Regulatory Perspectives on Establishing Specifications for Cell and Gene Therapy Products:

From Speculation to Specification

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What do we mean by “Specification”?

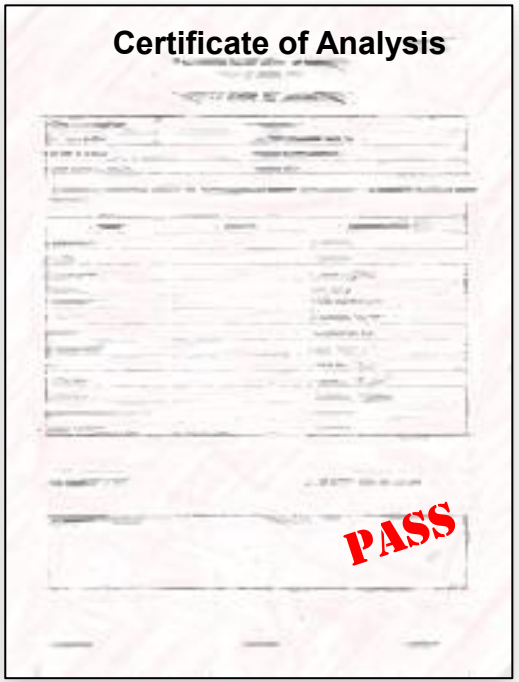
- **Specification:**
  - Combination of **test procedures** and **acceptance criteria**
  - Establish criteria to which drug substance, drug product, or materials should conform to be acceptable for its intended use
  - Reasonable expectation that the product is of the appropriate quality to provide the expected activity as claimed in the label
  - **Ensure safety, quality, and consistency**

Specifications are key to the overall product control strategy

- All aspects of product quality and process control are governed by specifications
- Choose them carefully
  - Appropriate samples
  - Appropriate assays
  - Appropriate acceptance criteria

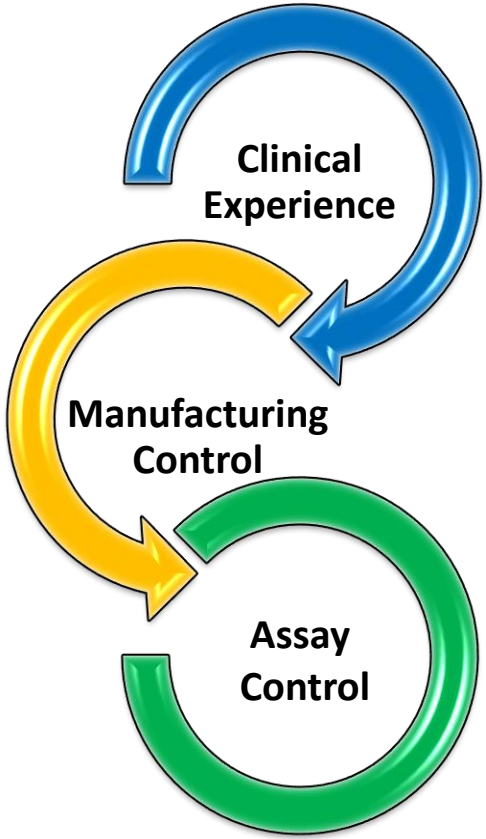
Types of specification

- **Safety**
  - Non-quantitative (e.g., microbial testing)
  - Quantitative (e.g., off-target genome editing)
- **Identity**
  - Binary
  - Can have quantitative readout
- **Impurities**
  - Often limit-based
  - Safety and manufacturing consistency
- **Content**
  - Dose determination
- **Potency**
  - Biological activity
  - Multiple potency assays



