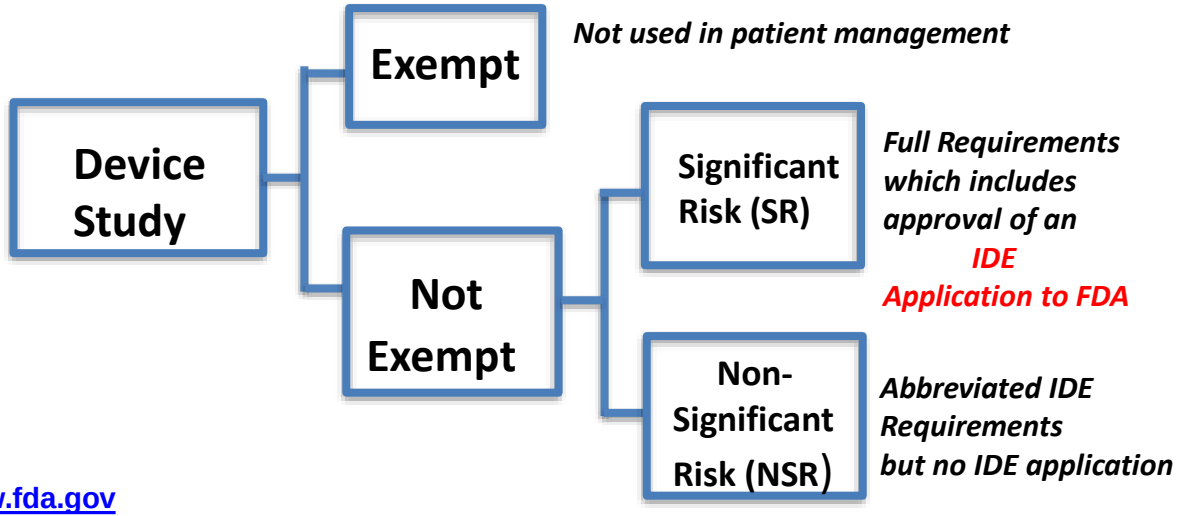
- IRB or FDA can make this determination
- Submit a Study Risk Determination Risk request either to CDRH, or in the IND (as part of Streamlined Risk Assessment)
- Describe why you believe the test is non-significant Risk (NSR) based on 4 criteria:

  1. Are patients foregoing effective treatments?
  2. A priori information about safety or efficacy in the biomarker subset?
  3. Will patients be exposed to excessive safety risks?
  4. Are there significant risk procedures for obtaining the specimen?

  Include details of the assay methods (molecular analysis, immunohistochemistry, etc.) including cut points for positivity and who will analyze the specimens

Do I need an Investigational Device exemption (IDE)?

- IDE enables use of an investigational test
- Tests used to select patients for investigational Rx are investigational
- Irrespective of phase or number of patients
- IDE requirements are also based on risks to patients.



Companion Diagnostic – Clinical Validation

Assay should be fully specified /locked down and analytical validation completed at time of confirmatory trial initiation

Need to avoid turning validation set into training set

- If you optimize your CDx based on results of your pivotal trial, you have turned that specimen set into a “training set” which can no longer be considered the “clinical validation set”

***Clinical validity is supported by the trial results*.**

Companion Diagnostics Summary

- Planning to develop a companion diagnostic can optimize risk/benefit in order to facilitate bringing single agents into clinical trials
- Identify biomarker and assay methodology early and submit details to FDA
- Study Risk/need for IDE may be determined by IRB but FDA is final arbiter
- Assay should be fully specified/locked down and analytical validation completed at time of confirmatory trial initiation
- Clinical validation at time of PMA/BLA submission

Resources – Companion Diagnostics

Draft Guidance on Principles for a Codevelopment of Companion Diagnostic Devices with therapeutic product (2016)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-codevelopment-vitro-companion-diagnostic-device-therapeutic-product

Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry (2019) https://www.fda.gov/media/112605/download

Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products (2020) https://www.fda.gov/media/120340/download

Useful CBER OTAT Information

- References for the Regulatory Process for the Office of Tissues and Advanced Therapies

  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

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

- Cell and Gene Therapy Guidances https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

  https://www.fda.gov/media/120267/download

- Cellular, Tissue and Gene Therapies Advisory Committee (next meeting June 9-10, 2022)

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Thank you!

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- **OTAT Learn Webinar Series:**

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