# Biologics & The Challenges in Clinical Supplies

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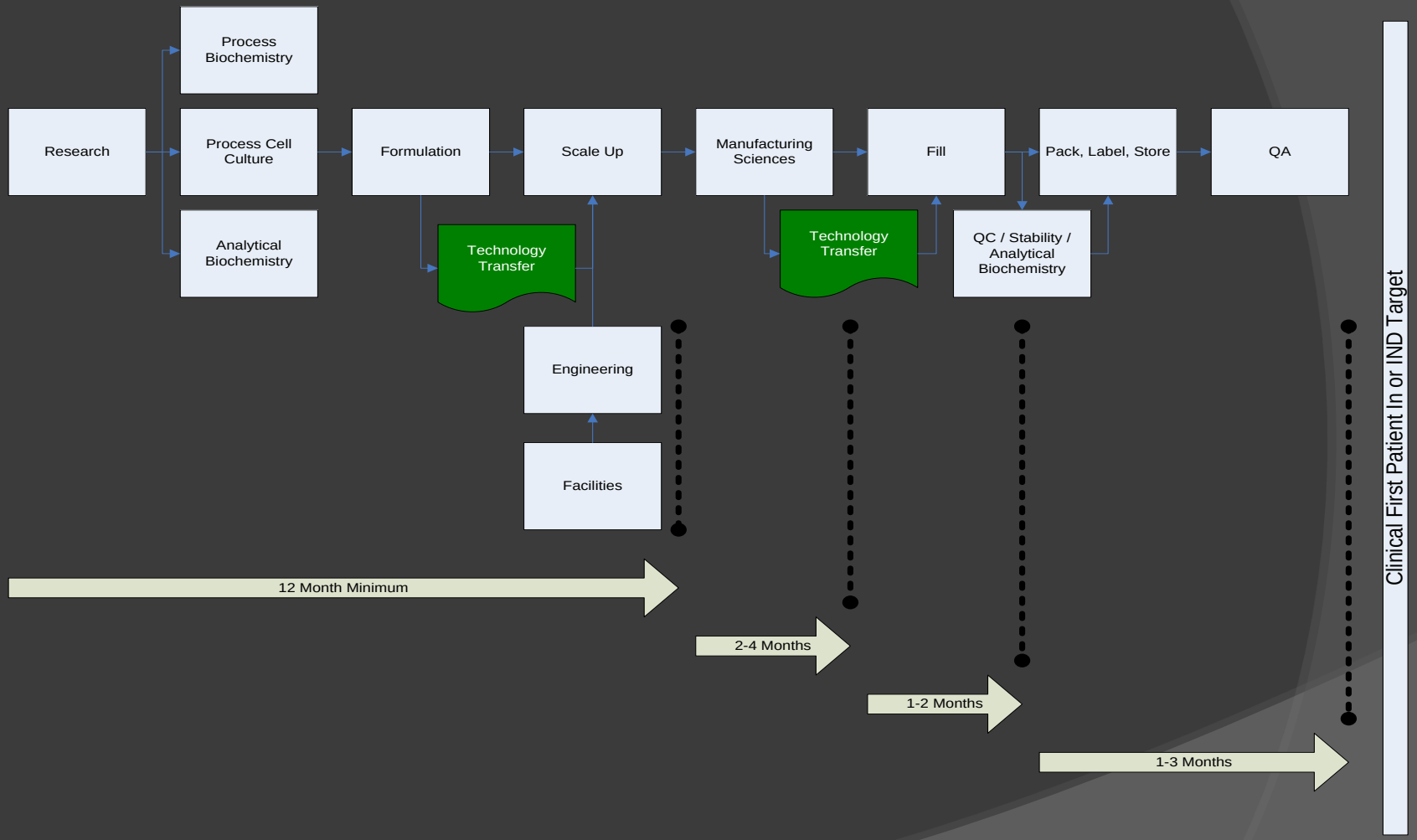
# Learning Objectives

- Summarize the challenges of producing biological clinical supplies
- Discuss & share some techniques for resolutions

