Cell Therapy Products: Framework for Relating Mechanism of Action, Potency & Efficacy

FDA Cell Therapy Liaison Meeting

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Issue: Confusion Regarding Mechanism of Action, Potency & Efficacy for Cell Therapy Products

- 4th Cell Therapy Potency Assay Summit (March 11-12, 2025)

- Tissue Engineering and Therapeutics: Takeaways from a Scientific Workshop, Alliance for Regenerative Medicine, 2024. Accessed February 14, 2024: https://alliancerm.org/tissue-engineering-whitepaper/

- Welch AR. CGT Potency Assays: When Will We Wake Up From The Nightmare? Cell & Gene Collaborative, 2022. Accessed August 23, 2024: https://www.cellandgene.com/doc/cell-and-gene-therapy-potency-assays-when-will-we-wake-up-from-the-nightmare-0001?utm_source=Onesignal&utm_medium=Pushnotification&utm_term=Assays

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Solution: Separate definitions for 6 concepts

Lab

Mechanism of action	**Effect:** an effect that one is trying to achieve
Potency	**Measurand:** attribute that is measured to see if the effect has been achieved
Potency test	**Measurement:** how the attributes will be measured

Clinical

Efficacy	**Effect:** an effect that one is trying to achieve
Efficacy endpoint	**Measurand:** attribute that is measured to see if the effect has been achieved
Efficacy endpoint test	**Measurement:** how the attributes will be measured

Potency ≠ Efficacy

"To me, potency means that the product is guaranteed to be effective."

Comment at 2015 NIST Cell Therapy Workshop

- Potency is often equated to clinical efficacy
- Concepts are mixed in 21 CFR 600.3(s)
  - Potency [21 CFR 600.3(s)]: **"**The specific ability or capacity of the product, as demonstrated 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."
- How can they be the same if you measure one by clinical trial & the other by lab test?
- "Potency is laboratory, efficacy is clinical & they are tied together by the MOA."

2023 FDA Draft Guidance - Potency Assurance for Cellular & Gene Therapy Products

> **Page 1, Lines 19-21:** "The goal of a potency assurance strategy is to ensure that every lot of a product released will have the specific ability or capacity to achieve the intended **therapeutic effect**."
>
> *Replace "therapeutic effect" with "mechanism of action"?*

ensure: to make sure, certain, or safe : guarantee (Merriam-Webster's)

Proposed

Potency: An attribute of a product that enables it to achieve its intended mechanism of action

Leave clinical out of it...

What if aspirin doesn't cure a headache?

- If a person takes an aspirin & their headache is not alleviated…
  - Does that mean the aspirin is not potent?
- Aspirin is probably potent, inhibits cyclooxygenase & blocks prostaglandin synthesis
- Headache may be caused by factors unrelated to cyclooxygenase or prostaglandins

Separate Measurand & Measurement
(separate “potency” from “potency test”)

Measurand: “the quantity or property intended to be measured”

- Use of “intended” is intentional
  - May be impossible to measure what you intend to measure
  - What is actually measured may not be what you intended to measure (experimental artifacts)

Measurement: “process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity”

Independently define the “measurand” (the attribute being measured) and the “measurement”

- Can be many different methods for measuring an attribute and the results may not agree
- No perfect measurements…all measurements have false positives & false negatives

Source of Definitions: International Vocabulary of Metrology - Basic and General Concepts and Associated Terms (VIM), 3rd Edition. Joint Committee for Guides in Metrology (JCGM) 200:2012

Measurand: Cell Viability	vs.	Measurements: MTT Assay & Trypan blue staining

Definition of a Viable Cell: a cell that is alive; often characterized by 1) an intact membrane and the ability to 2) metabolize nutrients, 3) proliferate & 4) react to stimuli (ASTM F2739)

Measuring Cell Viability: There are a >100 different methods for assessing cell viability

- Each method has a unique measurand (they measure different things)
- Results from the various methods may not agree, even when analyzing the same specimens