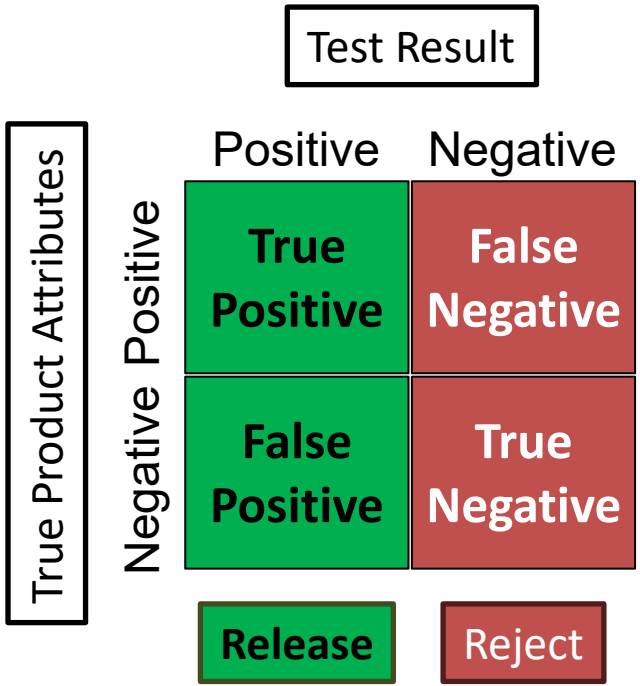
Considerations for setting AC

- Biological impact of attribute
- Clinical experience
- Process variability
- Phase of clinical development
  - Number of lots in clinical study
  - Data distribution
- Assay precision
  - Run-to-run variability
  - Assay control material
  - System suitability
  - Average of multiple replicates



Implications of AC

- AC determine which lots are released and rejected
- Desired outcome
  - Lots that conform to desired product characteristics to be released
  - Lots that don't conform to be rejected
- Balance the risk of releasing lots outside of clinical experience with rejecting lots that have benefit



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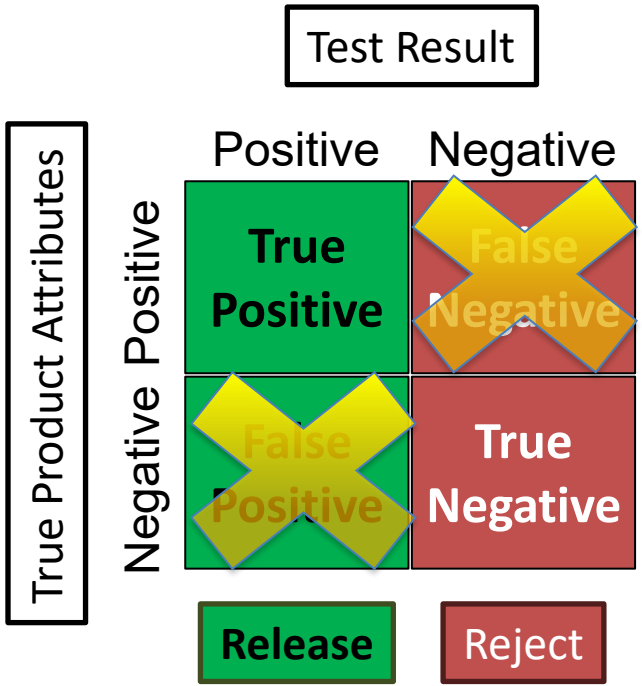
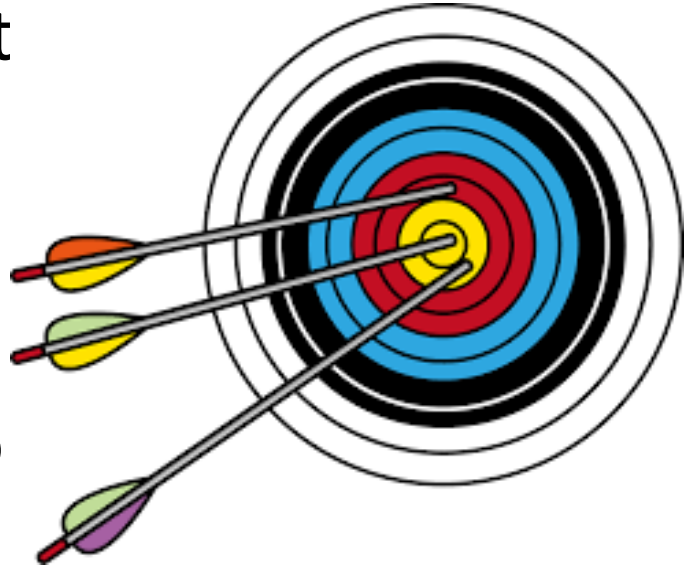


How do you set AC?

