ISCT
Laboratory Practices Committee
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Potency Testing in Cell and Gene Therapy Products

- Outline
  - FDA Requirement for Potency
  - Define Potency
    - Pharmaceuticals
    - Biologics
  - Methodologies of Potency Tests
  - Solutions/Standardization
  - Conclusions

Requirements for Biological Products

- Per 21 CFR Subchapter F: Biologics Subpart A – Release Requirements
  - Sec. 610.1
    - *"No lot of any licensed product shall be released by the manufacturer prior to the completion of tests of conformity with standards applicable to the product."*
  - Sec. 610.2
    - *"Upon notification of the Director, Center for Biologics Evaluation and Research (CBER), a manufacturer shall not distribute a lot of biological product until the lot is released by the Director, CBER: Provided, that the Director, CBER shall not issue such notification except when deemed necessary for the safety, purity, and* ***potency*** *of the product."*

- Requires manufacturers to generate and maintain potency data should CBER request it.

Accessed at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=610&showFR=1&subpartNode=21:7.0.1.1.5.1. Accessed on 8/6/22.

General Biological Products Standards

- Per 21 CFR Subchapter F: Biologics Subpart B – General Provisions
  - Sec. 610.10 *Potency*
  - Sec. 610.12 *Sterility*
  - Sec. 610.13 *Purity*
  - Sec. 610.14 *Identity*
  - Sec. 610.15 *Constituent materials*
  - Sec. 610.16 *Total Solids in Serums*
  - Sec. 610.17 *Permissible Combinations*
  - Sec. 610.18 *Cultures*

- Intended to quantitatively ensure product quality and characterization throughout phases of clinical research and following approval

Accessed at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=610&showFR=1&subpartNode=21:7.0.1.1.5.2. Accessed on 8/6/22.

What is *Potency?*

- Synonymous with ‘Strength’
- Pharmaceuticals (small molecules and tablets)
  - Concentration or Dose of Active Pharmaceutical Ingredient (API)
  - Key component of pharmacokinetic (PK) and pharmacodynamic (PD) evaluation with extrapolation to dose-response, toxicity, and clearance
- Biologics
  - 21 CFR 600.3(s) The word *potency* is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.
  - CGT ideally persist and do not adhere to traditional PKs and PDs

Accesed at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.3. Accessed on 8/6/22

What is *Potency?*

- May aid in defining efficacy by establishing correlation between biologic activity and clinical outcomes
  - Clinical outcome longitudinal studies required
  - Methodology of Potency tests not standardized
    - Product attributes and biological activities that contribute to function can vary from product to product
  - Assay(s) may evolve through clinical trials or true potency assay suboptimal for lot release
  - Results of potency tests not public record
    - Exist for CBER director review on an as needed basis

Accesed at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.3. Accessed on 8/6/22

2011 FDA Guidance

- Variable methods/flexibility by which potency can be measured for each Investigational New Drug or Biological License Application
- However, all Potency Tests/Assays must
  - Indicate potency (biological activity/activities) specific to the product (21 CFR 600.3(s) and 610.10; and 21 CFR 210.3(b)(16)(ii));
  - Provide test results for release of the product (21 CFR 610.1; 21 CFR 211.165(a));
  - Provide quantitative data (21 CFR 211.194; see also 21 CFR 600.3(kk); 21 CFR 211.165(d); 211.165(e);
  - Meet pre-defined acceptance and/or rejection criteria (21 CFR 211.165(d); see also 21 CFR 600.3(kk); and 21 CFR 210.3(b)(20));
  - Include appropriate reference materials, standards, and/or controls (see 21 CFR 210.3(b)(16)(ii) and 211.160);
  - Establish and document the accuracy, sensitivity, specificity and reproducibility of the test methods employed through validation (21 CFR 211.165(e) and 211.194(a)(2));
  - Measure identity and strength (activity) of all active ingredients (21 CFR 211.165(a); see also 21 CFR 210.3(b)(7));
  - Provide data to establish dating periods (see 21 CFR 600.3(l) and 610.53(a)); and
  - Meet labeling requirements (21 CFR 610.61(g)(3) and 610.61(r))
- Applies to Autologous and Single Dose Allogeneic products where lot may consist of a single dose

Accessed at https://www.fda.gov/files/vaccines,%20blood%20%26%20biologics/published/Final-Guidance-for-Industry--Potency-Tests-for-Cellular-and-Gene-Therapy-Products.pdf. Accessed on 8/6/22

