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LIFE SCIENCES

Life Cycle-Aligned Specifications:
Ensuring Quality and Consistency Throughout Cell and Gene Therapy Development

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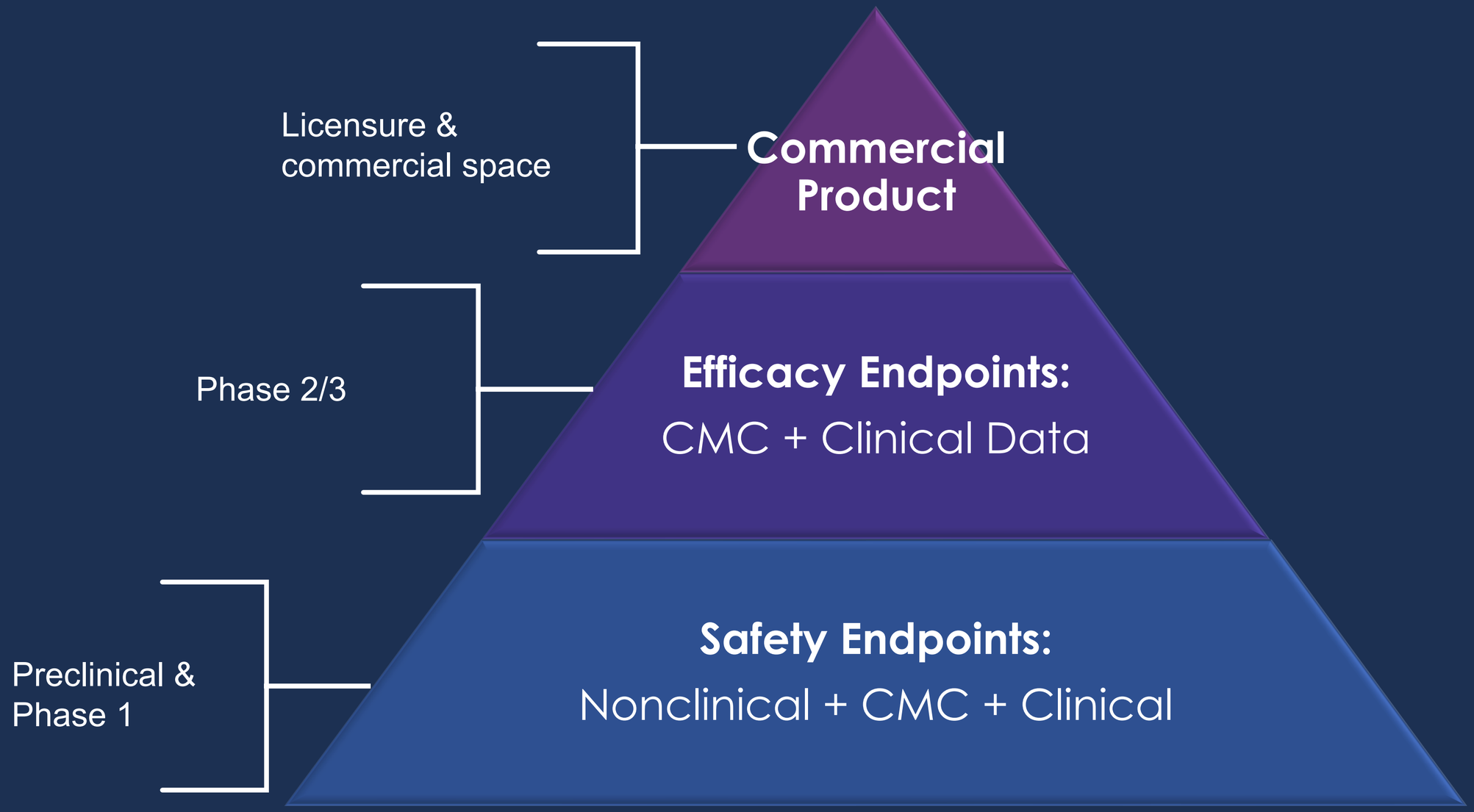
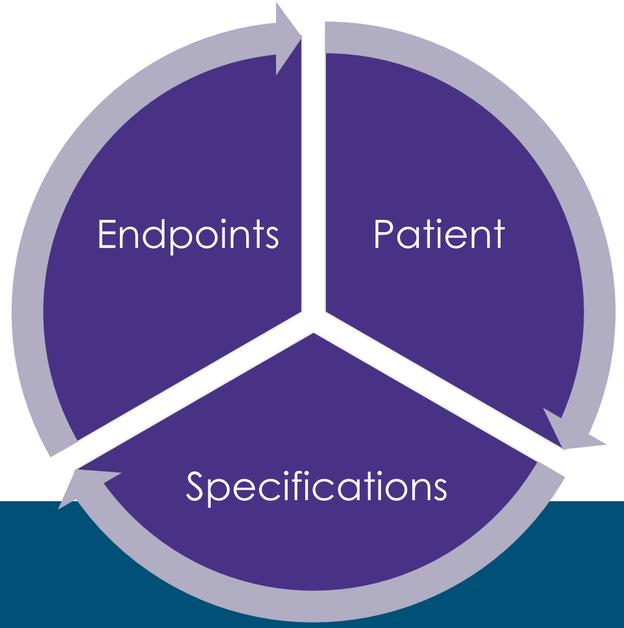
Principal Consultant

Regulatory Clarity –
thought to finish.

Overview of Life Cycle Stops



Who Guides CGT Specifications



"Patient-based risk view"

- Andrew Chang, PhD (Novo Nordisk) CASSS DC, April 2026 – ICH Q6

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*ICH Q6B: restricted to proteins and polypeptides from cell-culture expression systems

