Opportunities and Challenges in Biopharmaceutical Process Modeling

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My Definition of Model

An abstract representation of production alternative which predicts:

1. The production requirements
2. The production capacity
3. The value of the production alternative

The process model is a key tool for process optimization, debottlenecking, capacity planning and portfolio management

Overview

Describe the three fundamental requirements for biopharmaceutical process/economic models

1. Correctly Predict the Process Requirements
2. Use the Right Valuation Metric
3. Account for Variability and Risk

Part 1 - Correctly predict the process requirements

a) Determine the requirements at scale
b) Avoid linear scaling
c) Use a general recipe

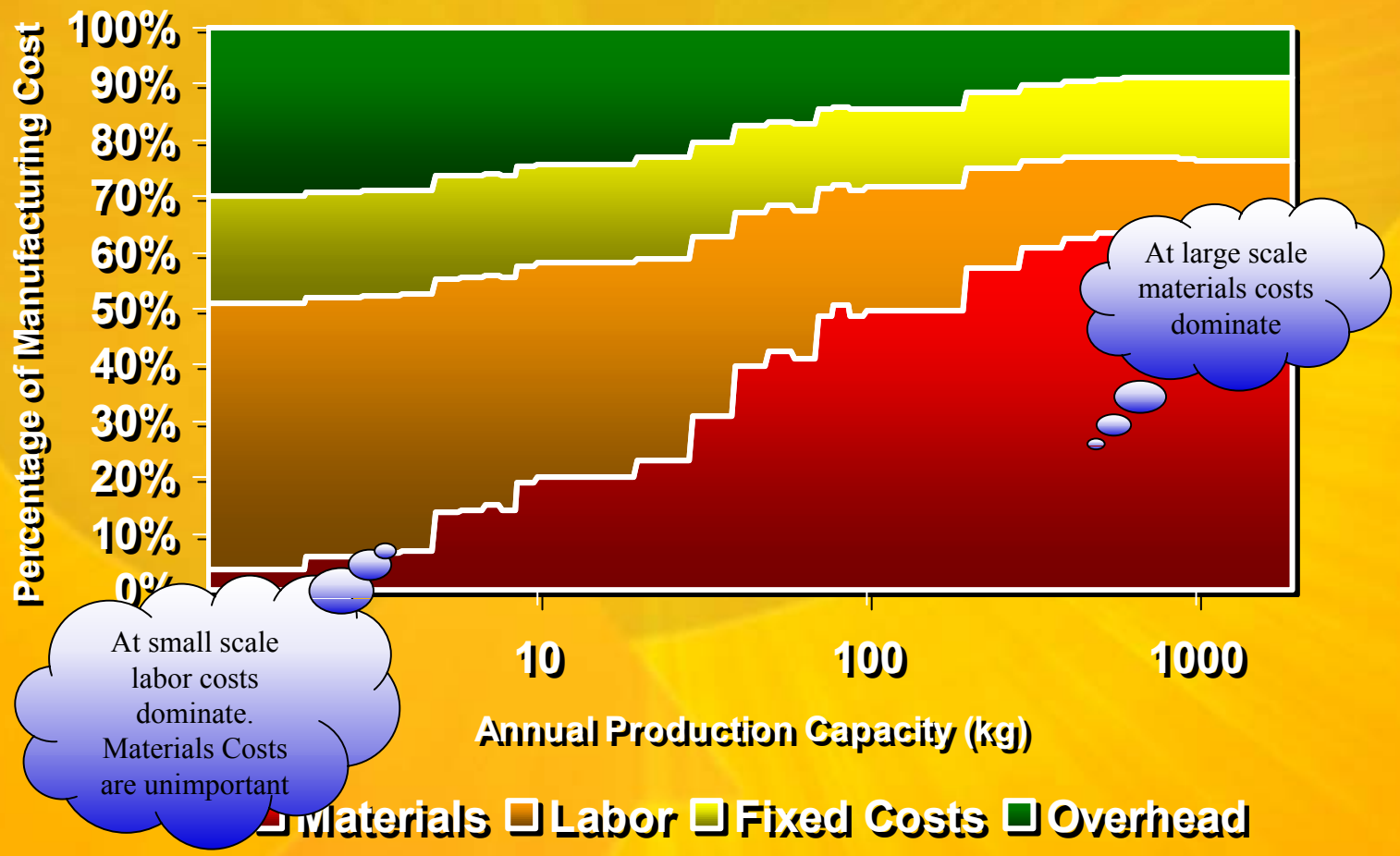
Process Requirements Key Responses

- Direct Material Requirements (qty/lot)
- Consumable Requirements (qty/packing)
- Waste Disposal Requirements (qty/Lot)
- Labor requirements (Skills & FTE hours)
- Equipment Requirements (qty and size)
- Cycle Time (hours/lot)

1.(a) Determine Requirements at Scale

- Equipment available in discrete sizes
- Existing process scale may use different technologies
- Existing process scale may use different materials
- Process extensive variables may change with scale