# Agenda

- Manufacturing Challenges
- Supply Chain Challenges
- Blinding Challenges
- Expiration Dating Challenges
- Cold Chain Storage/Distribution Challenges
- Administration Challenges

# Manufacturing ‘Upstream’- Ideal

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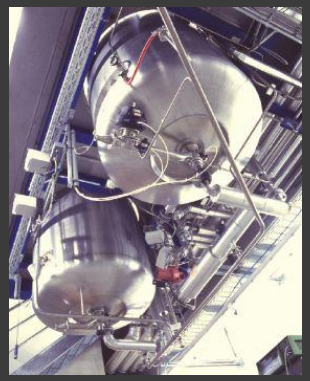
# Manufacturing Challenges

- 'The unknown quantity'
  - Final Dose therefore Product Concentration and Fill Volume
  - Clinical Demand (# of cohorts, subjects, sites and vials)
  - Scale and Number of DP and DS Lots Required
- Scale-up challenges
  - Industry push to reduce time to market causes R&D crunch…



*Stable product but 'less than ideal' commercial presentation*
*vs.*
*Less stable product but more suited to commercial presentation*

*Where does the higher risk lie?*

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# Manufacturing Challenges

- Early development - Possibly the1st time the product has been in a large scale bioreactor
  - Unfamiliar ‘cell culture’ timing and likelihood of success
  - ‘Controlled’ Bioreactor Environment
    - pH
    - Temperature
    - Agitation
    - Dissolved Oxygen
    - Flow Rates (Oxygen, Carbon Dioxide, Nitrogen)

*‘No Promises’ and ‘No Guarantees’!*

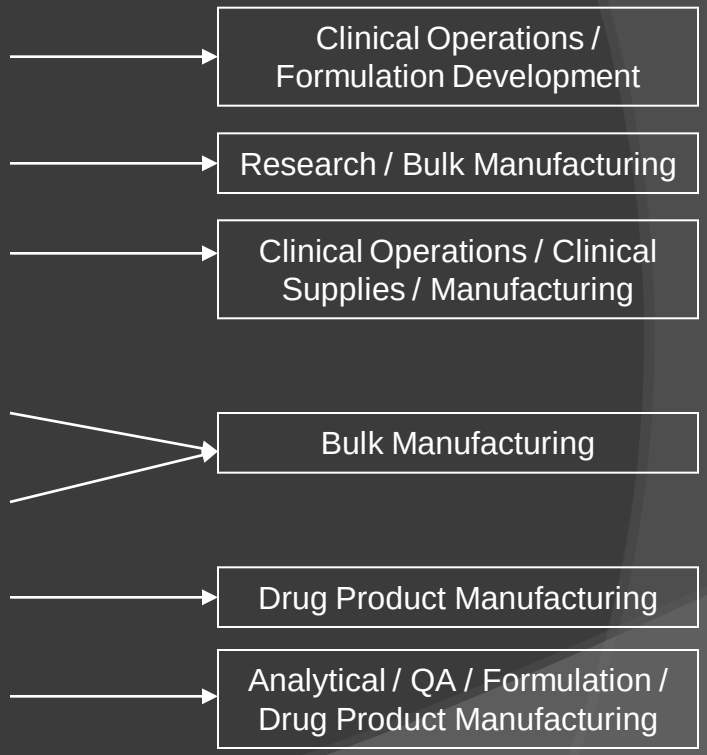
# Manufacturing Challenges

- Other Issues
  - *Materials Management*
    - *Ordering Lead Time*
    - *Expensive Product (esp. Purification Resins)*
  - *Clinical Manufacturing Prioritization Disputes*
  - *Lack of Room for scheduled / planned failures*
  - *Very High Sample Volumes (Stability / Sterility etc)*

*Communication Issues*

# The ‘Unknown’ Quantity

| | |
|---|---|
| **Fill volume per vial (vial / components)** | **1.25mL** |
| **Titer** | **2g/L** |
| **Production Concentration** | **100 mg/mL** |
| **Bioreactor Scale** | **500L** |
| **Bioreactor Yield** | **60%** |
| **Fill Yield** | **90%** |
| **Samples to be taken** | **250 vials** |

