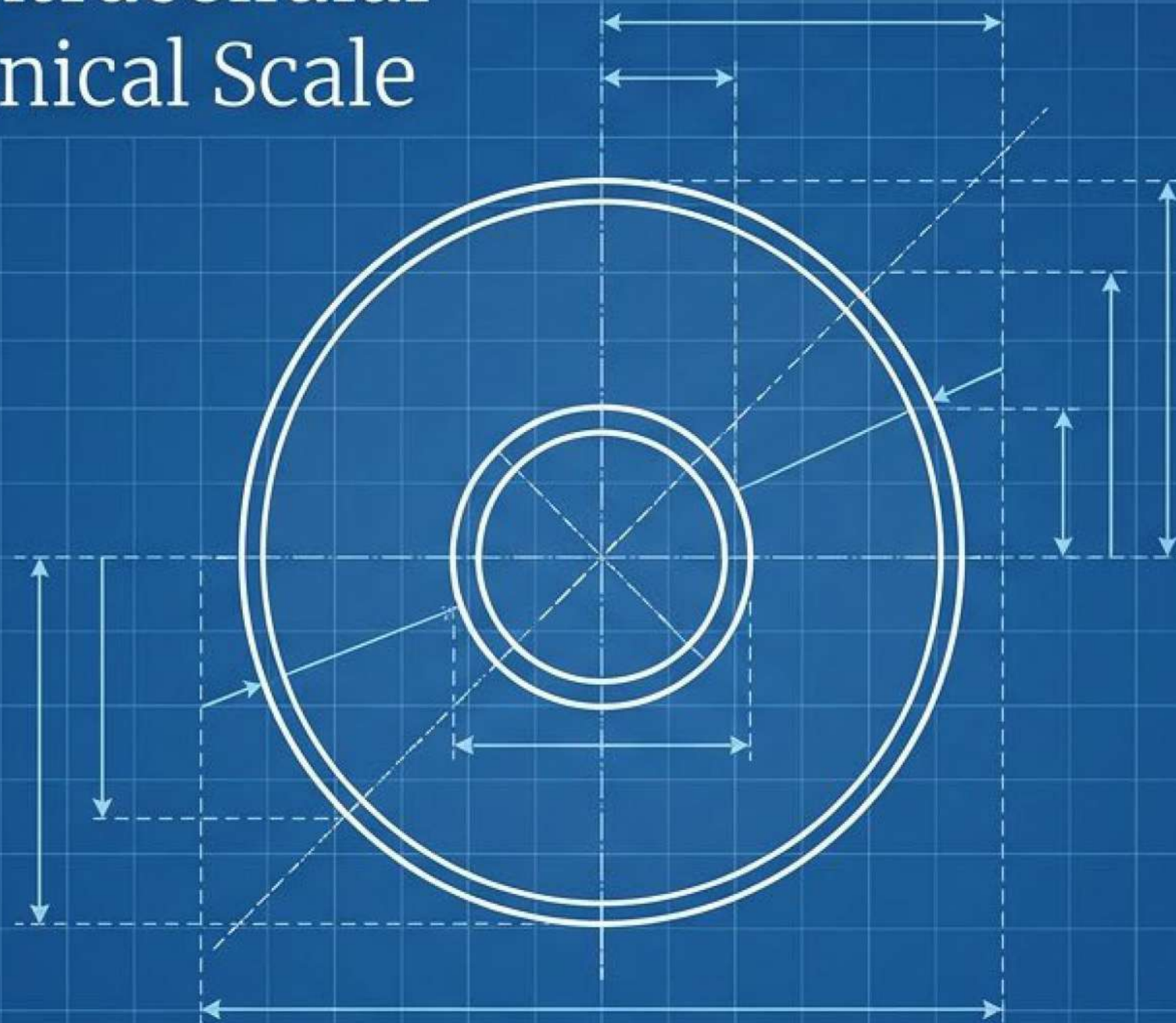


# Engineering Extracellular Vesicles for Clinical Scale



A Blueprint for cGMP Manufacturing,  
Quality Control, and Commercial Reality

Focus Area: iPSC-derived CPC Secretomes

# Restoring Mobility in Heart Failure



**The Baseline:** NYHA Class 3 Heart Failure (Severe limitation, shortness of breath after 10 meters).

**The Intervention:** iPSC-derived CPCs secreting targeted Extracellular Vesicles (EVs).

**The Result:** Progression to NYHA Class 2. Patients walk 100 meters without severe distress. A massive shift in quality of life.

