Module 3: Bench to Clinic

Models of Product Development: Moving vaccine candidates into Phase I Testing

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Michael Pensiero, Ph.D.
Chief, Vaccine Translational Research Branch

Presentation Outline

Moving vaccine candidates into Phase I Testing

A Case Study: Moving HIV Env proteins Forward

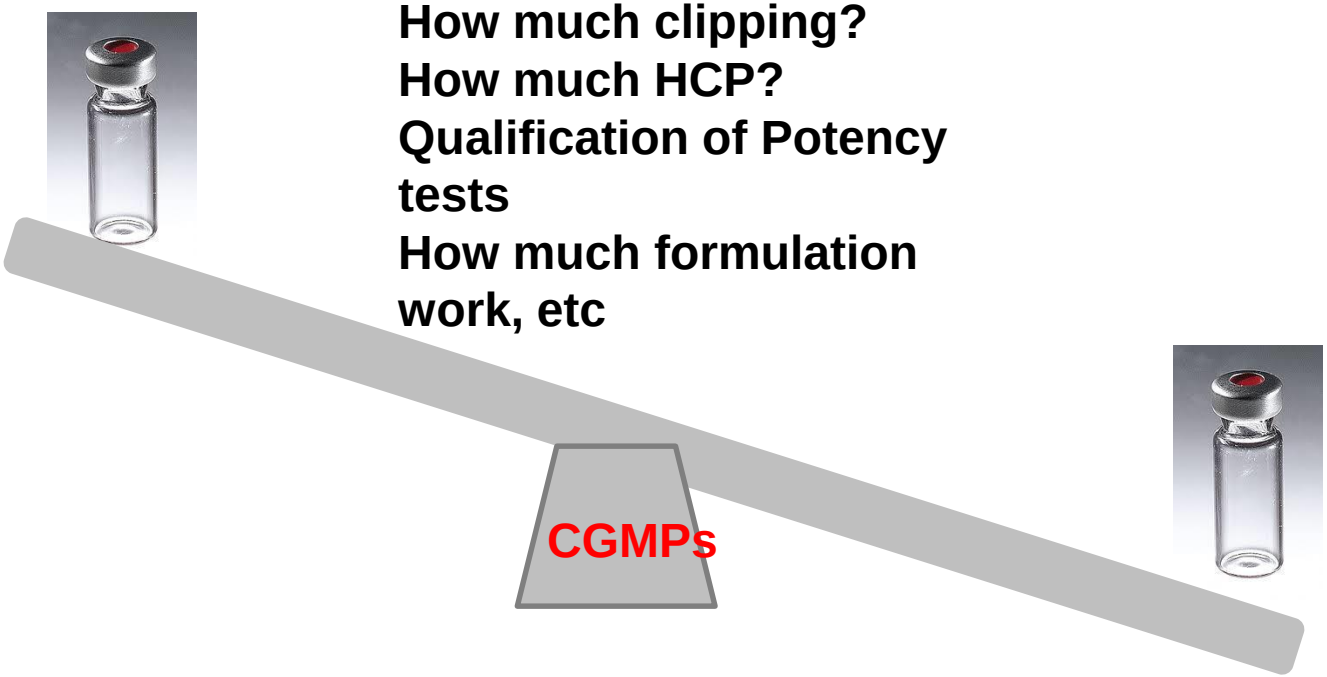
- **Myths vs Reality**
  - **"*True*" Product Development Road Blocks**
- **Current Env Manufacturing Models**
- **Ways to move forward**
  - **Phase Appropriate manufacturing**

HIV Env-Case Study for Moving Candidates into Phase I testing

HIV Env vaccines

- **Biologically complex molecule**
- **Inherently a low producer by design**
- **Many of the processes for manufacture are geared for commercial manufacture of mAbs**
  - **The mAb model is not the best fit**
  - **Result in waste of time and resources**

Balance between how much Product Characterization and Process Development to be able to get a Product into Phase 1 testing



GMPs we need for Phase 1 should speak to the Safety and Quality of the Product NOT process Validation, etc

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Product Development Road Blocks for HIV Env

Myth # 1

“You don’t need GMPs for Phase 1”
or
“More Phase 0 or Exploratory INDs Clinical studies Needed”

Myth #1 “No GMPs for Phase 1”