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# Clinical Operations uncertainty causes Bulk Manufacturing disruption

| Clinical Operations Drivers | Impact on Manufacturing |
| --- | --- |
| Unknown dosage/dosing regimen | Optimal DP concentration? – Affects Tech transfer & delays Mfg |
| Clinical protocol delayed | Manufacturing Delays - Scheduling & Materials Mgmt |
| Low or slow enrollment | Excess inventory – Storage issues Limited stability data – expiry |
| High or fast enrollment | Mfg limitations, budget overruns & high COGs |

## Communication Issues!

# Perform a Pareto Analysis
## *The '80:20' Rule*

**Most Frequent Clinical Protocol Changes**

Addition / Removal of Cohorts, Countries, Sites & Patients

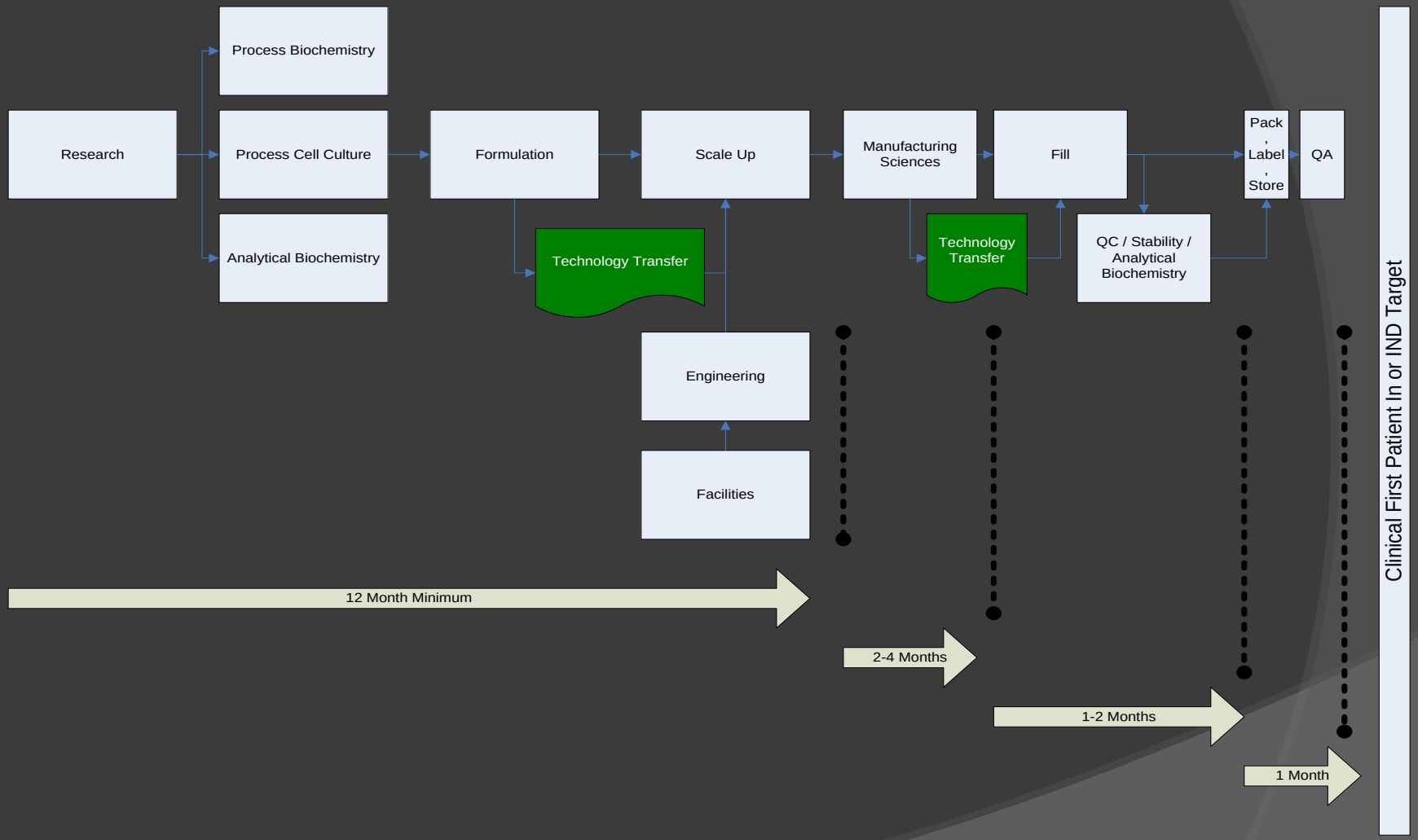
Dose Escalation Planning

Drug Stability / Expiration Dating