## Phase 1 Dosing Architecture

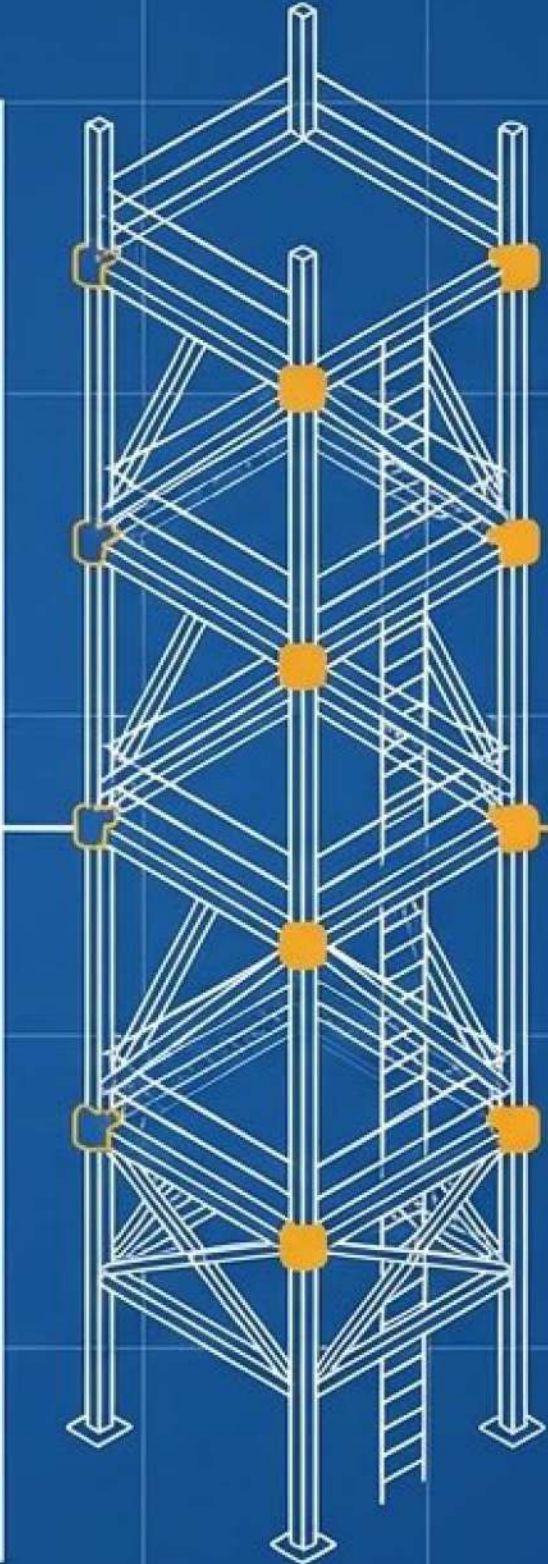
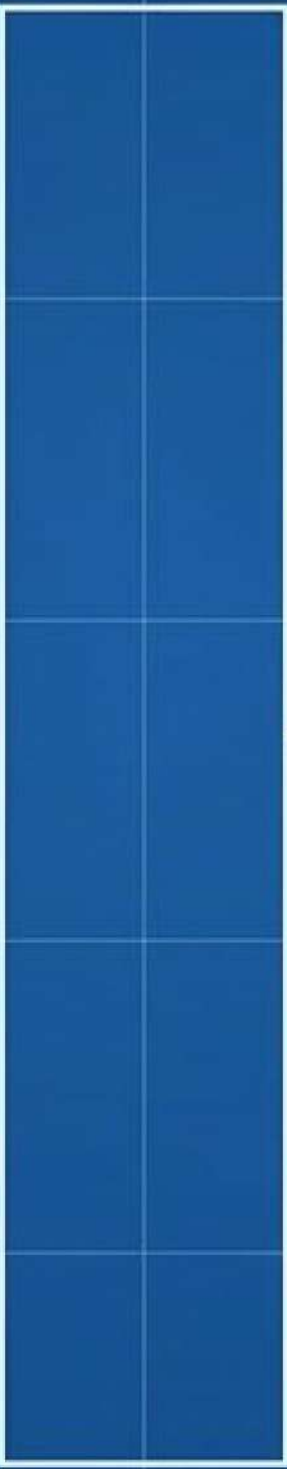
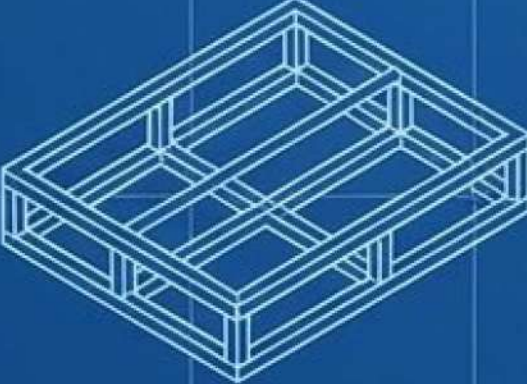
Cohort 1 (4 Patients): 20 billion EVs x 3 doses.

Cohort 2 (8 Patients): 40 billion EVs x 3 doses.

# The Gap Between Discovery and Production

**Platform 1:**  
Research Use Only (RUO)

- Focuses purely on biological efficacy.
- Driven by discovery.
- Tolerates variability.