Case 1: Cell under a stress

High Dehydrogenase Activity => MTT => Live

Poor Membrane Integrity => Trypan blue => Dead

Case 2: Cell under a different stress

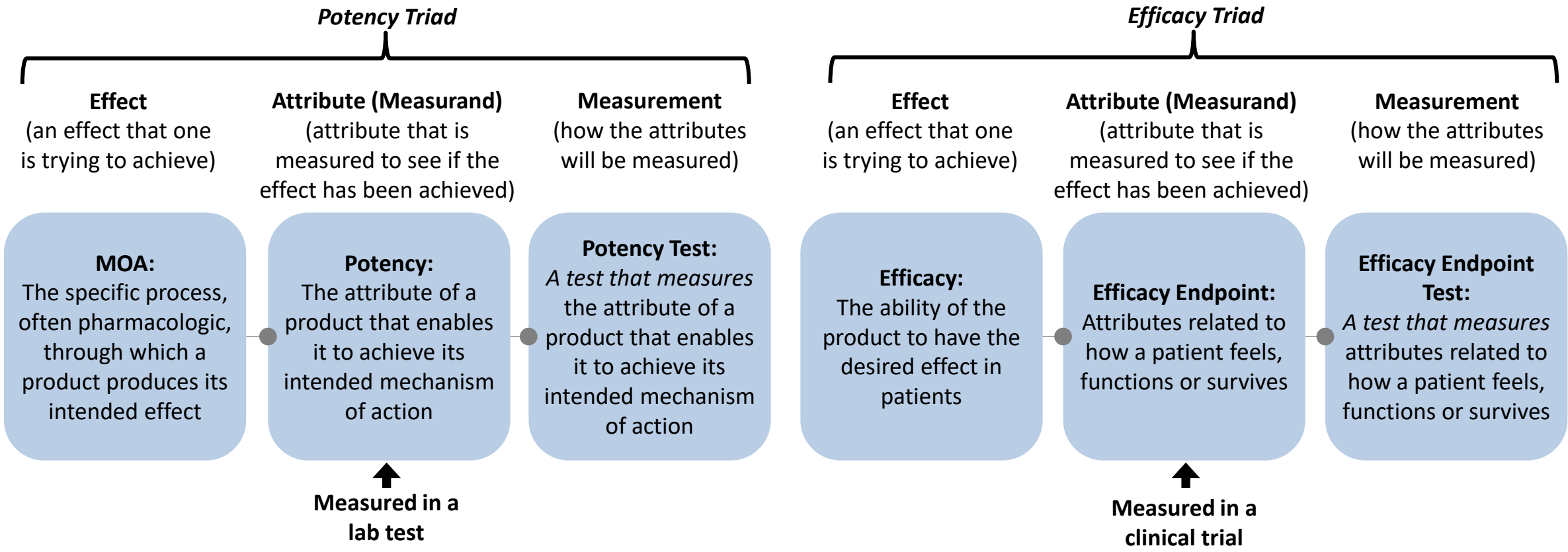
Low Dehydrogenase Activity => MTT => Dead