CGTs are not Well-Defined Biologics, Vaccines, or Other

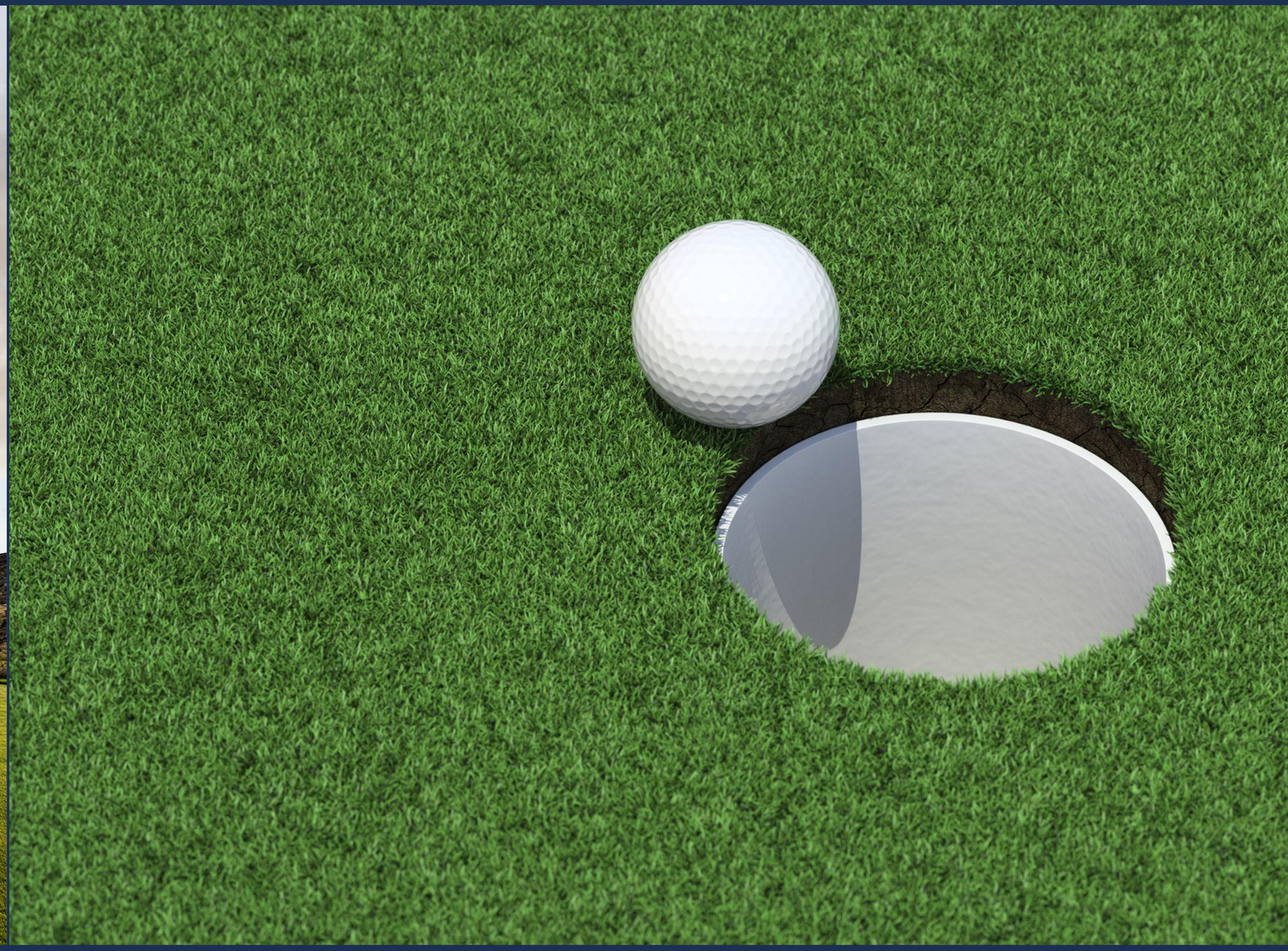
Inappropriate approaches and rationale

Program failures

Inadequate data for licensure, analytical methods, tests, quality attributes

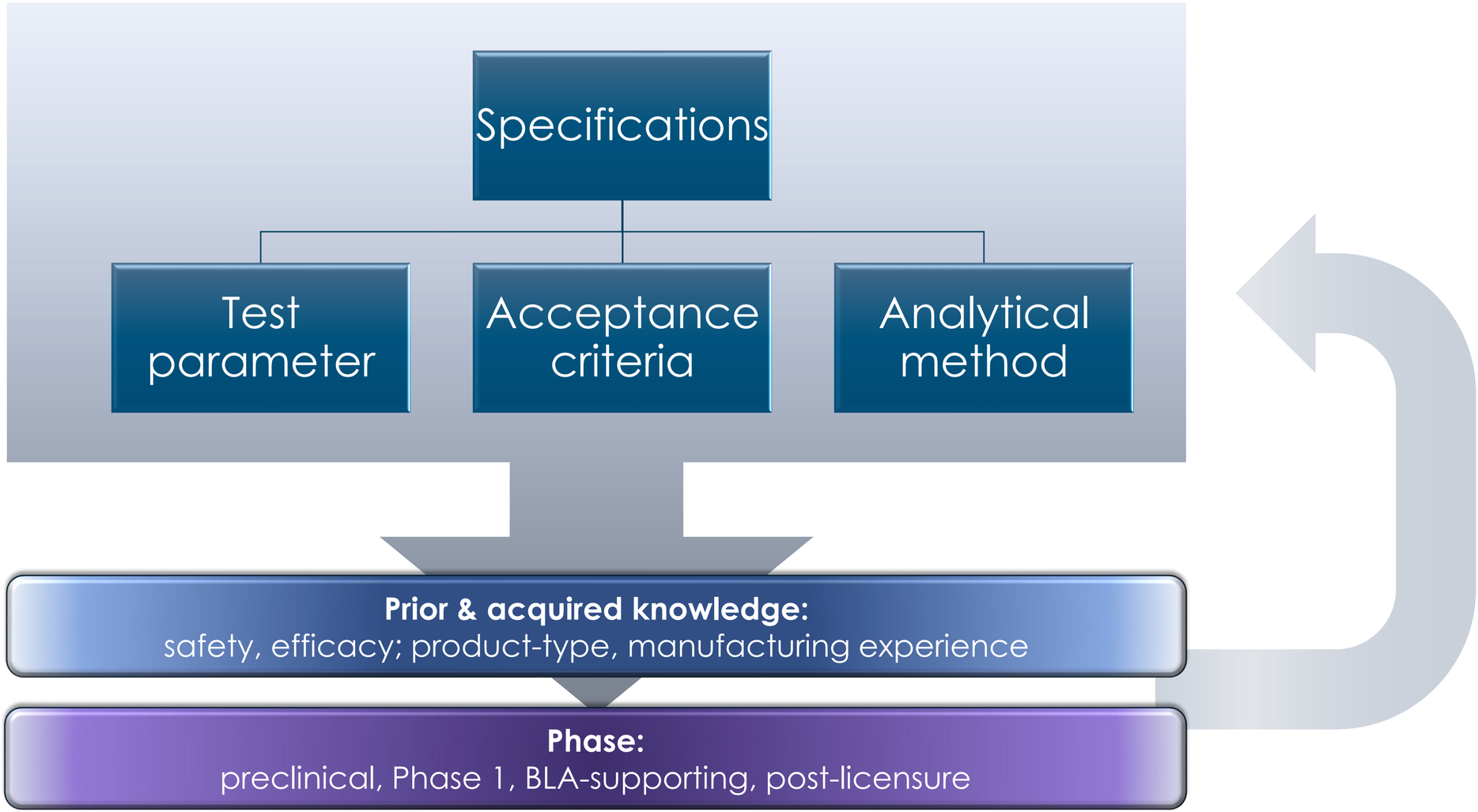
End goal the same; approach highly varied