- No need to invent “exploratory medicine” or “Phase 0” INDs
- Phase 0
  - Establish pharmacokinetics/pharmacodynamics at a sub-therapeutic levels
  - Term not recognized by the FDA for vaccines
- Exploratory INDs
  - Involves limited human exposure, and no therapeutic or diagnostic intent (screening, microdose studies)
- GMPs are required even for Investigational Products
  - FDA guidance exempts Phase I products from complying with 21 CFR Parts 210 and 211 (licensed products)
  - Safety (Sterility) and Quality (Purity, Potency, Identity, and Stability) still must be ensured per Federal Statute
    - Products made for Phase 2/3 are NOT exempt
  - Key: Product still NEEDS to be SAFE for Phase 1
  - Key: Manufacturing processes do NOT need to be validated for Phase 1

Myth#1: Reality - GMPs are Critical for Phase I

• Product Safety	• Product Quality

• GMP requirements provide protection to subjects from an unsafe product that may result from manufacturing errors
  • Contamination
  • Cross-contamination
  • Omission of critical steps
  • Critical testing
	• Phase 1 vaccine endpoints always includes safety endpoints and typically include immunogenicity endpoints. Immunogenicity endpoints are considered potential markers for future vaccine efficacy.
	• Immunogenicity endpoints in a Phase 1 trial are frequently used to make Go/No Go decisions for initiation of Phase 2 and Phase 3 trials.
	• The ability to consistently manufacture the same product is critical for reproducing clinical results.

GMP requirements provide a framework that ensure adequate controls to maintain both product safety and product consistency/comparability from lot to lot

Myth # 2

The GMPs/Regulatory Compliance are major road blocks to product development – creating timeline delays and unnecessary compliance requirements

Myth #2 “The GMPs/Regulatory Compliance = Major Delays”

- The GMPS are **NOT** the issue.
  - True, a research method may need to be modified to produce material for human use and scale-up is a technical issue, but developing/writing batch records are NOT the issue.
- GLP repeat-dose toxicity studies are **NOT** usually rate-limiting
  - Can be done on bulk product or engineering material as long as it is comparable to proposed clinical material
  - The FDA has waived the need for toxicity studies on multiple vaccine platforms if adequate experience with type of product is available
    - CH505 TF protein (no additional studies needed on highly related protein variants)
    - gp145 trimer protein – no tox study needed when mixed with aluminum hydroxide
    - gp140 mosaic protein – no tox study needed due to availability of preclinical and clinical information with gp140 Clade C trimer protein in combination with Ad/MVA vaccination.
    - DNA mosaic prime/ MVA-CMDR boost – no toxicity study required
    - Adenovirus vector

Myth # 3 CMOs

“We just need more CMOs”

“$$$ to CMO = high quality GMP product suitable for human use”

“$$$ to CRO = high quality GLP Tox Study”

High Level CMO Lessons Learned for HIV Env

- Recognize translating from research to manufacturing is a technical hurdle
  - Products are usually biologically complex
  - Not a GMP issue, yes scale up and developing a suitable manufacturing methods takes time and expertise
  - More CMOs are not always the answer:
    - Non-vested team, a la carte mentality, B team variable quality
    - Not always willing or able to develop a Phase I process
    - Analytical development takes time
- Multiple stakeholders involved, multiple organizations involved (contractors, subcontractors, etc) making communication challenging