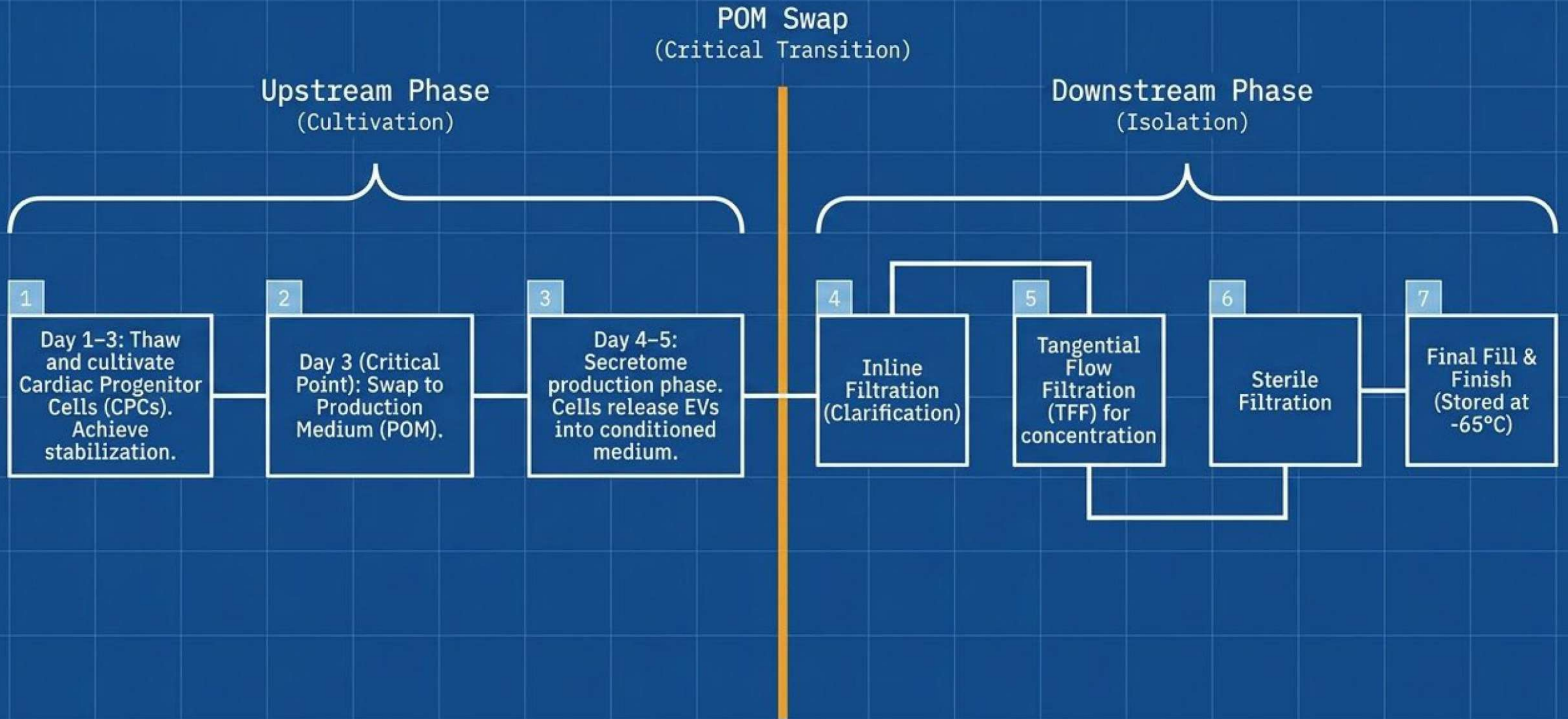
**Platform 2:**  
cGMP Manufacturing

- Focuses on unyielding consistency.
- Mandates absolute sterility & compliance.
- Driven by risk mitigation.

# Structural Upgrades Required for Human Trials

RUO Parameters	cGMP Requirements
Environment: Standard laboratory bench.	Environment: Grade B cleanroom encompassing a Grade A processing zone. Strict particulate monitoring.
Documentation: Technical manuals and basic lab notebooks.	Documentation: ICH Q9 integration. Mandatory risk assessment frameworks for every discrete process step.
Materials: Basic Certificate of Analysis (COA).	Materials: COA, Certificate of Origin (COO), and rigorous equipment safety/approval certificates.
Quality Control: Basic cell counts and viability.	Quality Control: Intense, bifurcated gating for both in-process cells and the final product.