- Adequate control for consistent product dosing
- Correlation with clinical outcome may determine AC
- Adequate clinical experience to support the proposed range
- **AC establishment is data driven**



Unique challenges for CGT products

- Uncertainty regarding mechanism of action (MOA) and critical quality attributes (CQAs)
- Rare diseases = Small number of lots
- Rapid development through clinical trial phases
- Often first in class products
- Non-compendial assays
- Variability of biological material
- Interpretation of lot-level data (e.g., autologous products)
- High efficacy

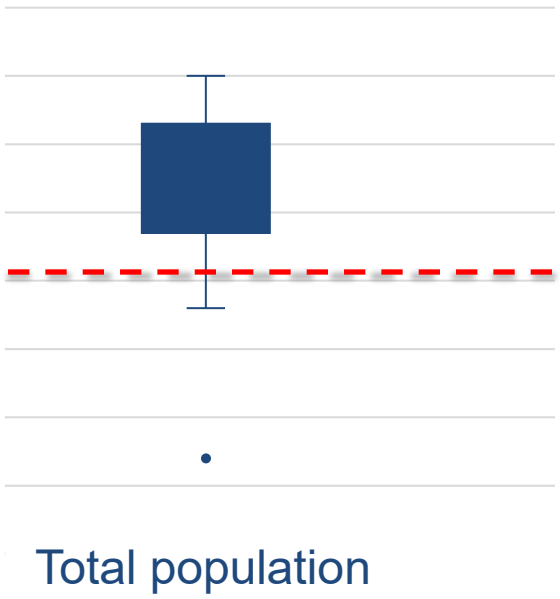
General life cycle expectations

	Early Phase (P1)	Mid-Phase (P2)	Commercial
Data	Limited	Less limited	Least limited
Non-compendial Assays	Under development	Qualified	Validated
Establish acceptance criteria based on	Engineering runs (may not fully represent clinical lots); platform knowledge (if available)	Early clinical lots	Lots shown to be safe and effective in clinical studies
Acceptance criteria	Wide AC tolerated	Refine based on early clinical data	Refine further

General expectations: AC can start wide but expected to refine through development as experience accumulates; **Justification is important**

Establishing and evaluating AC

- Totality of evidence is used to determine AC
  - Conventional drugs: Mix of responses for each lot
  - Autologous: Lot level data
- Range of experience is considered



Establishing and evaluating AC

- Totality of evidence is used to determine AC
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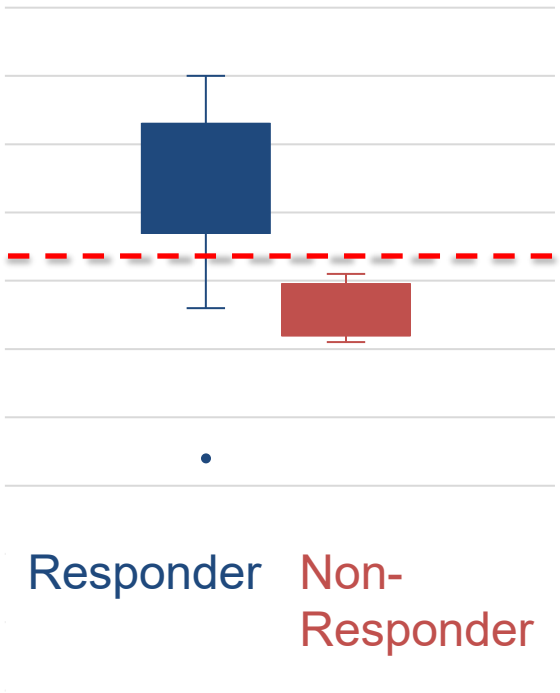
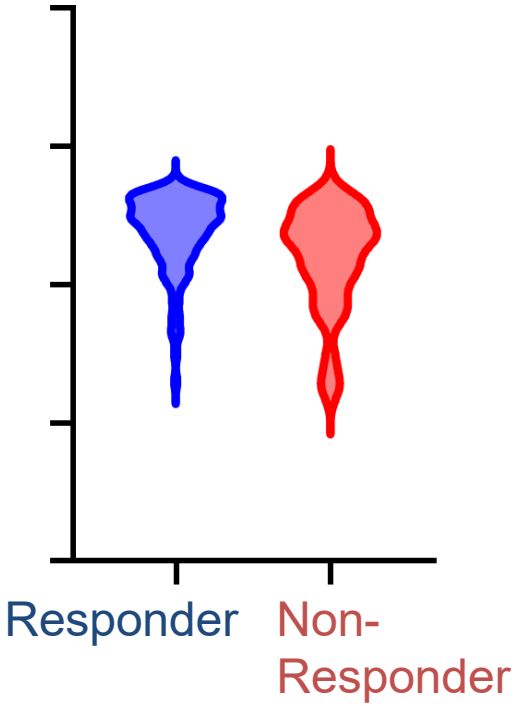
- Set AC based on responders?
- Commercial AC are finalized during review for licensure