Additional / Removal of Protocols & Studies

Study Dosing Hold / Cancellation (e.g. S.A.E)

# Manufacturing 'Upstream'- Realistic

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# Reducing the Crunch

Earlier Material Availability to Clinical Supplies

*requires*

Earlier Fill

*Requires*

Earlier R&D Technology Transfer to Fill / Finish

*Requires*

Earlier Bulk Drug Manufacturing

*Requires*

Earlier R&D Technology Transfer to BDS Mfg Locations

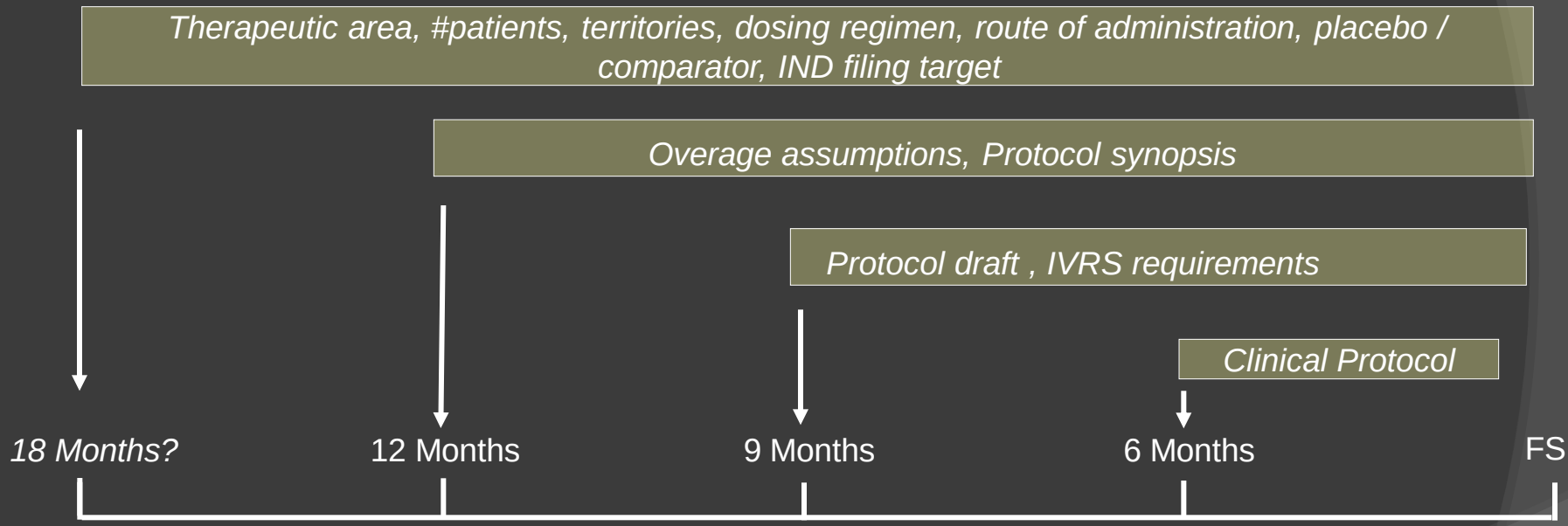
*Requires*

Earlier Clinical Protocol Assumption

*How?*

Service Level Agreement on Assumptions

# Example Service Level Agreement



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# Blinding

- Placebo blinding
  - Viscosity
  - Color
  - pH
- Dose preparation
  - Weight based dosing
    - 10mg/kg, 20mg/kg
    - Require different number of vials