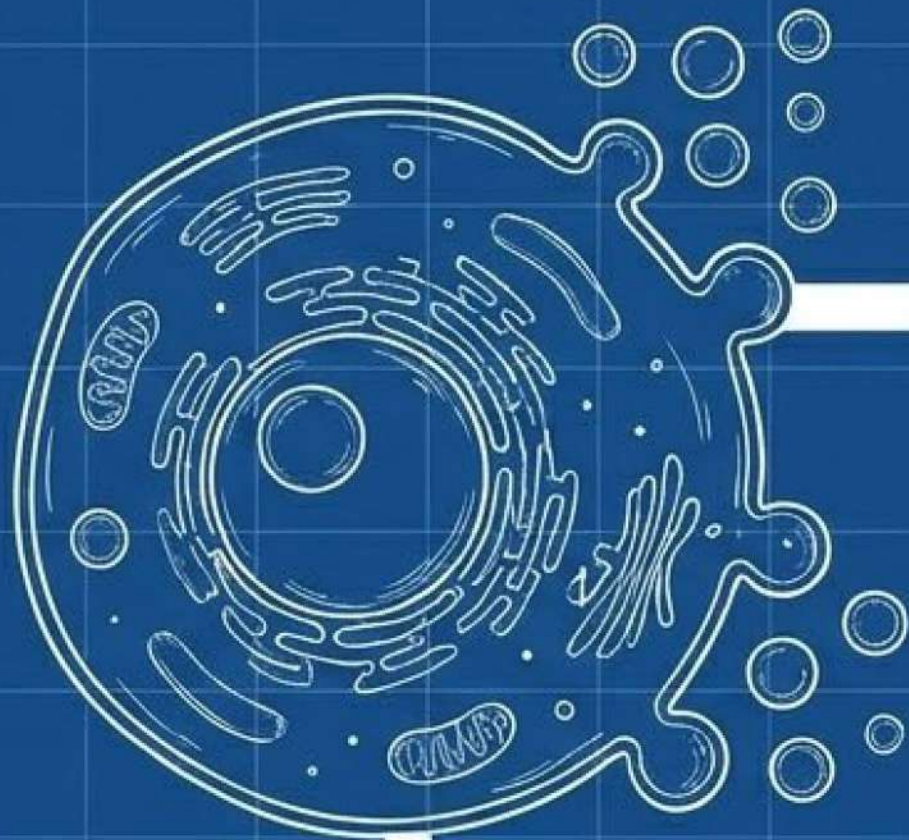
# The 5-Day Manufacturing Engine



# Quality Control Requires Two Distinct Focal Points

The Challenge: Producing EVs is a dynamic biological process.

The Solution: Simultaneous, parallel monitoring architectures.



## Focal Point 1: The Engine (In-Process Cell)

Ensuring the CPCs maintain their identity and do not differentiate improperly during the 5-day cycle.

## Focal Point 2: The Output (Final Product EV)

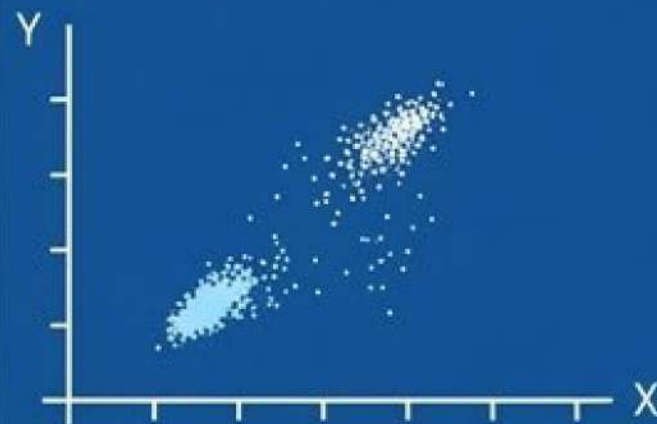
Ensuring the resulting Secretome meets exact specifications for size, purity, and safety.

# In-Process Monitoring: Tracking the Cell

**Target:** Cardiac Progenitor Cells (CPCs)

**Critical Risk:** The Day-3 POM media swap induces stress. Cells may spontaneously differentiate out of the acceptable identity range.

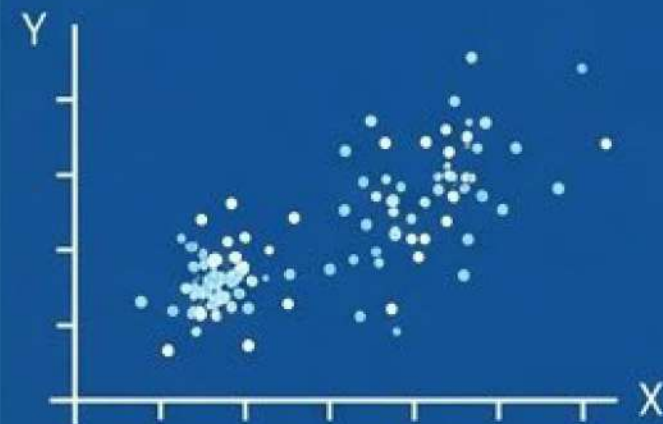
IDENTITY MARKER ANALYSIS



## Identity Markers

Continuous Flow Cytometry targeting CD56 and CXCR4 to confirm CPC status.