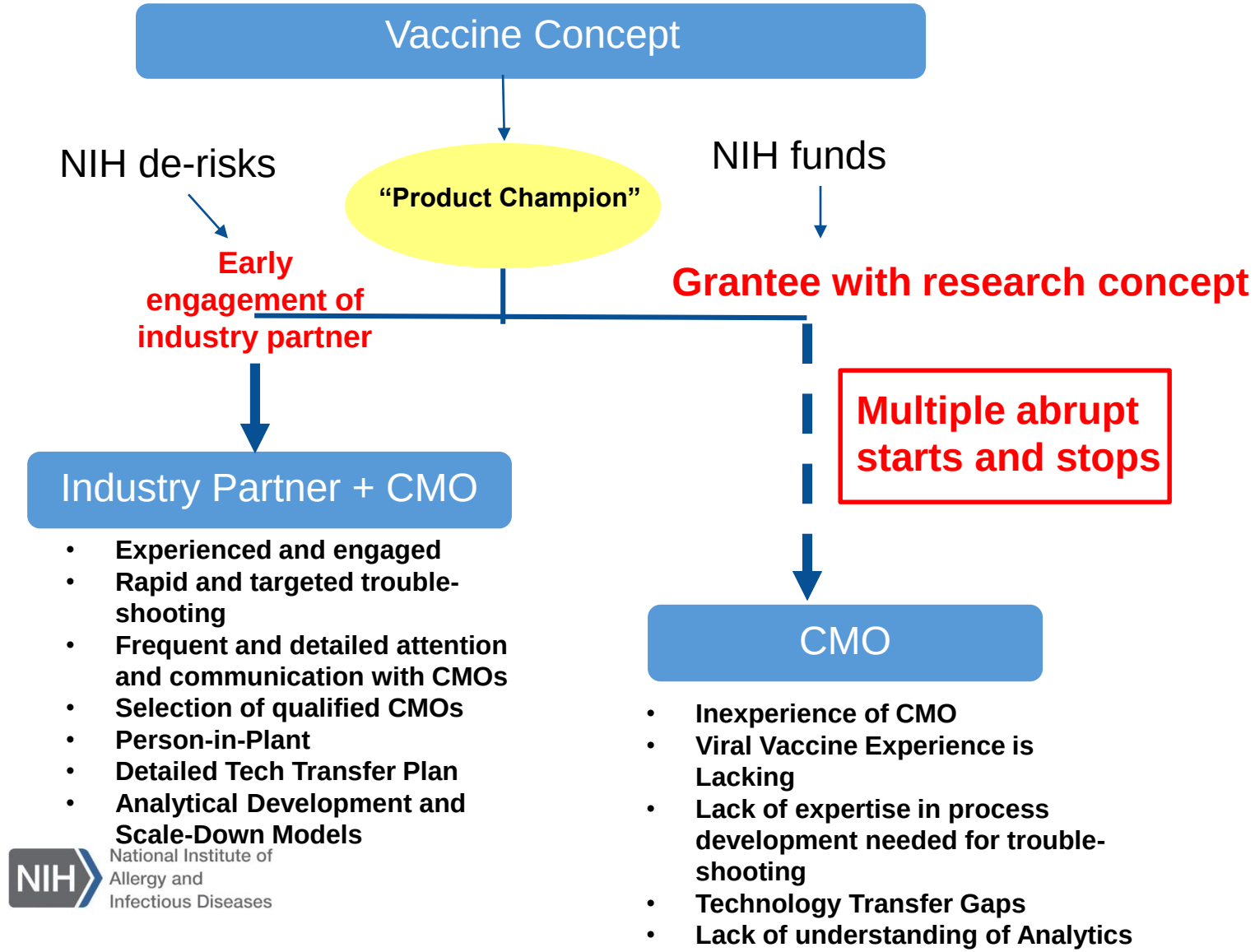
High Level CMO Lessons Learned for HIV Env

CMO-Product Driver Balance:

- Finding the right CMO involves both a Technical and Quality (GMP) Assessment.
  - Governed by a good Quality Agreement
- An integrated, focused project team, led by a full-time PM, is often key to success.
- Need to have QA resources to address unexpected results during manufacture/testing
  - e.g., deviations, investigation to identify root cause, product impact and implementation of CAPA
- Early Analytics development

Current NIH Models for HIV Env Phase I Manufacturing

Current Operating Models for HIV Env Manufacturing at NIH



- Experienced and engaged
- Rapid and targeted trouble-shooting
- Frequent and detailed attention and communication with CMOs
- Selection of qualified CMOs
- Person-in-Plant
- Detailed Tech Transfer Plan
- Analytical Development and Scale-Down Models

- Inexperience of CMO
- Viral Vaccine Experience is Lacking
- Lack of expertise in process development needed for trouble-shooting
- Technology Transfer Gaps
- Lack of understanding of Analytics

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2015 Reality: Current Operating Model

Vaccine Concept

"Product Champion"

Early engagement of industry partner

Grantee with research concept

reality

CMO

highly unlikely

Realizing this is the most likely path, how can we gain learning efficiencies moving forward and translate that into acceleration?

Major Obstacle: Slow accumulation of learning efficiencies

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Realizing the Gap: How do we address HIV envelope manufacturing hurdles?