Finding CGT Commercial Specifications

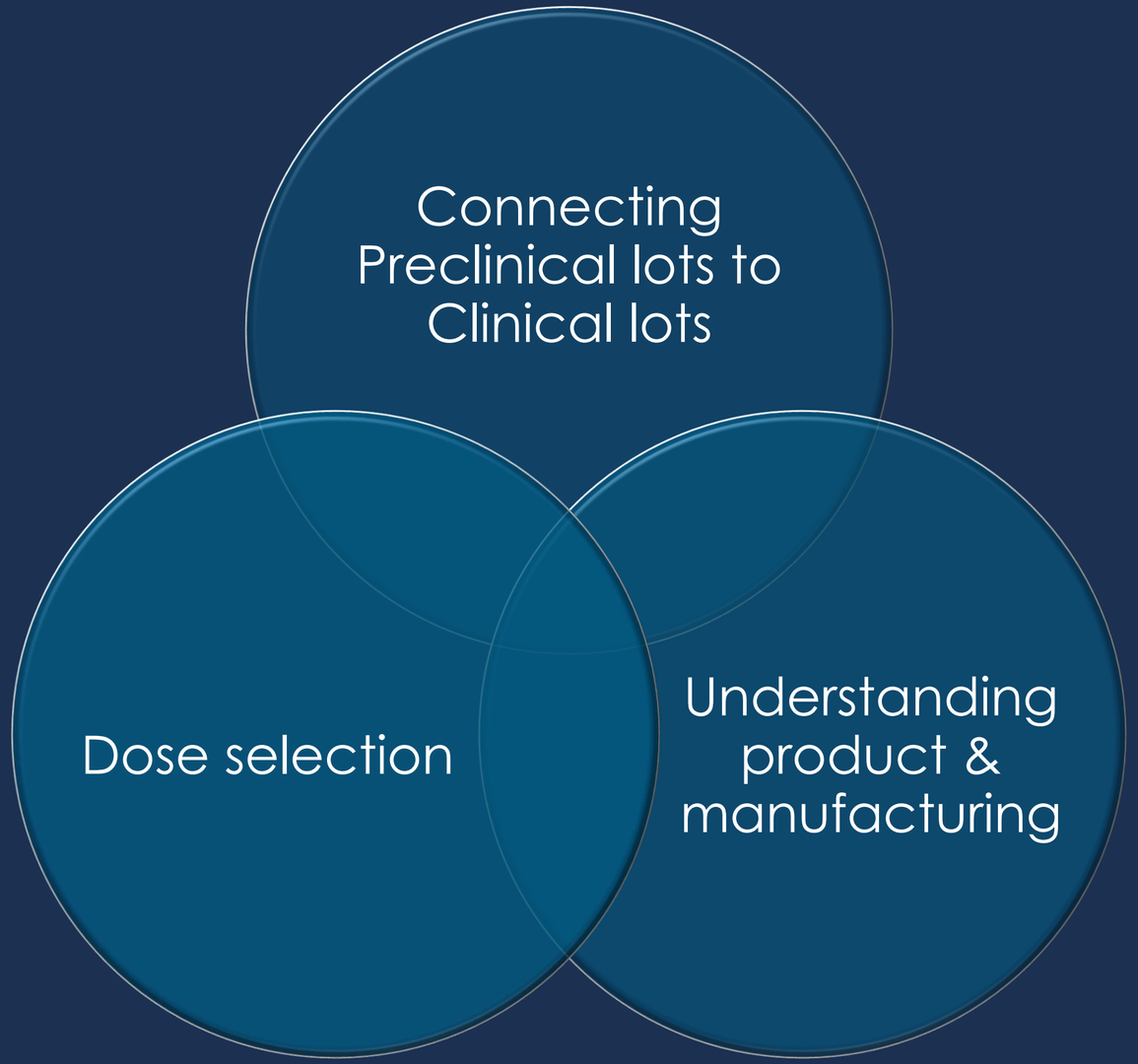


* Hypothetical examples based on common issues – expect exceptions

Context is Everything… & Context Changes in Life Cycle



Preclinical & Phase 1



Context: Preclinical and Phase 1

Menu of Options

- Replication-competent retrovirus testing
- Large T-antigen packaging
- Titer
- Mature capsid p24
- Sequence identity
- On-target genome editing
- Off-target genome editing
- Chromosomal stability
- Viability
- Cytokine release
- CAR T expression
- Sterility
- Endotoxin
- Mycoplasma
- Residual host cell proteins
- Residual host cell DNA
- Residual plasmids
- Residual Benzonase
- Residual cytokines
- Residual gene editing components
- Transgene sequence
- Cell surface markers
- Adventitious agent testing
- Etc.

Too many options
Limited DP or Indication evaluation → Specification paralysis

Context: Preclinical & Phase 1

Menu of Options

- **Replication-competent retrovirus testing**
- **Large T-antigen packaging**
- **Titer**
- **Mature capsid**
- **Sequence identity**
- **On-target genome editing**
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- Etc.

Regulatory Requirements

- Strength
- Purity
- Identity
- Safety

Clinical Trial

- Nonclinical study relevance
- Safety
- Efficacy
- Manufacturing control
- Comparability
- Defined commercial product

Q. Can the CDMO/CTO Select Specifications?

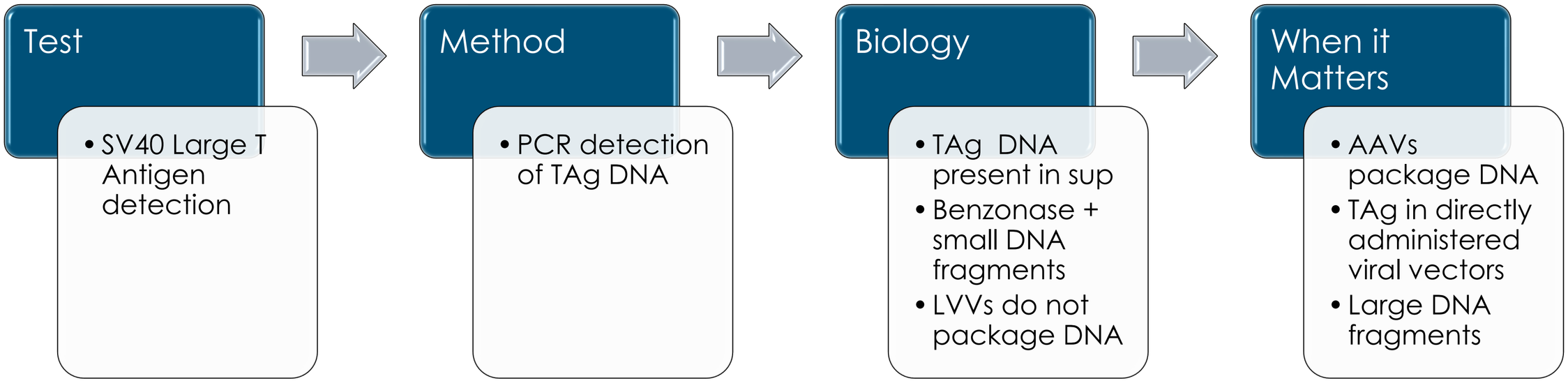
A. Yes & No.

- Sponsor responsible for
  - Product-specific spec development
  - Drug substance, product, and in-process
  - Meeting regulations

- CDMO/CTO valuable insight

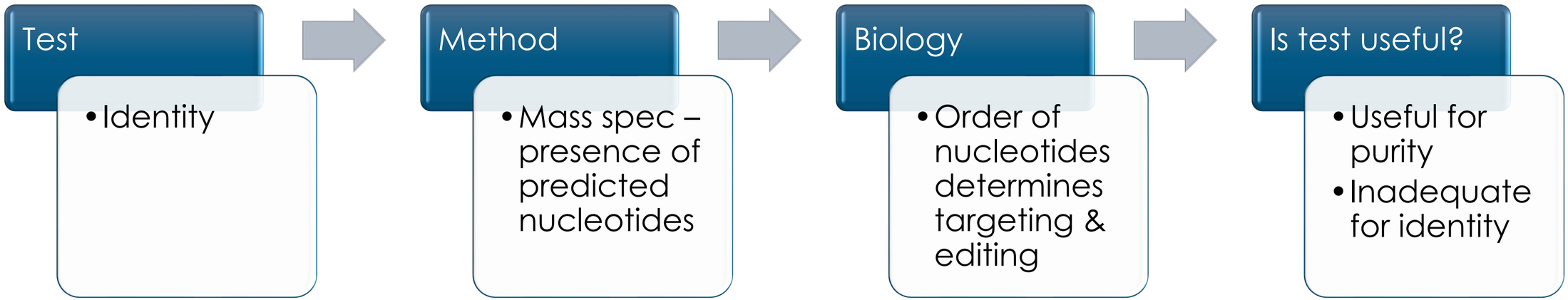
Example 1: Phase 1 Specifications

A lentiviral vector is produced in HEK 293T cells. The CDMO provides a list of recommended testing for LVV release that includes Large T antigen detection



Example 2: Vendor Specifications

You source a gRNA that will be used in a gene editing product. The CDMO COA for the gRNA includes: Identity testing by mass spec. Therefore, Identity is adequately controlled.