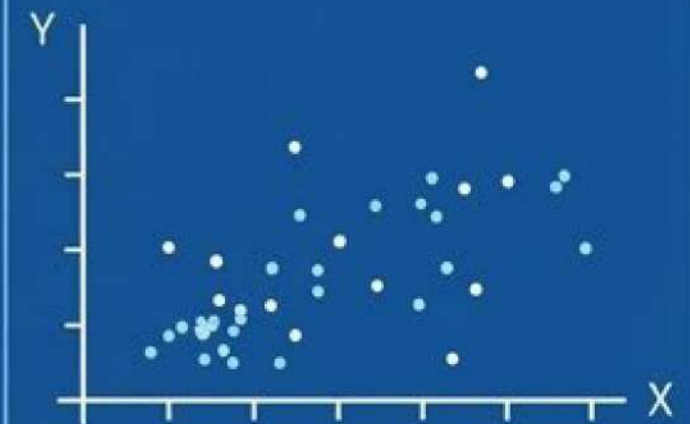
GENETIC STABILITY ASSESSMENT



## Genetic Stability

Karyotyping to ensure chromosomes remain normal under manufacturing stress.

STERILITY SCREENING



## Sterility

Continuous screening for mycoplasma and contaminants throughout cultivation.

# Final Product Characterization: Verifying the Secretome

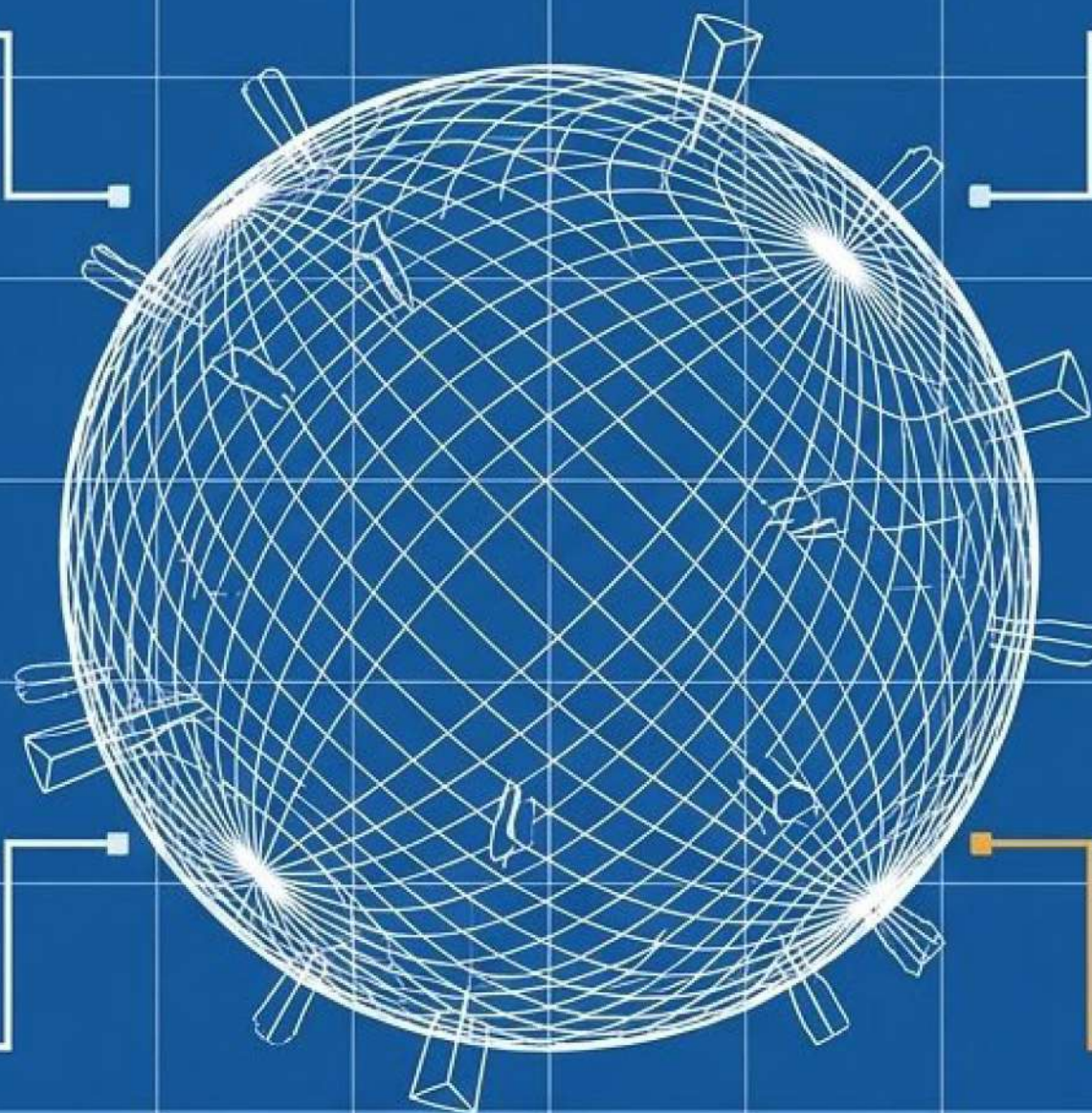
Target: The Isolated  
Extracellular Vesicles (EVs)

## Physical Specifications:

Particle size  
distribution and  
concentration mapping.