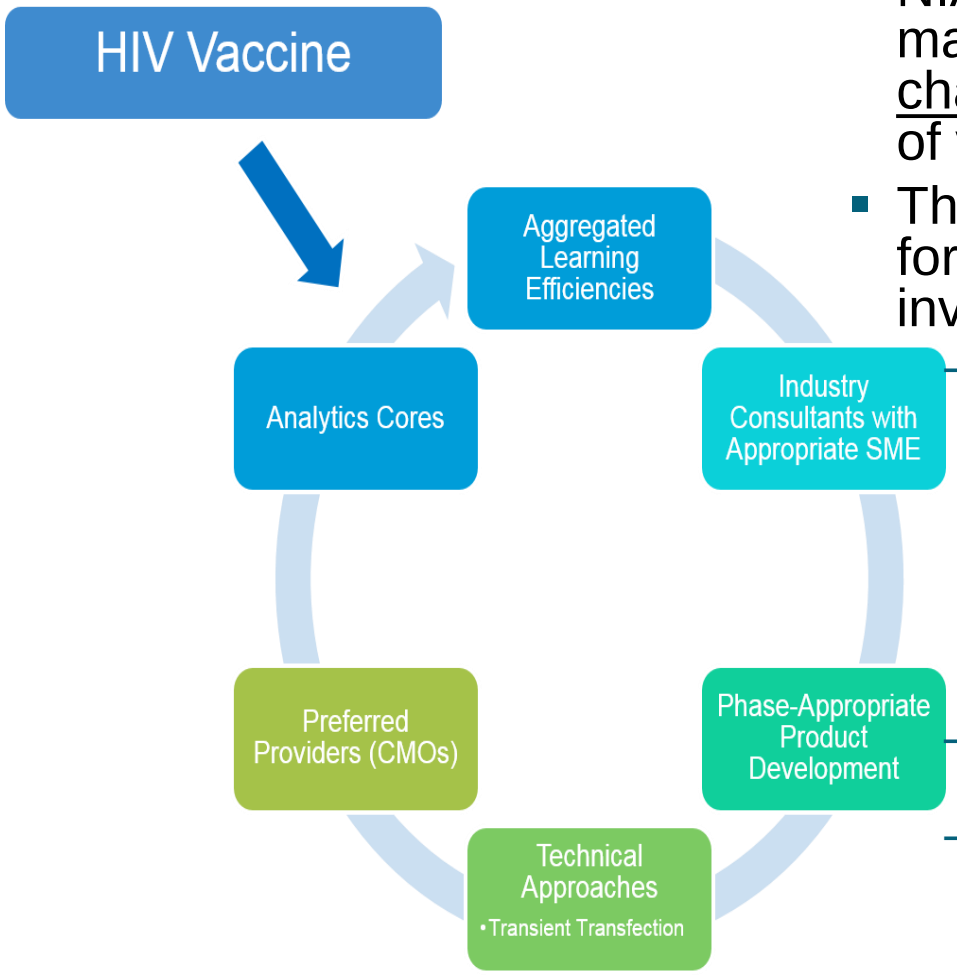
Success with the Pharma Model

Reality

Realizing this is the most likely path, how do we address the gap?

Proposals for Acceleration: Phase Appropriate GMPs

Proposed Approaches for Acceleration



- NIAID/DAIDS is funding efforts to manage product development challenges for clinical evaluation of vaccine candidates
- The aim of is to provide support for product development for investigational testing by:
  - Developing a **pool of experienced, preferred vendors** to take advantage of lessons learned and have consistent systematic procedures for obtaining data
    - **Analytic and Process Development Cores**
  - Employing **phase-appropriate product development strategies**
  - **Investigating novel technologies** that may accelerate product development for early phase clinical trials
    - **Transient Transfection**