# Blinding

- Comparator
  - Drug product container
    - Size and shape
    - Fill volume
  - Method of administration
    - Oral
    - Intravenous
    - Subcutaneous

# Blinding

- Resolutions
  - Match product/placebo/comparator during development
    - Viscosity, color, pH
  - Use of translucent color labels on primary container
    - Color, viscosity

# Blinding

- Resolutions
  - Site pharmacist to be unblinded
  - Double blind, double dummy trial design
    - Methods of administration

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# Expiration Dating

- Tend to be less stable products
- Require cold chain (storage &/or distribution) in order to maximize stability
- Each product may have very specific temperature limits

# Expiration Dating

- Start with short expiry dating
  - Over-labeling
    - Monitor time out of appropriate storage temp during the over-labeling process
    - May limit international depot selection based on ability to perform over-labeling
  - Can’t over-label – smaller P&L jobs

# Expiration Dating

- Expiry date filing - international
  - Real time data -v- projections
    - Some countries only allow 6 months of projections
    - Some countries do not allow projections

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# Storage

- -20 °C & -70 °C
  - Freezer space at vendors & sites
  - Label adhesive for ultra-low temperatures
  - Specialized P&L operations
  - Site temperature monitoring
- 2 – 8 °C
  - Dedicated space availability (particularly sites)
  - Site temperature monitoring

# Distribution

- -70 °C
  - Plan ahead for dry ice availability
  - Increased shipping costs
  - Dangerous goods shipment
  - Receipt inspection
  - Few temperature monitors are available for this range

# Distribution

- Advantages of dry ice shipments
  - Easy pack-out
  - Easy to replenish
  - Easy to calculate shipment viability time
    - More ice = longer time

# Distribution

- -20 °C & 2 – 8 °C
  - Requires packaging configuration plan
    - Ice bricks keep temperature only for a certain amount of time
    - Replenishments require courier to follow pack-out diagram

# Distribution

- Shipper validation
- Temperature monitors
  - Variety of types available
  - Plan for data capture & site notification of use
- Increased cost

# Temperature Variations

- Stability/Development
  - Protocols to stress the labeled storage conditions
  - Maximum amount of time of exposure
  - Minimum/Maximum temperature exposure

# Temperature Variations

- Quality Assurance
  - Approve stability/development protocol
  - Review & approve the results
  - Provide supporting documentation

# Temperature Variations

- Use of stability/development information
  - Monitor in/out times during P&L operations
  - Monitor shipping and storage
  - Determine if any impact on the product

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# Administration

- Administration components
  - IV bags, syringes, IV administration sets
- Issues
  - Time exposure in these components
  - Low doses
    - Dilutions
  - How does drug product behave?

# Administration

- Challenges
  - Adsorption of drug to components
  - Aggregation of the drug due to components
  - Solution compatibility
  - Light sensitivity

# Administration

- Resolutions
  - Special IV bag protectant/diluent
  - Extensive compatibility testing
  - Supply all necessary administration components

# Weight-based Dosing

- Body weight or body surface area
  - Lean body weight vs. actual body weight
  - Baseline measurement vs. current measurement
  - BSA calculation can vary

# Weight-based Dosing

- Challenge to forecast CTM requirements
  - Patient-specific dosing
  - Variability in body weights
    - Men vs. Women
    - Cultural differences
    - Geographical differences

# Weight-based Dosing

- Challenge to determine best packaging configuration
  - Prevent wasted drug
  - Minimize # of kits used/patient

# Summary

- New products – New challenges
- Agree assumptions for planning
- Consider the upstream
- Plan accordingly (allow time)
- Communicate!

# Questions?