## Biological Identity:

Presence of essential  
exosome markers CD63  
and CD81.



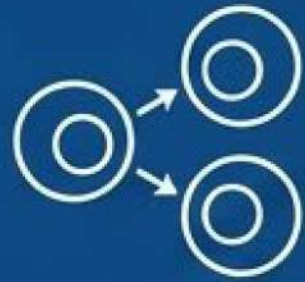
## Safety & Purity:

Rigorous screening for  
host-cell protein  
residue, endotoxins, and  
absolute sterility.

## Durability:

Mandatory 3-year  
stability testing  
protocols under  $-65^{\circ}\text{C}$   
storage conditions.

# Proving Functionality Before Human Application



**Panel 1: Proliferation Assays**  
Testing the EV's ability to stimulate cell survival using human umbilical vein endothelial cells (HUVEC).



**Panel 2: Angiogenesis Assays**  
Utilizing targeted scratch tests to measure the speed and efficacy of cellular repair and migration.



**Panel 3: Toxicology & Safety**  
Mandatory in vivo toxicology screening and tumorigenesis profiling to guarantee the EVs will not trigger unintended growth or adverse reactions in humans.

# Navigating the Web of Intellectual Property

**The IP Bottleneck: Manufacturing success does not equal commercial freedom.**

## Foundational Constraints:

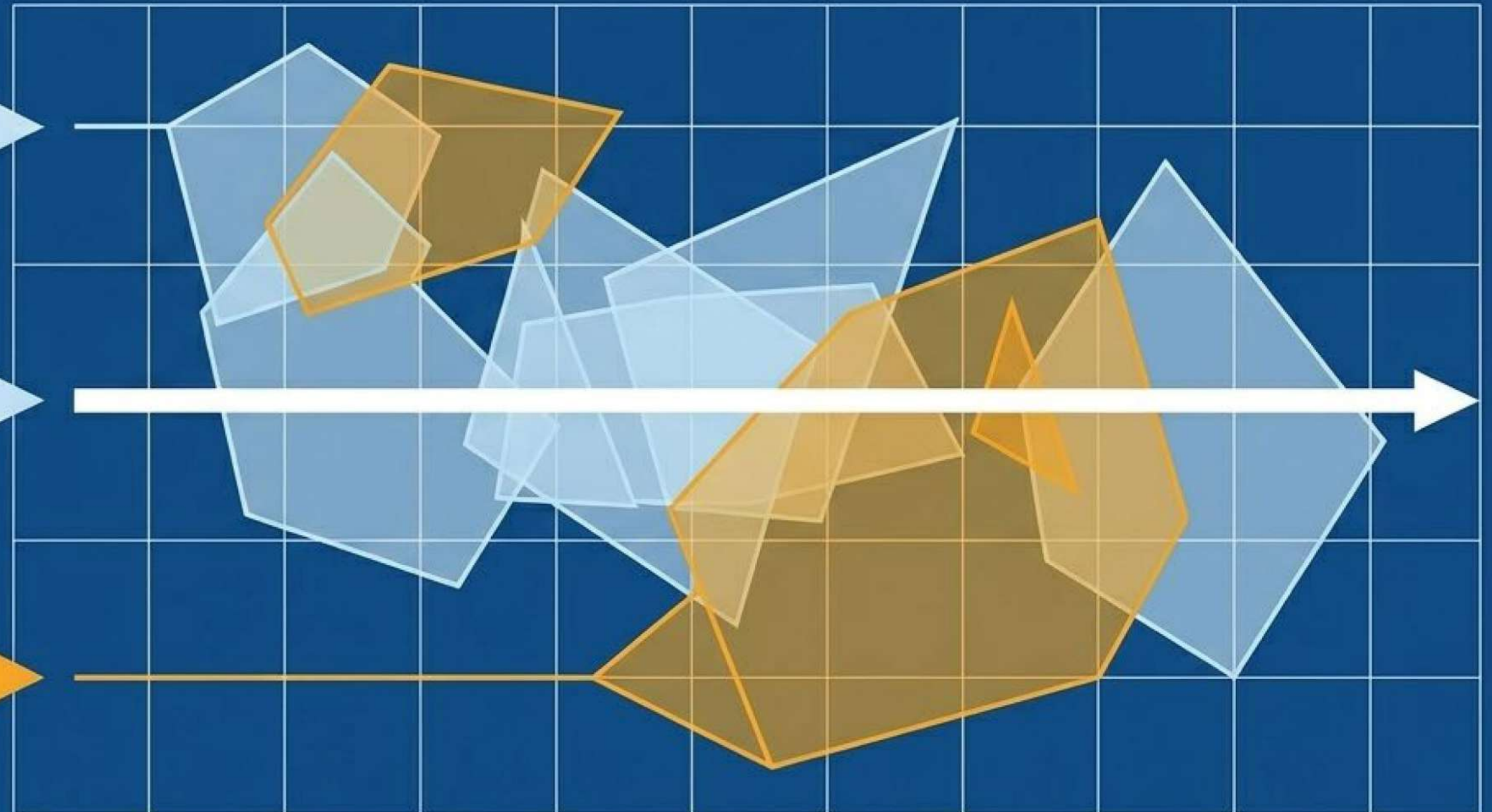
The baseline use of iPSCs (induced pluripotent stem cells) is heavily locked down by existing patents.