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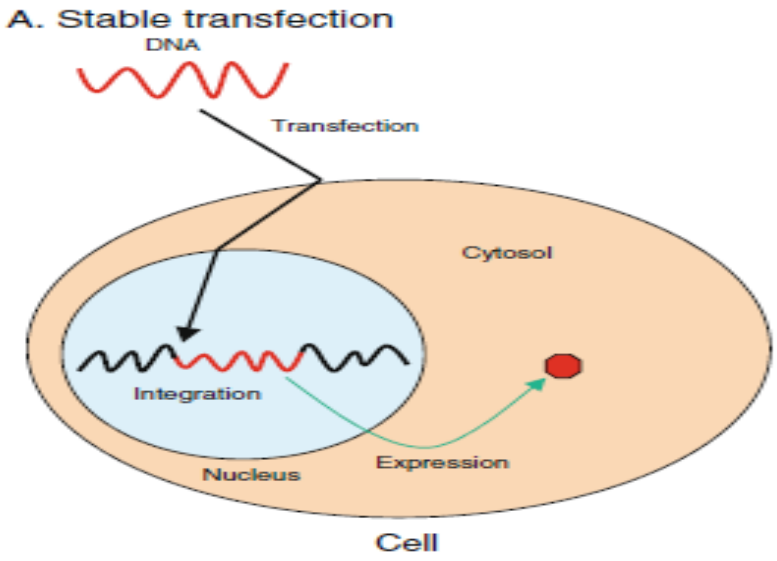
Stable vs Transient Expression