*Anonymized data from submission

But (often) it's not that simple

- Totality of evidence is used to determine AC
  - Conventional drugs: Mix of responses for each lot
  - Autologous: Lot level data
- Uncertainty at the trailing end of data
- Statistical analysis is critical to establish AC



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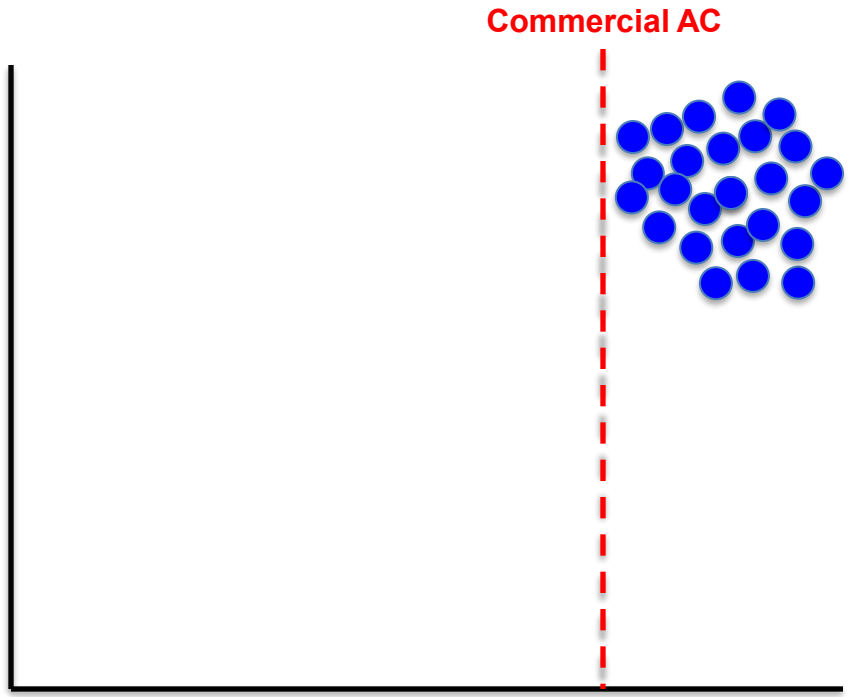
The post-approval problem

- Commercial AC established from lots shown safe and effective in clinical studies (limited sample size) ●