Phase 1 to Phase 2/3

Efficacy, safety & quality attributes	Changes to specs	Support future BLA
Define product and shelf-life	Comparability	Meet regulatory requirements

Context: Clinical Gameplan for Commercial Specs

- ✓Product knowledge from in Phase 1
- ✓Knowledge gaps
- ✓Planned CMC changes
- ✓Methods weak, vulnerable, not commercially suitable
- ✓Timing of biological potency assay
- ✓Identify strong areas of understanding

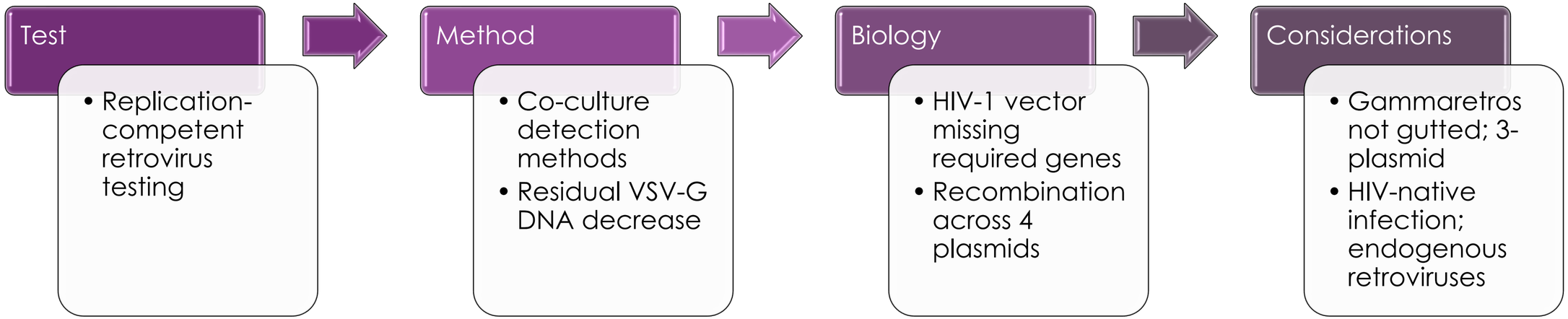
Q: Do I have to tell regulators about all analytical testing?

A. No.

- Backup methods are common
- Characterize and understand product and intermediates
- Sponsor ultimately responsible for adequate specifications
- Regulatory agencies: not their responsibility to tell sponsors testing is excessive

Example 3: Reducing Specifications

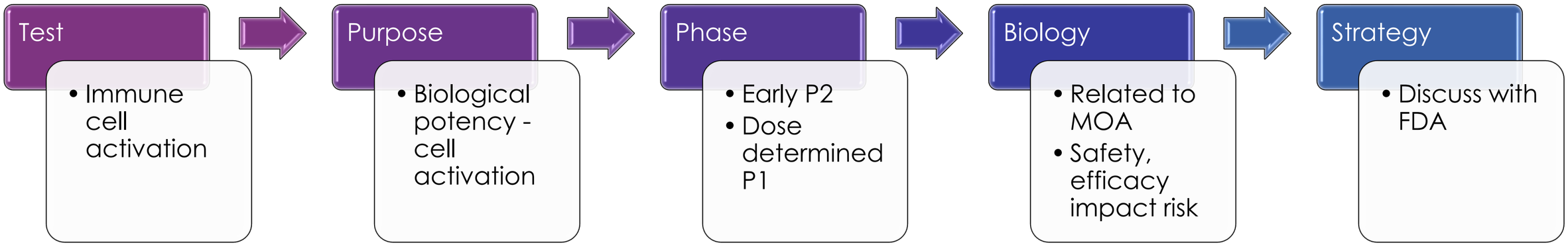
You use a 3rd generation, 4-plasmid split-design, SIN lentiviral vector.
50 autologous CAR T product lots have tested negative for replication-competent retrovirus.
Is continued RCR testing required for an autologous CAR T product?



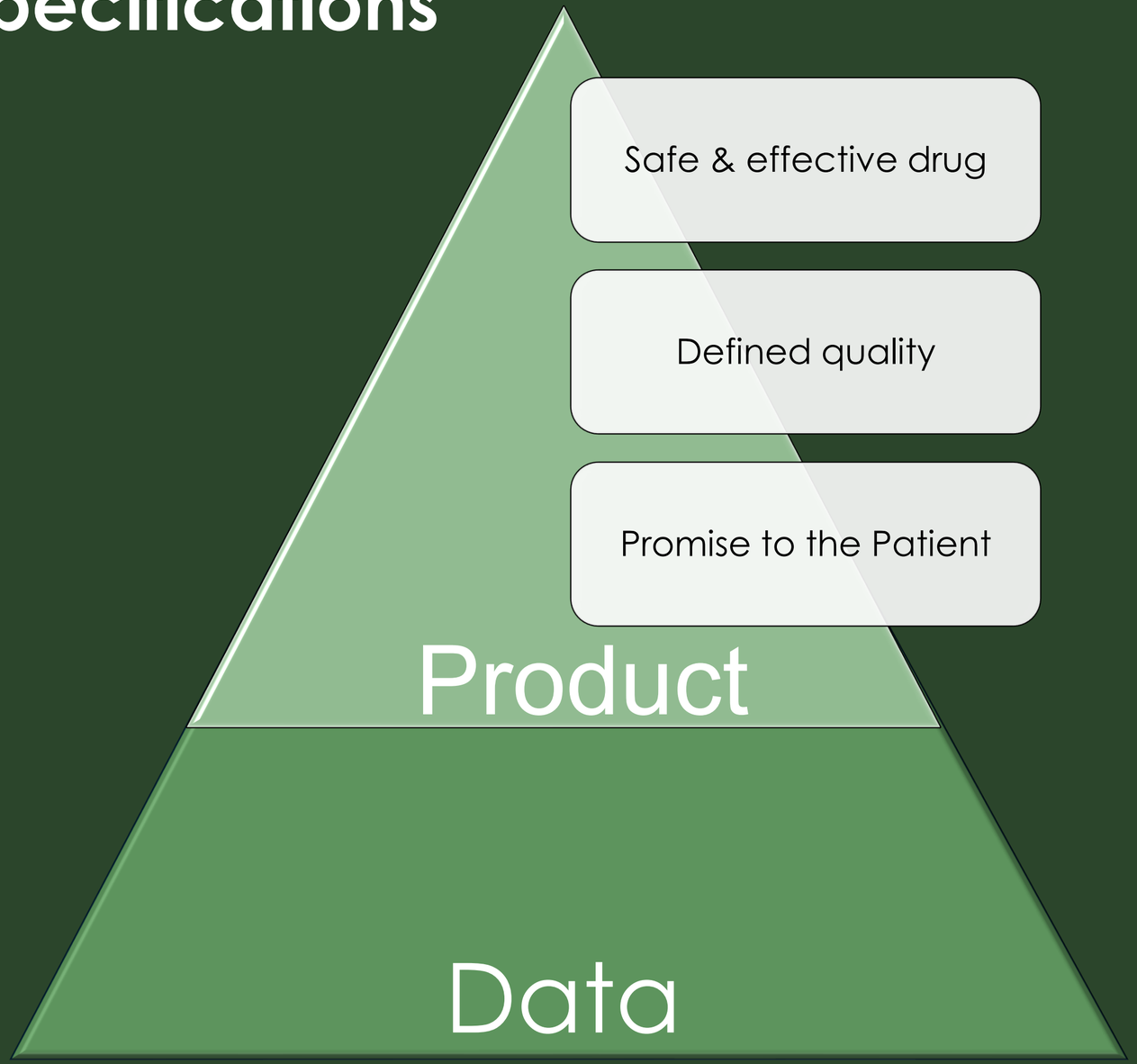
FDA Guidance: https://www.fda.gov/media/113790/download
Meeting FDA Guidance recommendations for replication-competent virus and insertional oncogenesis testing: Molecular Therapy Methods & Clinical Development