Good Membrane Integrity => Trypan blue => Live

Assume this for all measurement systems

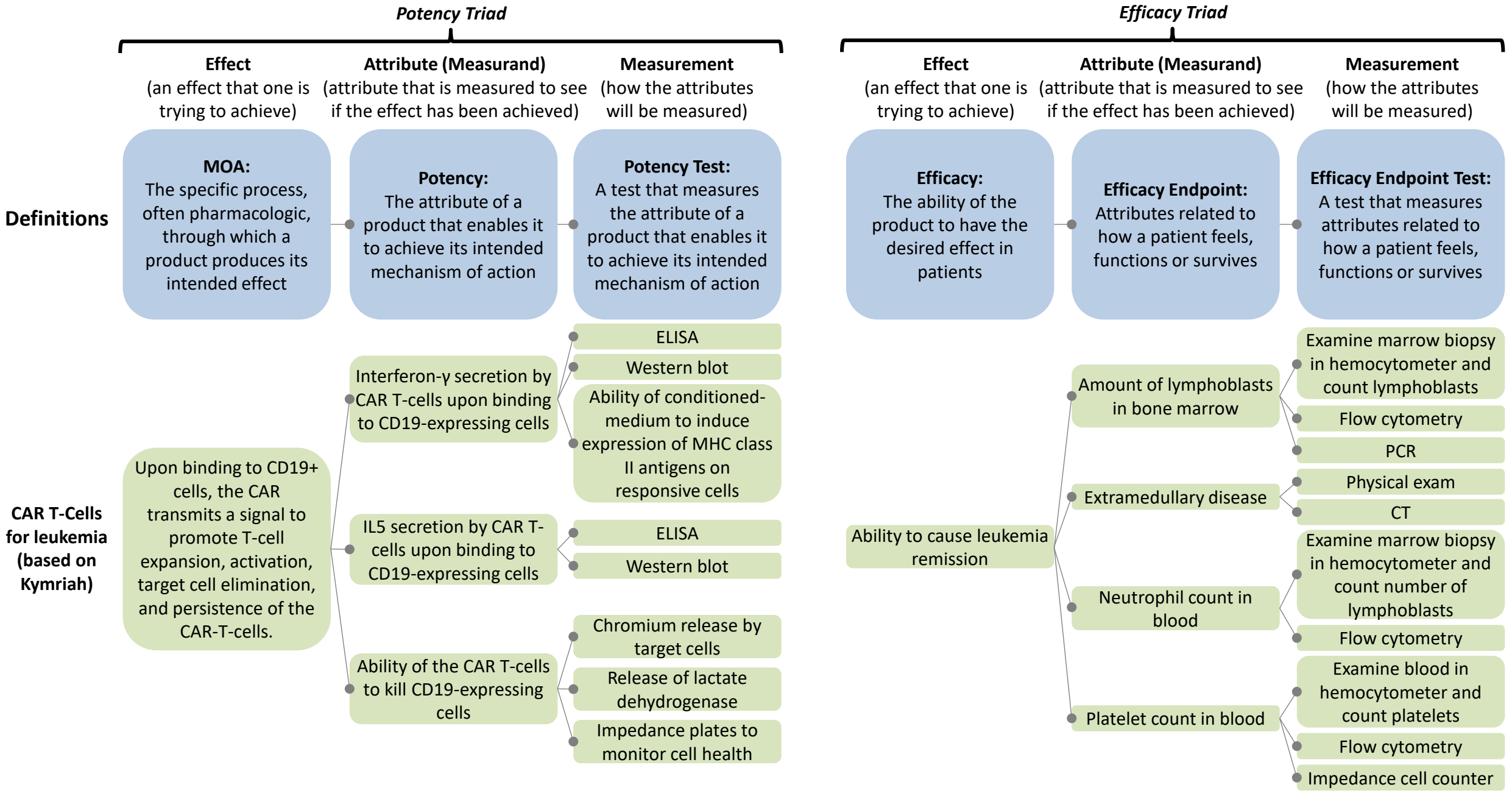
[that different measurements of an attribute may not agree]

Potency & Efficacy Charts

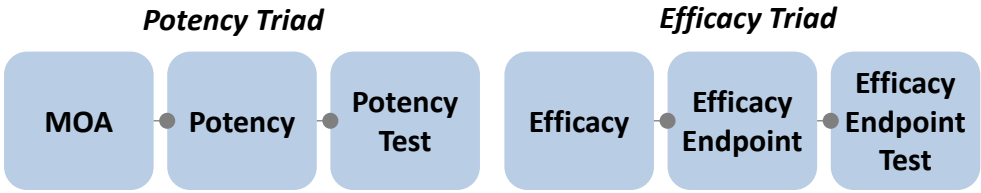


- Define potency independently of efficacy (potency is lab; efficacy is clinical)
- Separate measurement from attribute…attribute definition should not refer to how the attribute is measured
  - No measurement is perfect; all measurements have false positives & false negatives
  - There may be multiple ways to measure an attribute