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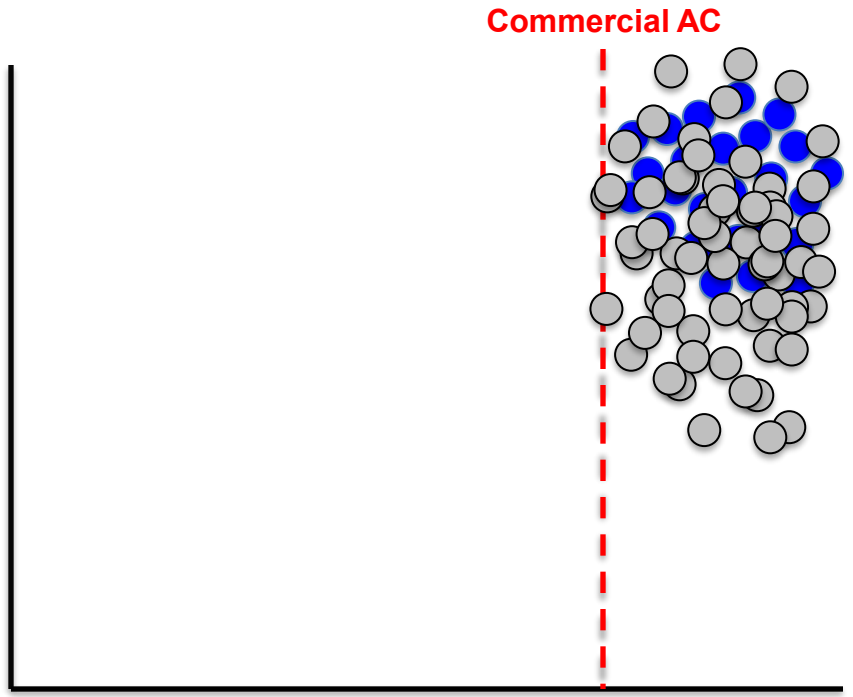

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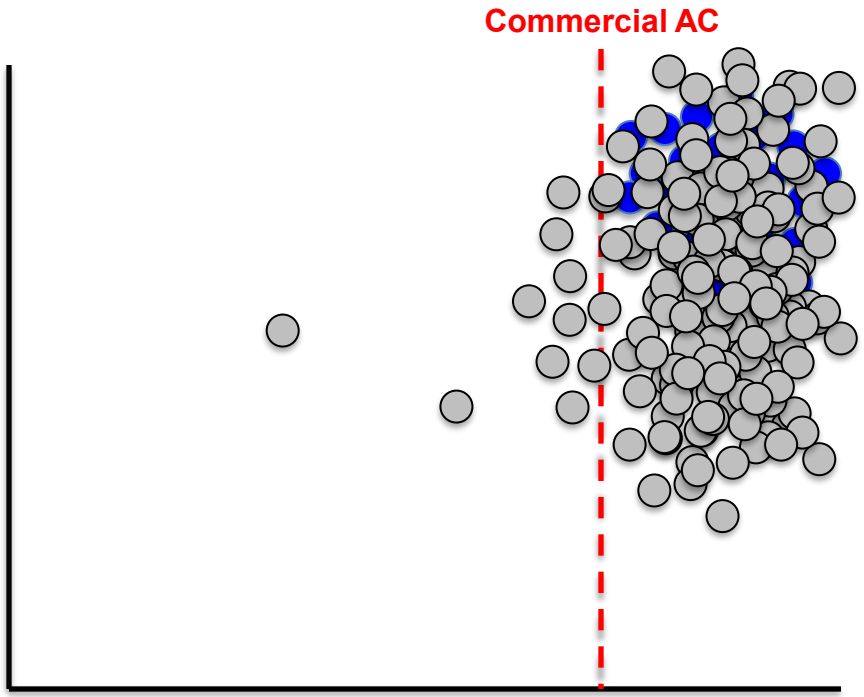