Example 4: Revising Specifications

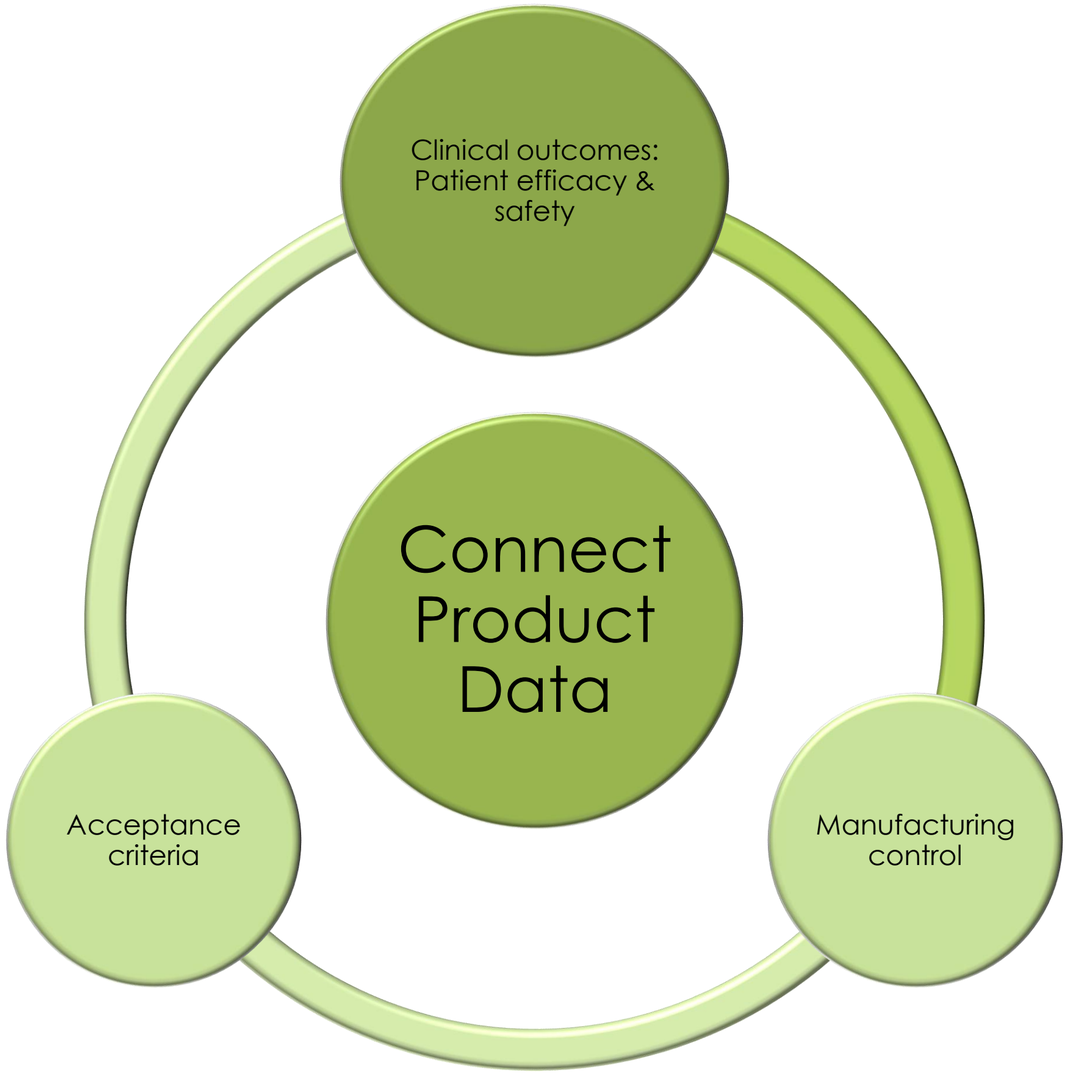
You implement major manufacturing changes in Phase 2. After completing the comparability assessment, there is a major difference in the biological potency data between pre- and post-change product. You can terminate the program or...



BLA-Ready Specifications

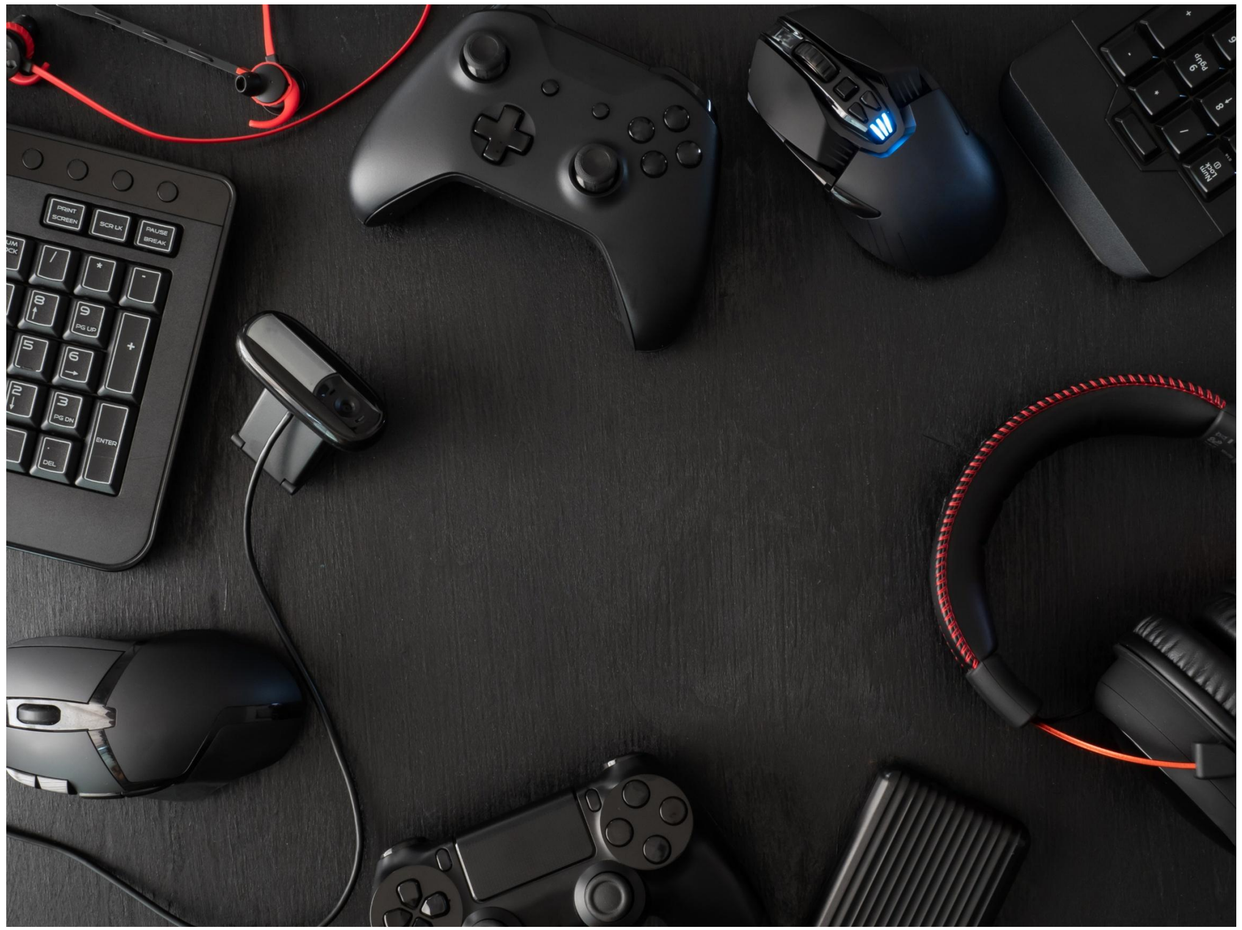


Context: BLA Specifications – Commercial Product



BLA Specifications – Streamlining

- **Tests that matter & why**
- **Tests that do not matter & why**
- **Show state of control**
  - ✓Validation
  - ✓Robustness
  - ✓Control of reference materials
  - ✓Trending
- **Supports**
  - ✓Control of manufacturing
  - ✓Safety
  - ✓Efficacy
  - ✓Shelf-life



Discard what is obsolete with justification

Q. Must acceptance criteria and analytical methods be finalized prior to initiating BLA-supportive studies?

No.