Apply to an Example: Kymriah



Potent but Not Efficacious

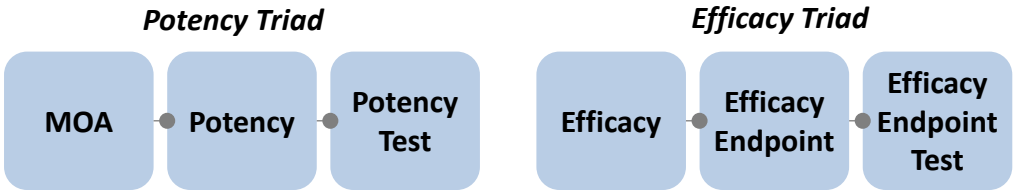


- *Example 1: Wrong patient population*
  - Imagine giving a potent chemotherapeutic drug to a patient with bronchitis
  - Imagine the product is truly potent for its intended MOA & is truly efficacious when used as intended for treating cancer
  - Yet, the chemotherapeutic will not help the patient with bronchitis
    - Wrong patient population or misdiagnosis
- *Example 2: Hypothesis incorrect*
  - Imagine that the therapeutic is potent, does what it is supposed to do & achieves its MOA
  - However, the hypothesis regarding the MOA is incorrect & it does not affect the targeted medical condition: it is potent, but not efficacious.
    - Achieving the intended MOA does not have an effect in treating the intended indication

This example may seem irrelevant, but…

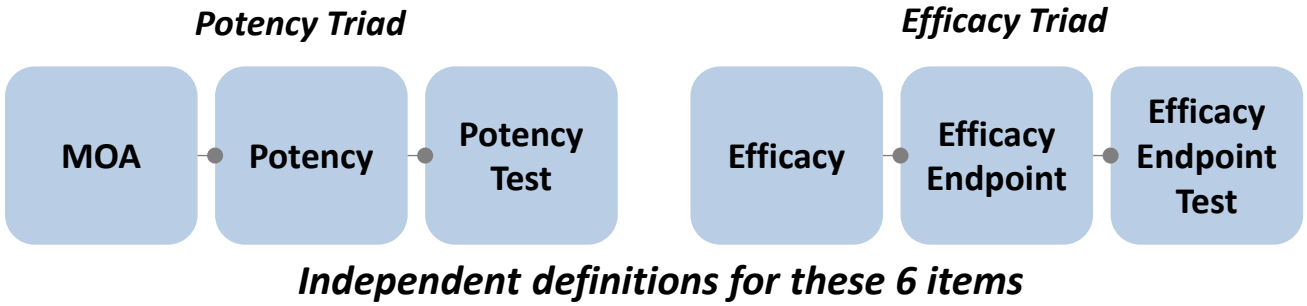
- Identifying indication and clinical trial inclusion/exclusion criteria are critical
- When significance not observed in a clinical trial, there are often controversial post-hoc subgroup analyses to identify responsive cohorts.
- *Kymriah* very carefully worded indication (5 criteria): "patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse"
- *Lantidra* indication (6 criteria): "The treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education."
- *Companion diagnostics:* screening breast cancer patients and treating HER2/neu-positive patients with Herceptin, an anti-HER2/neu antibody drug (169 approved CDx)

Not Potent but Efficacious



- *Example 1:* Alternate MOA
    - The proposed MOA is incorrect, but the product is effective due to another MOA (perhaps an unknown biological activity).
    - Imagine a therapeutic is truly not potent for its intended MOA, but the therapeutic is truly effective in treating the intended indication.
    - Example: Potency of an efficacious CAR T-cell therapy is not due to its ability to secrete IFN-γ upon binding to target cells, but instead due to secretion of IL5 upon binding to target cells (or ability of CAR T-cells to kill target cells via perforin-granzyme or Fas-Fas ligand interactions)
- *Example 2:* False negative potency test
    - Imagine therapeutic is truly potent, is able to achieve intended MOA and achievement of intended MOA is truly effective in treating intended indication. Yet, potency test indicates that therapeutic is not potent.
    - The potency test is giving false negative results. For example, the potency test may not be stable and reagent degradation results in intermittent false negatives.

Conclusions



FDA Ask:

- Consider adopting the definitions and framework?
  - As an appendix to 2023 draft potency guidance?
- Or, propose alternative framework that…
  - Separates potency & efficacy
  - Separates measurand & measurement
  - Separates the 6 terms
  - Allows a product to be…
    - Potent but not efficacious
    - Efficacious but not potent

- "Potency is laboratory, efficacy is clinical & they are tied together by the MOA."
- Definitions & framework align with current regulatory guidelines

Thank you for your attention!

Thank you for considering the definitions & potency-efficacy framework ☺!

END