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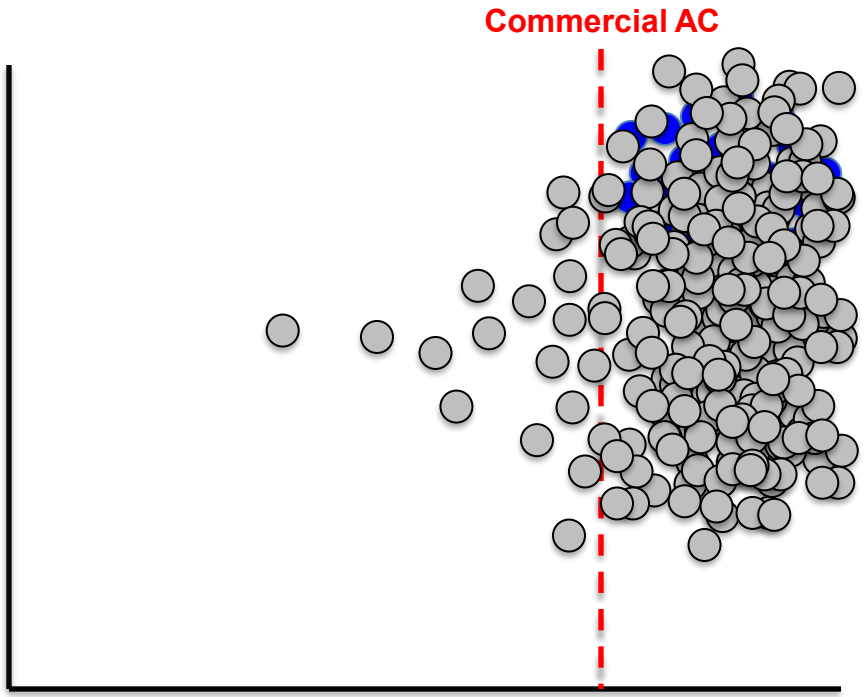

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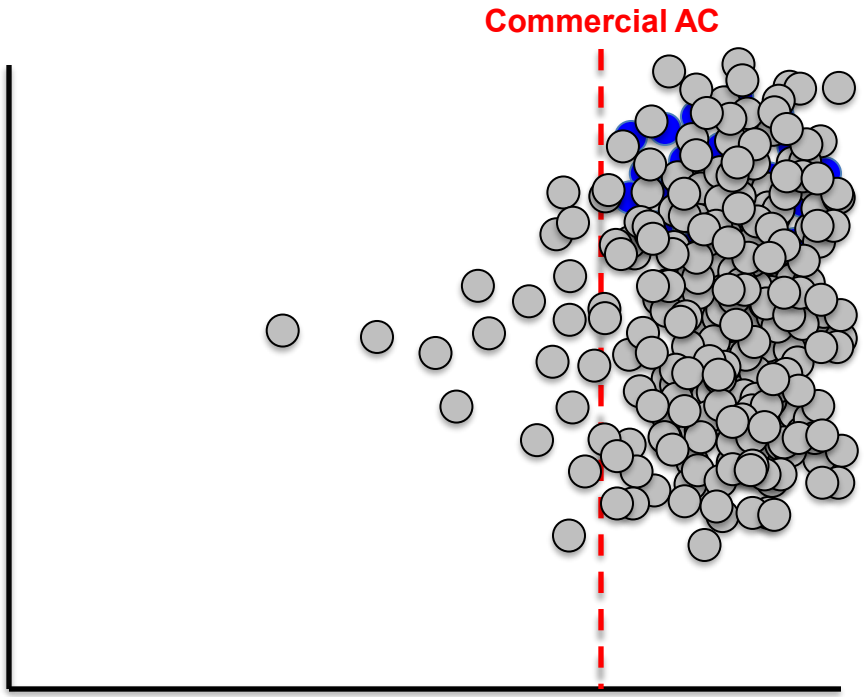
- Has manufacturing process changed?
- Are OOS lots safe and effective?



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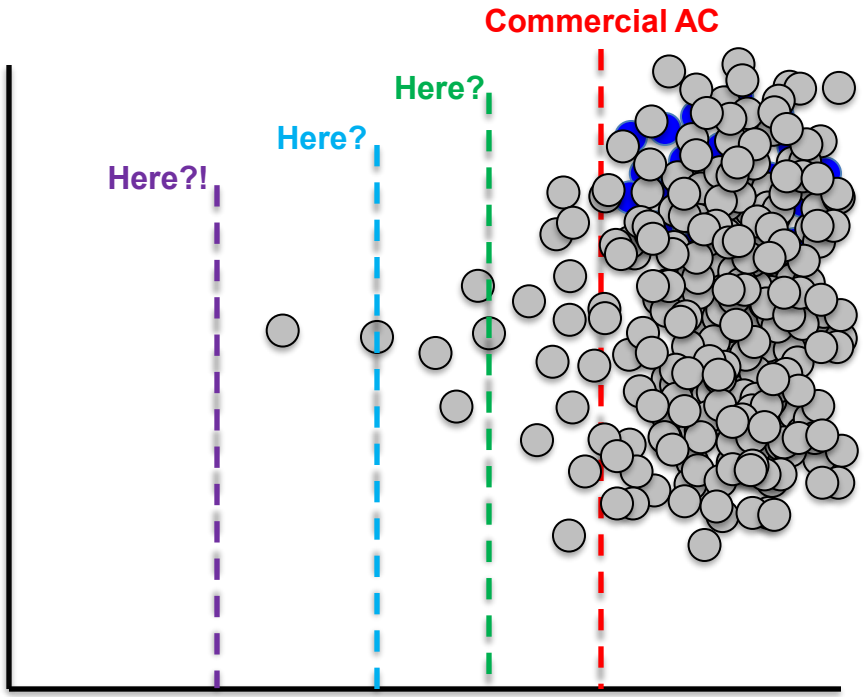
- Where would the new AC be set?