- Commercial acceptance criteria & analytical methods do not need to be finalized prior to the BLA.
- **Hindsight: data not collected**
  - **Biological potency**
  - **There is only one Timepoint 0**
  - **Not a well-defined biologic**

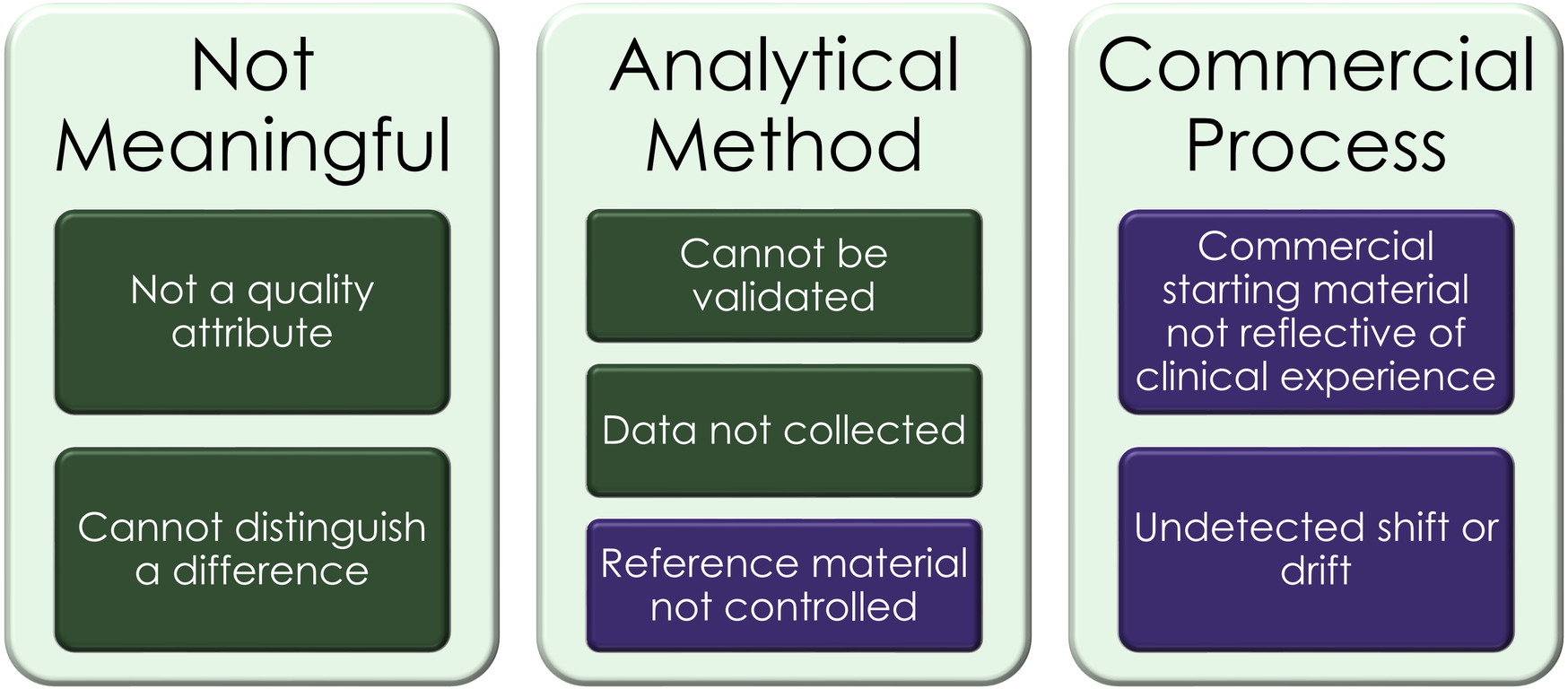
Example 5: Refine Commercial Specifications

A reagent is used to manufacture a drug substance; the reagent is a potential residual.
You assess manufacturing residuals in 100 lots of drug product.
90 DP lots show < LOD 5 ng/mL for the reagent.
10 DP lots show 6 - 10 ng/mL. Is testing required for the commercial DP release specifications?

Same scenario, except: The reagent is used to manufacture a drug product. Is testing required?

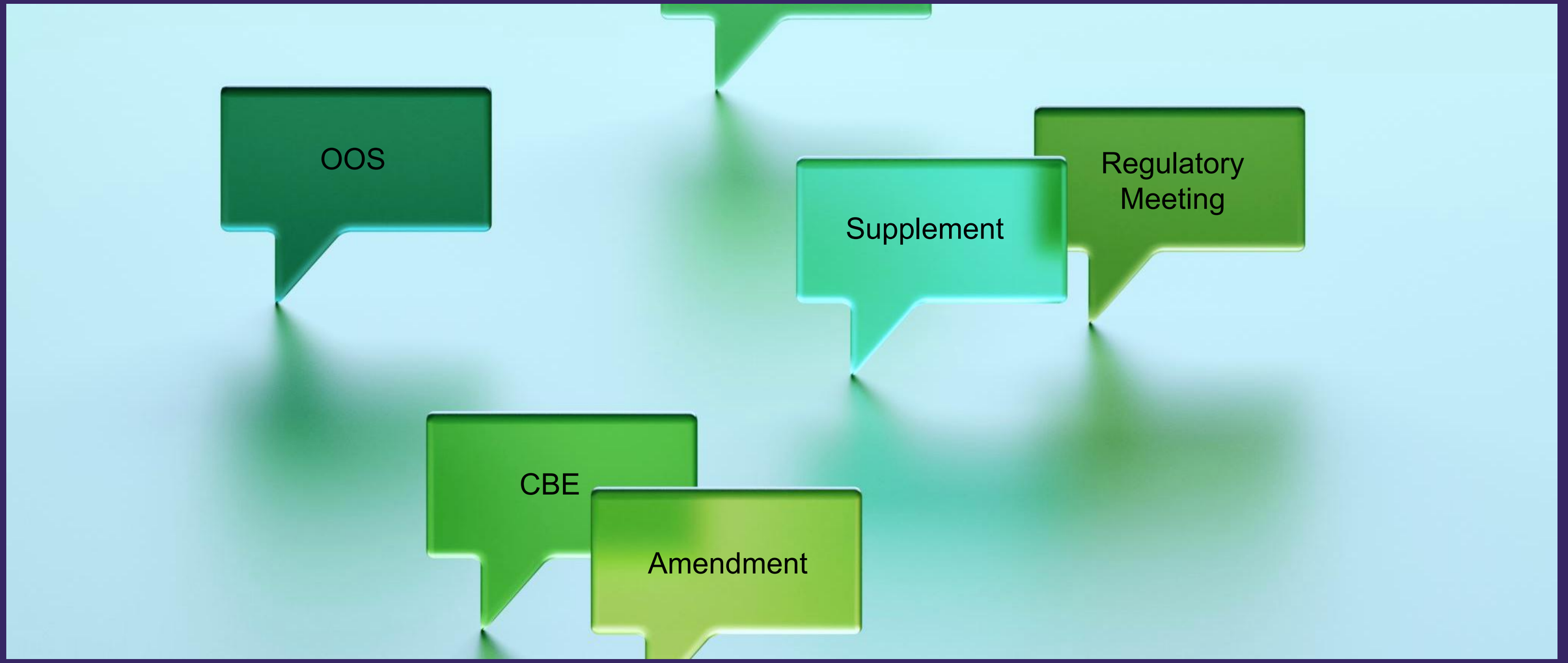
- Low toxicity
- DS is tested
- A similar residual is tested
- Large number of lots tested