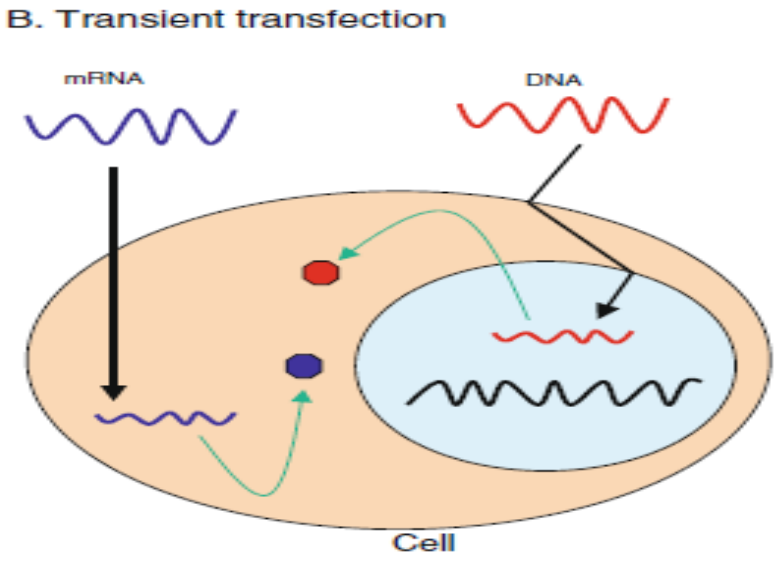
Stable

- Integration
- Long-Term expression
- Time-lines are longer
- More homogenous

Transient

- No integration
- Short-Term expression
- Time-lines shorter
- Less homogenous





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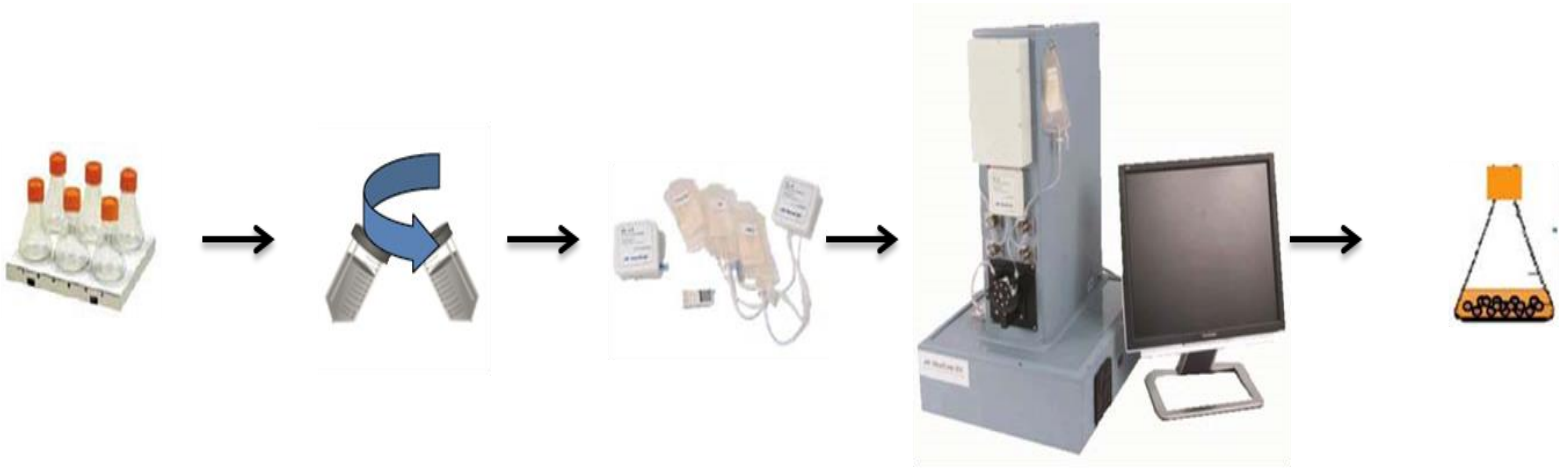
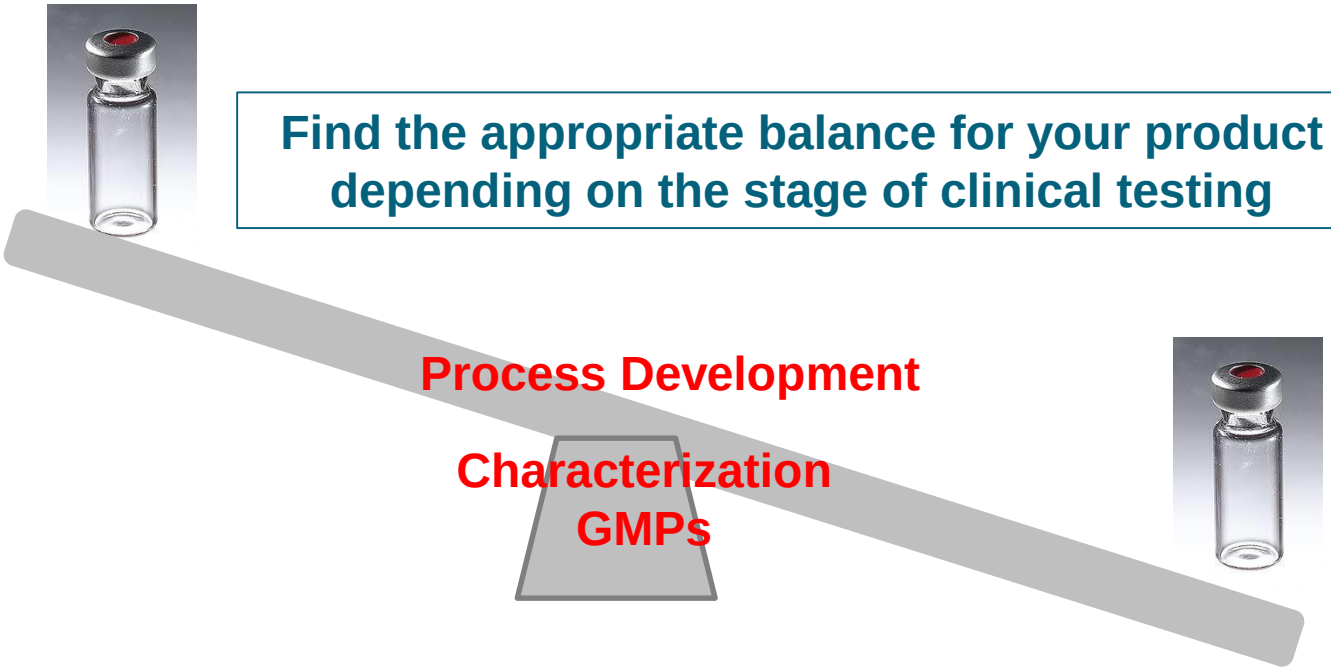
Stable vs Transient Expression



Suspension cells **CHO-S** exponential phase in serum free medium	Concentrate/ rinse/ exchange into EP medium	Mix cells @ 2 x 10^8 cells/mL with DNA **CH505 TF gp120** transfer to processing assemblies,	Electroporate using MaxCyte STX in static (small scale) or flow-thru mode	Resuspend at desired density, incubate and sample for expression analysis (FACS, ELISA, etc.), purify for characterization

Conclusions

- Help dispel some common misperceptions regarding GMP manufacturing and replace with realistic expectations
- Your clinical product must be **SAFE** and **CHARACTERIZED**



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