## Process Constraints:

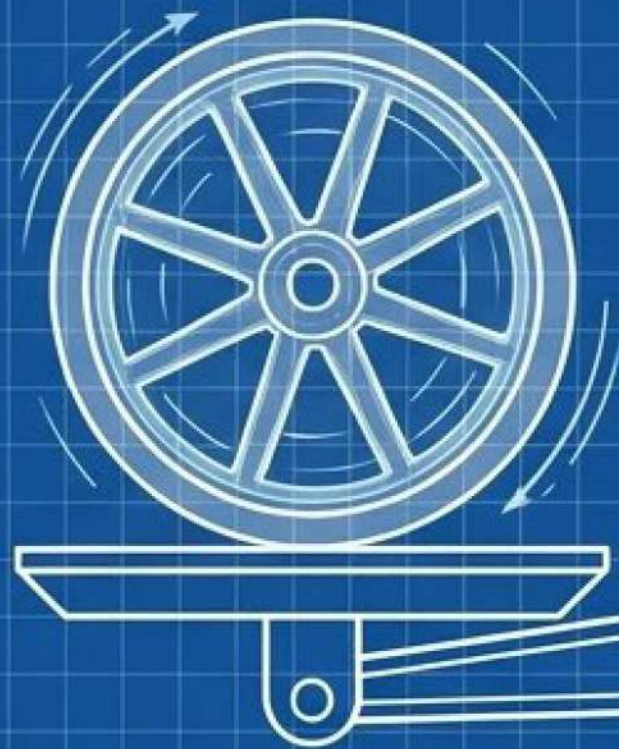
Overlapping IP rights cover specific isolation methods, proprietary media formulations, and filtration techniques.

## The Commercial Threat:

Developing a perfect cGMP process can still result in a product that cannot be legally sold without costly sub-licensing agreements.



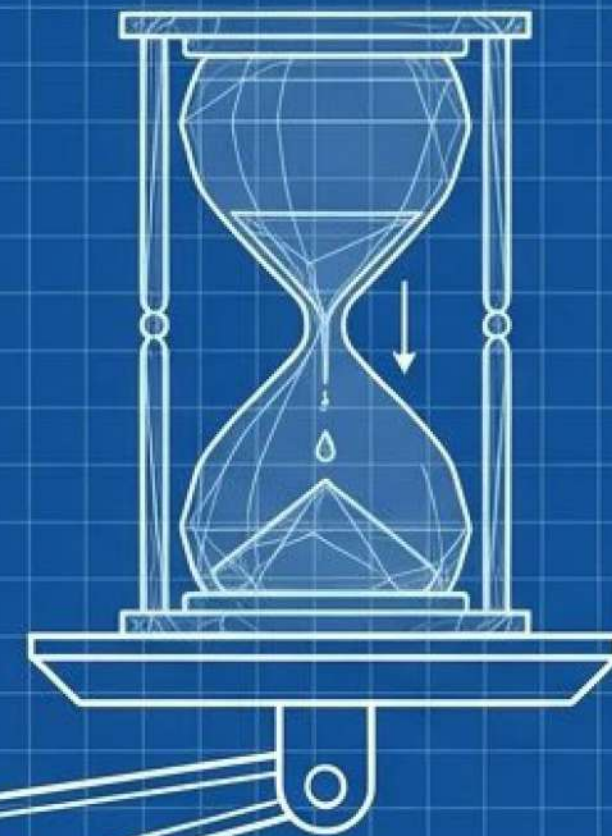
# The Macroeconomics of Biotech Cash Burn



## The Hardware Model (e.g., ASUS)

Generates roughly ~60 Billion NTD per month (~2 Billion NTD per day).

Immediate consumer revenue. High volume, rapid iteration.



## The Biotech Model

Zero consumer revenue for 10+ years.

Requires massive daily cash burn to fund cGMP facilities, 3-year stability tests, and specialized talent just to treat one specific patient cohort in a clinical trial.