BLA Specifications – Failures

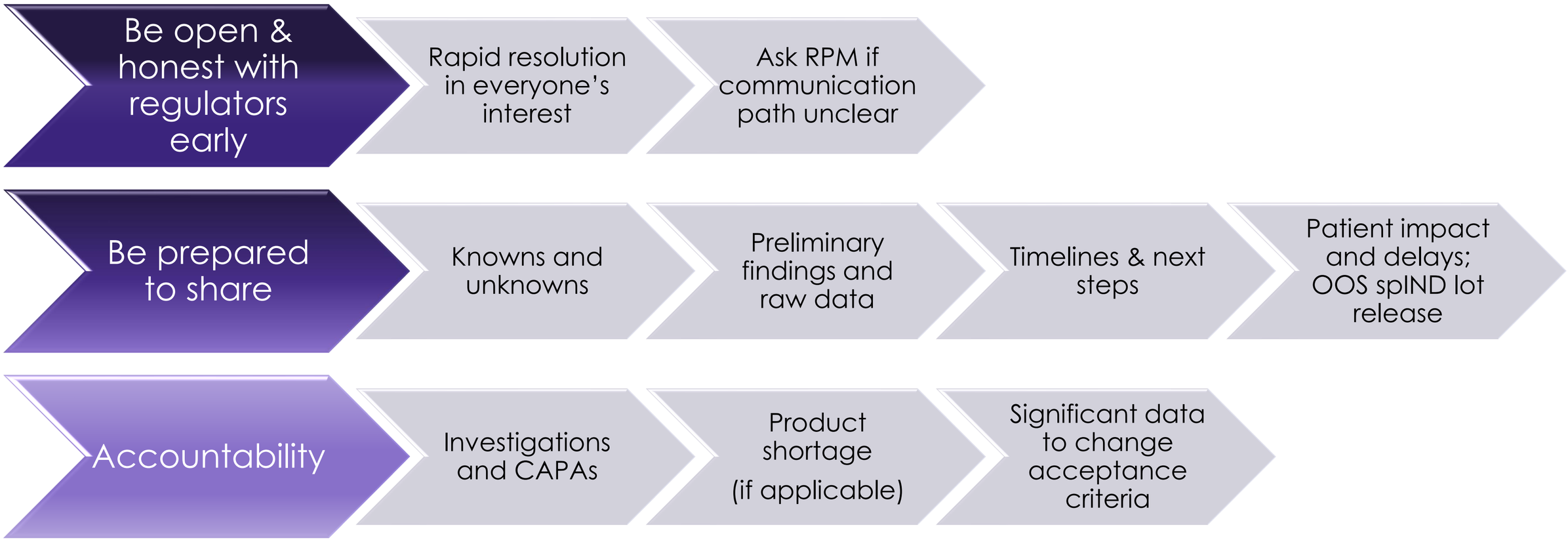


- Controlled failure can add value
- Blind-eye to failure can be catastrophic

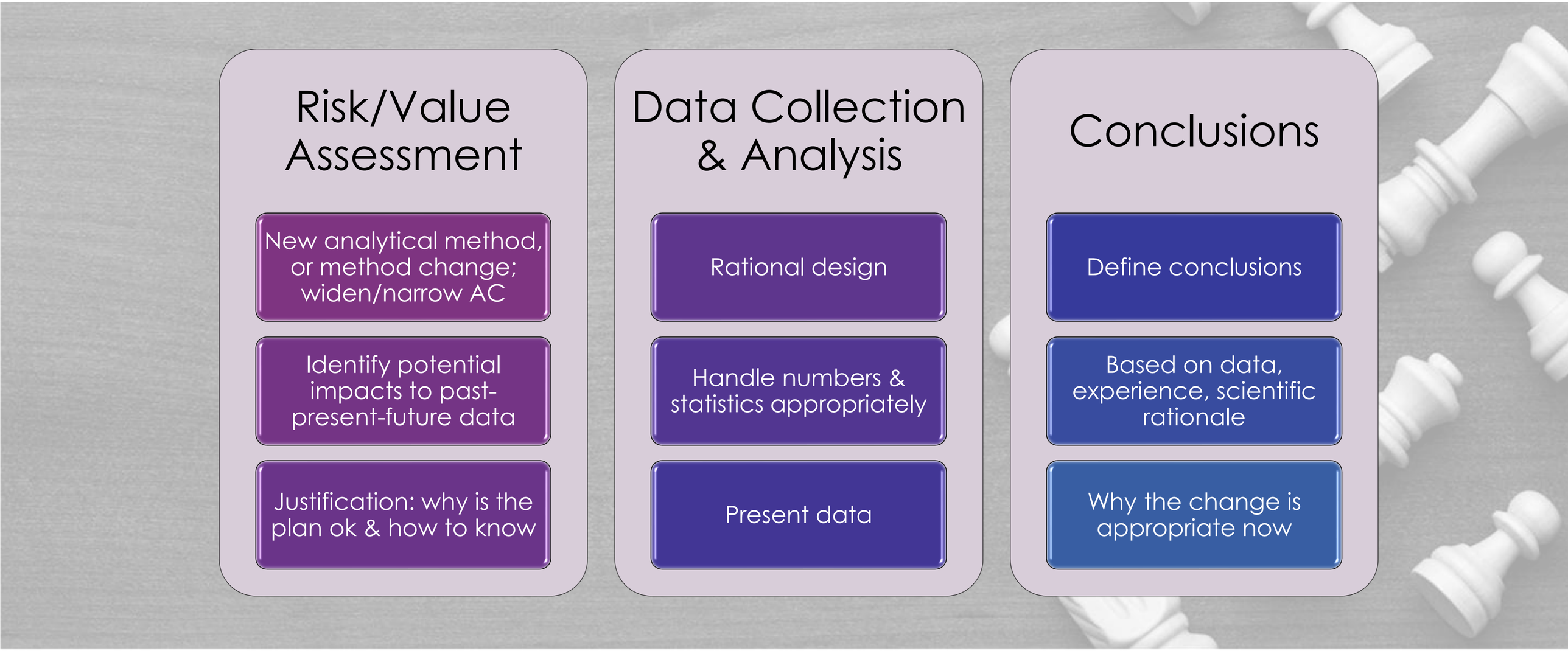
Communications



Regulatory Communications: Commercial Problems



Communications - Regulatory: General
Give Details to get Feedback



Risk/Value Assessment

- New analytical method, or method change; widen/narrow AC
- Identify potential impacts to past-present-future data
- Justification: why is the plan ok & how to know