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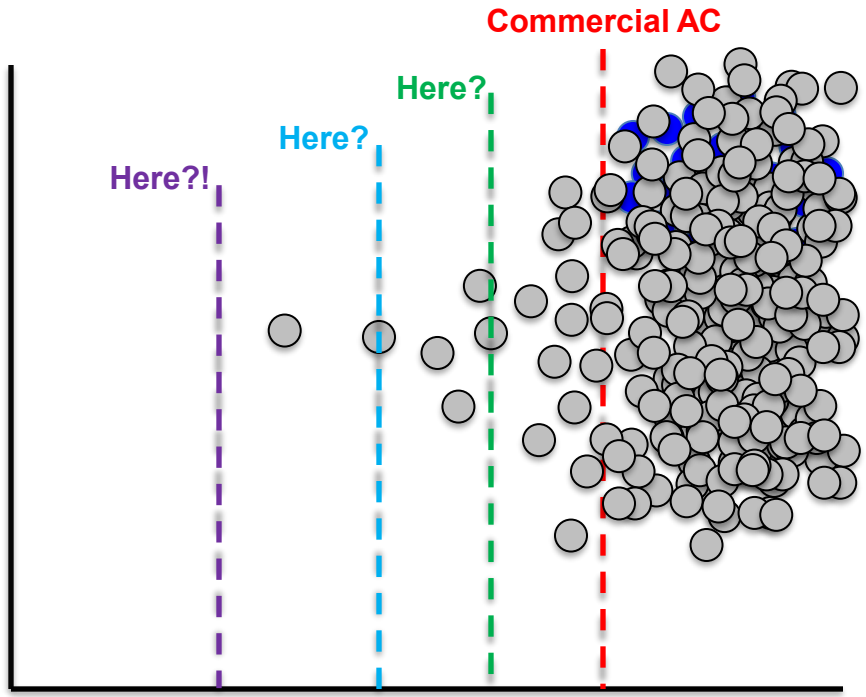
How low can you go…

…without compromising safety and efficacy?



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What do you have data to support?

- Collection of additional clinical data (safety and efficacy) to support AC change (e.g., autologous CAR T cells
  - Reclassify and release non-conforming products as clinical lots under expanded access programs
  - Not always feasible
  - Different specifications for different indications?

Challenges for other product types

- Allogeneic products or gene therapy vectors (e.g., AAV) can treat more patients per lot.
- But often have limited amount of data at approval: Complicates establishing commercial AC
- Possible approaches
  - Commitment to reassess AC after additional lots manufactured (e.g., AAV products for rare diseases)
  - Leverage platform data/prior knowledge

How to get from speculation to specification?

- **Knowledge about the product is critical**
  - Identify and measure product CQAs
  - Characterize multiple product attributes
  - Leverage available prior knowledge
  - Use appropriate (and robust) analytical methods
  - Understand sources of variability
  - Establish a consistent manufacturing process
- **Use this information to inform specification**

Final thoughts

- CMC development must keep pace with fast moving clinical programs
- Specification impacts multiple aspects of product development and control
- Product characterization is key to setting acceptance criteria for specification
- Assay development is critical
- It’s hard work…
- But establishing specifications shouldn’t be guesswork

Contact Information

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