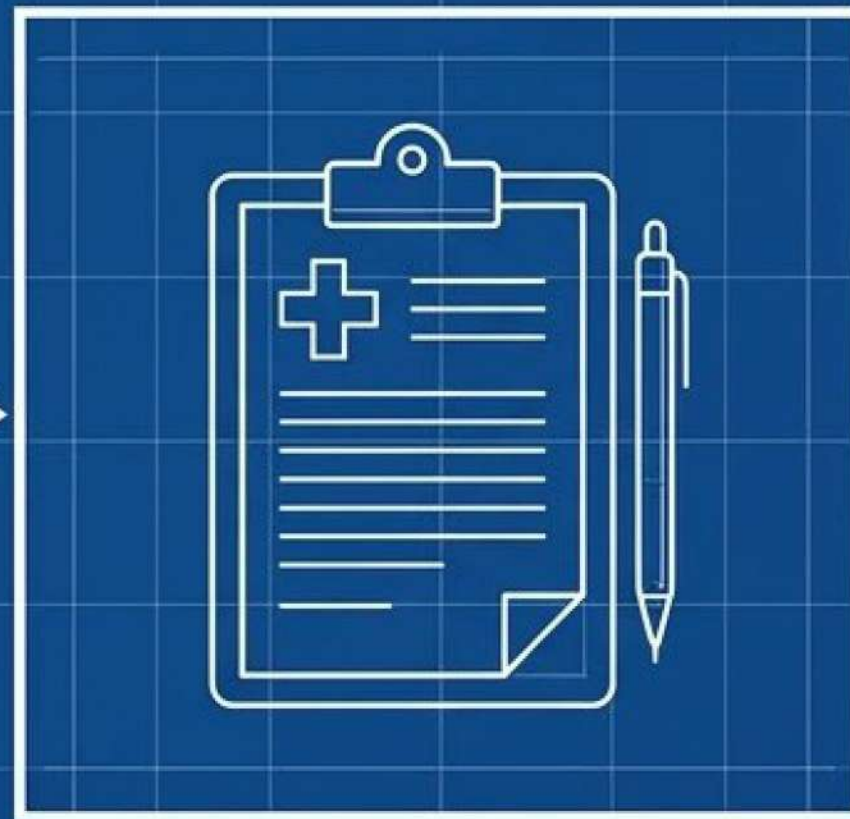
# The True Exit Strategy in Life Sciences

Biotech is not a direct-to-consumer industry. The goal is rarely to build a standalone pharmaceutical sales empire from scratch.



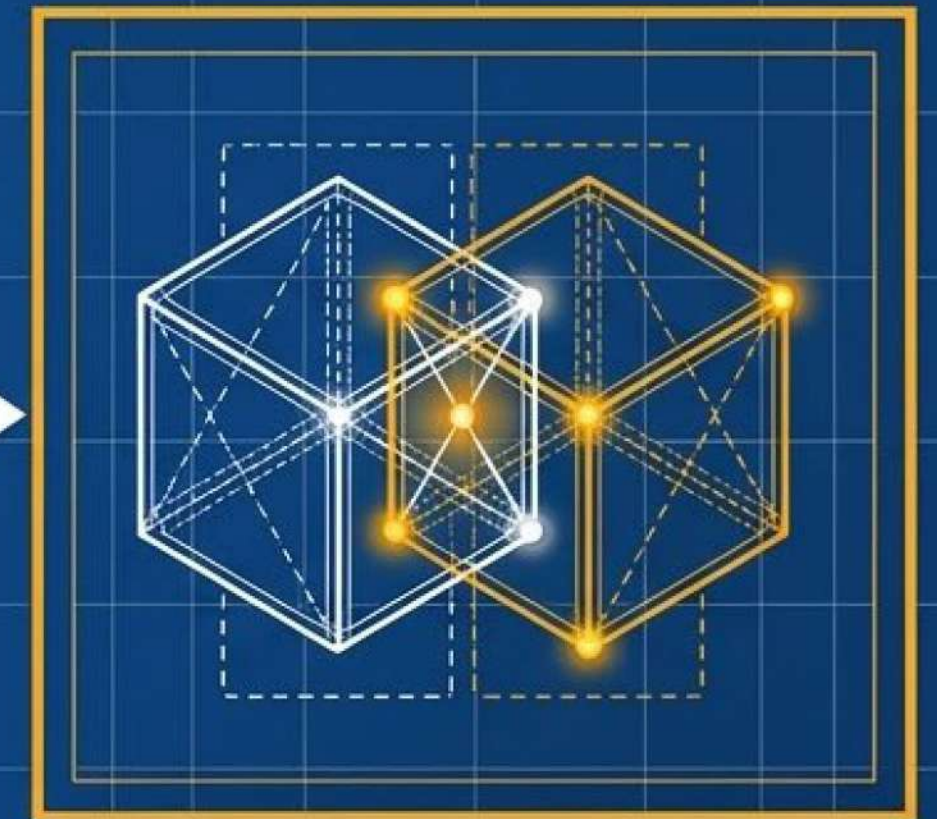
## Step 1: Absorb the Risk

Secure funding to survive the cGMP gauntlet and navigate the IP web.



## Step 2: Prove the Science

Achieve undeniable clinical efficacy in Phase 1 and Phase 2 trials.



## Step 3: The Acquisition

The ultimate customer is not the patient; it is Big Pharma. Big Pharma buys the de-risked startup, acquiring the IP, the cGMP process, and the clinical data to integrate into global pipelines.