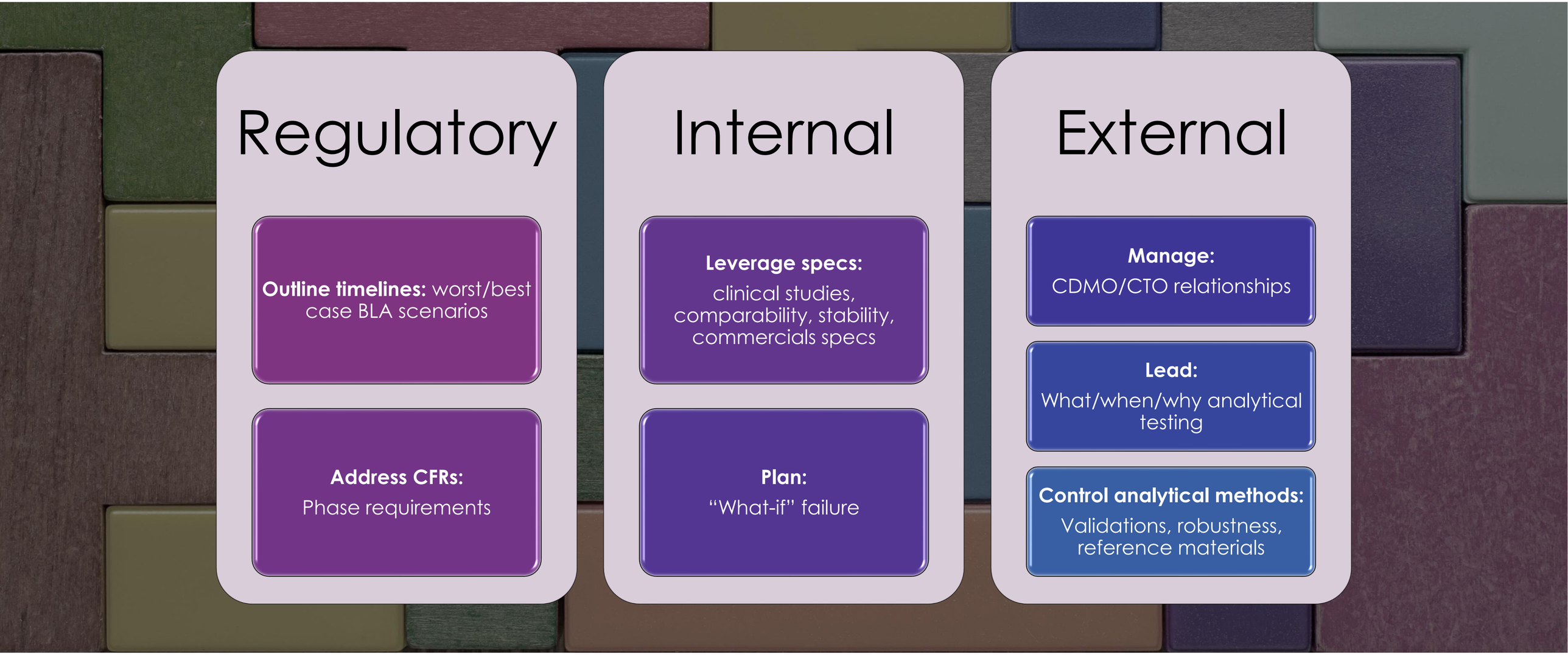
Data Collection & Analysis

- Rational design
- Handle numbers & statistics appropriately
- Present data

Conclusions

- Define conclusions
- Based on data, experience, scientific rationale
- Why the change is appropriate now

Communications Strategy: Parties



Regulatory

Outline timelines: worst/best case BLA scenarios

Address CFRs:
Phase requirements

Internal

Leverage specs:
clinical studies, comparability, stability, commercials specs

Plan:
"What-if" failure

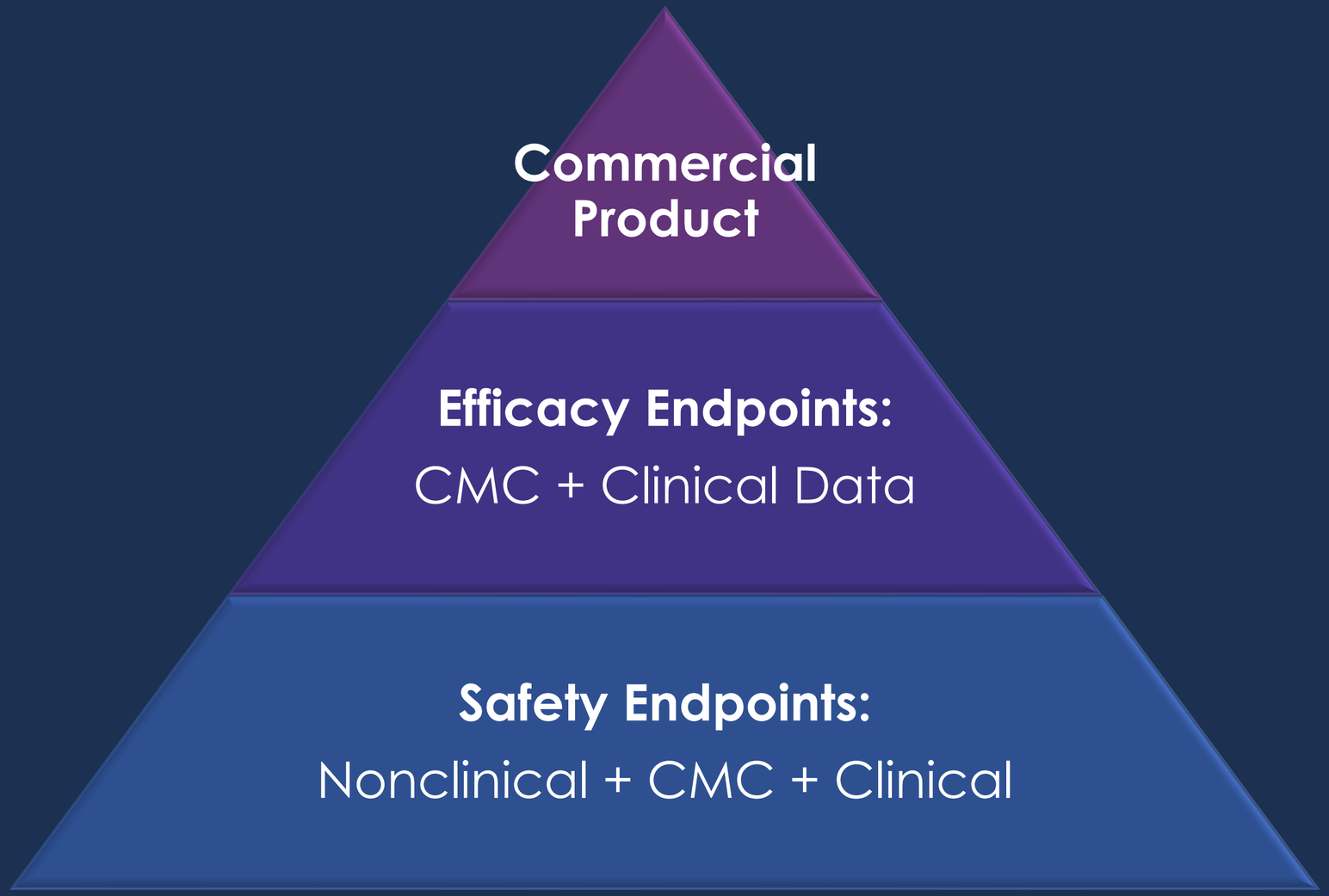
External

Manage:
CDMO/CTO relationships

Lead:
What/when/why analytical testing

Control analytical methods:
Validations, robustness, reference materials

Clinical Data is Important
But there's no Product without Specifications



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