2011 FDA Guidance

Challenges to Potency Assay Development for CGT products:	Examples:
Inherent variability of starting materials	• Autologous and allogeneic donor variability • Cell line heterogeneity • Error-prone replicating viruses
Limited lot size and limited material for testing	• Single dose therapy using autologous cells suspended in a small volume
Limited stability	• Viability of cellular products
Lack of appropriate reference standards	• Autologous cellular material • Novel gene therapy vectors
Multiple active ingredients	• Multiple cell lines combined in final product • Heterogeneous mixtures of peptide pulsed tumor and/or immune-modulatory cells • Multiple vectors used in combination

Accessed at https://www.fda.gov/files/vaccines,%20blood%20%26%20biologics/published/Final-Guidance-for-Industry--Potency-Tests-for-Cellular-and-Gene-Therapy-Products.pdf. Accessed on 8/6/22. Adapted from Table 1 on page 6

2011 FDA Guidance

Challenges to Potency Assay Development for CGT products:	Examples:
The potential for interference or synergy between active ingredients	• Multiple genes expressed by the same vector • Multiple cell types in autologous/allogeneic cell preparations
Complex mechanism of action(s)	• Multiple potential effector functions of cells • Multiple steps required for function such as infection, integration, and expression of a transgene • Vectors containing multiple genes
In vivo fate of product	• Migration from site of administration • Cellular differentiation into the desired cell type • Viral or cellular replication • Viral vector infection, uncoating, and transgene expression

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Accessed on 8/6/22. Adapted from Table 1 on page 6

2011 FDA Guidance

- Examples of Potency Analytical Methods
  - Bioassay – quantitative measurement of activity in living biological system
    - *in vivo* animal studies
    - *in vitro* organ, tissue, or cell culture system
    - Combination
  - Non-biological – surrogate measurement of biological activity/attributes with correlation studies
    - Immunochemical
    - Biochemical
    - Molecular
  - Multiple Assays/Assay Matrix – multiple complementary assays that measure different product attributes associated with quality, consistency, and stability
    - Combination of biological, biological and non-biological, or non-biological assays
    - Results
      - Quantitative in units of activity
      - Qualitative (Pass/fail) – should be accompanied by one or more quantitative result(s)
- The more methods employed the more variables present and complicated a potency assay may become

Accessed at https://www.fda.gov/files/vaccines,%20blood%20%26%20biologics/published/Final-Guidance-for-Industry--Potency-Tests-for-Cellular-and-Gene-Therapy-Products.pdf. Accessed on 8/6/22

2011 FDA Guidance

- Potency Assay validation plan includes assessment of:
  - Accuracy
  - Precision (Repeatability, Intermediate Precision)
  - Specificity
  - Linearity and Range
  - System Suitability
  - Robustness

Accessed at https://www.fda.gov/files/vaccines,%20blood%20%26%20biologics/published/Final-Guidance-for-Industry--Potency-Tests-for-Cellular-and-Gene-Therapy-Products.pdf. Accessed on 8/6/22

What is the Best/Right Potency assay?

- As of yet – undefined
- Estimate >15,000 patients treated with CAR-T therapy[1], every dose of which should have Potency Assay results
  - Wealth of data that could identify most efficacious potency targets through multivariate analysis
  - Potency of CAR-T therapy may not translate directly into NK, Dendritic, TIL, allogenic, solid tumor, or any other CGT
- Public-Private partnership
  - Required to advance the CGT field
  - Synergistic opportunities to improve patient outcomes[2]
  - Policies that provide access to Potency Assay data at clinical trial sites and willingness of industry partners to release data would likely overcome this hurdle

[1]Accessed at https://www.pennmedicine.org/news/news-releases/2022/may/penn-medicine-and-chop-announce-partnership-with-costa-rica-for-car-t-cell-therapy#:~:text=%E2%80%9CAt%20least%2015%2C000%20patients%20across,therapies%2C%E2%80%9D%20said%20Carl%20H. Accessed on 8/6/22

[2]Tierney, W.M., Meslin, E.M. & Kroenke, K. Industry Support of Medical Research: Important Opportunity or Treacherous Pitfall?. *J GEN INTERN MED* **31,** 228–233 (2016). https://doi.org/10.1007/s11606-015-3495-z

Conclusions

- Potency Assays are required by the FDA for lot release even for single dose products
- Purpose of Potency Assay is to ensure quality/activity of the product
  - Ideally provide data to correlate to efficacy
  - Multiple methods available for flexibility of manufacturers to develop Potency Assays
  - CGT products are complex potentially resulting in complex potency assays for efficacy or potentially more simple assessments for lot release
- Methods for Potency Assays include Bioassays, Non-bioassays, or Matrix assays with specific components assessed during validation plan
- The ideal Potency Assay is not defined
  - Conundrum that Potency is required for lot release and may not reflect efficacy
  - Potency Assay data as of this snapshot has not be analyzed