Scale Dependency Example – Manufacturing Cost Breakdown for Typical Antibody

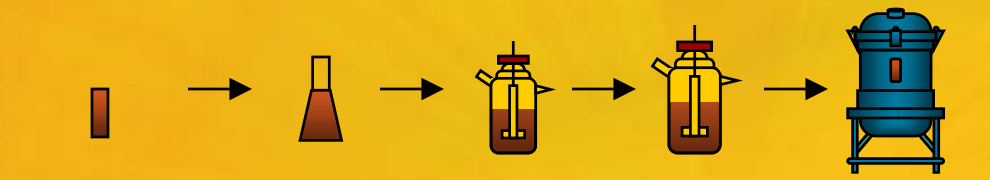


1.(b) Avoid Linear Scale-up

- Linear scale-up is easy
- Requires knowledge only of current scale requirements
- Process volumes increased proportional to scale-up factor
- May be grossly inaccurate

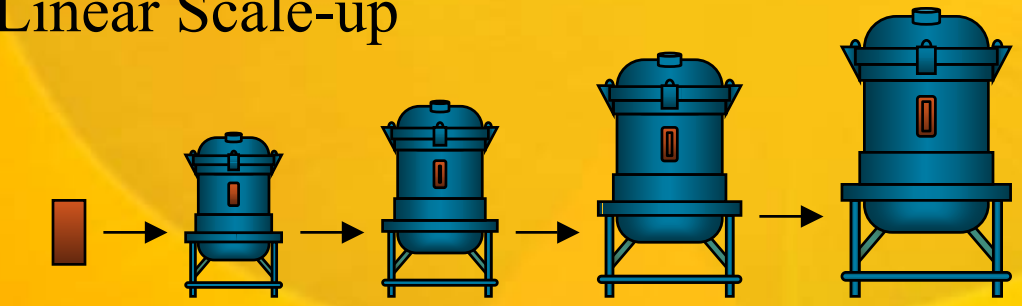
Linear Scale-up Example
100x scale-up of Cell Culture

Original Scale



1 milliliter
80 milliliter
5-10 days
0.4 Liters
3-6 days
2 Liters
3-6 days
10 Liters
12-16 days

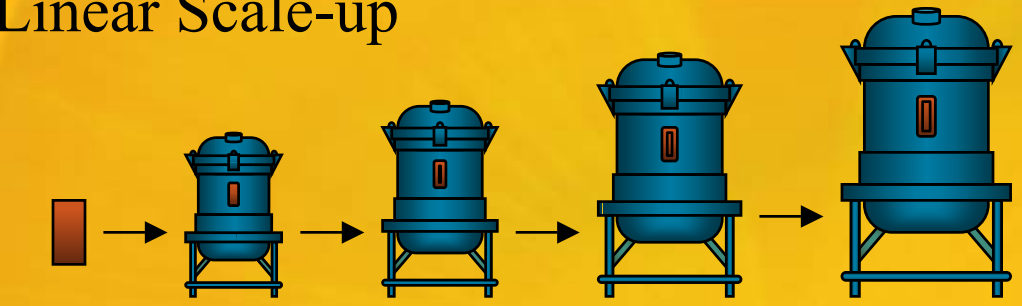
Linear Scale-up



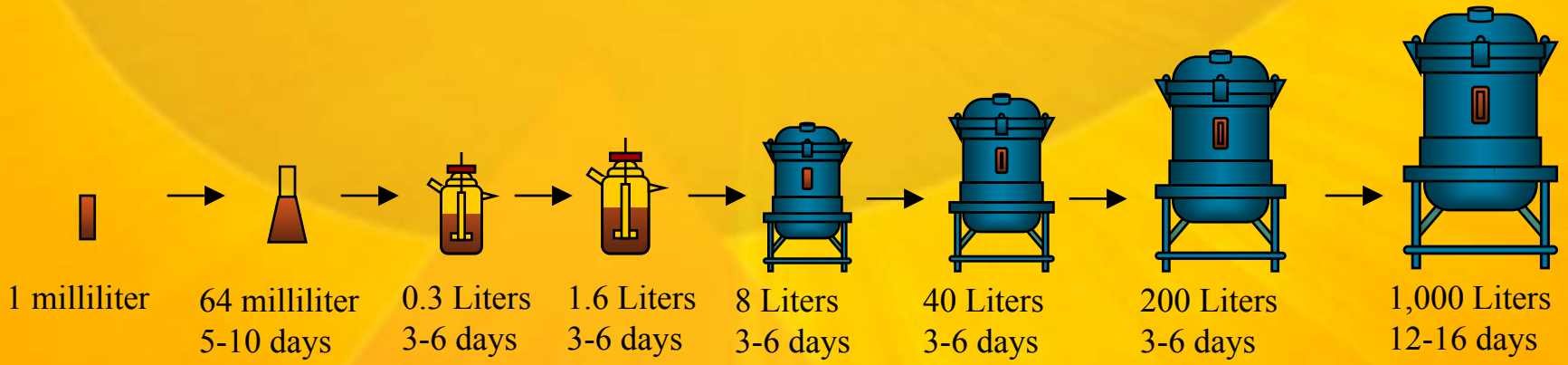
0.1 Liter
8 Liters
5-10 days
40 Liters
3-6 days
200 Liters
3-6 days
1,000 Liters
12-16 days

Linear vs. Rational Scale-up

Linear Scale-up



Rational Scale-up

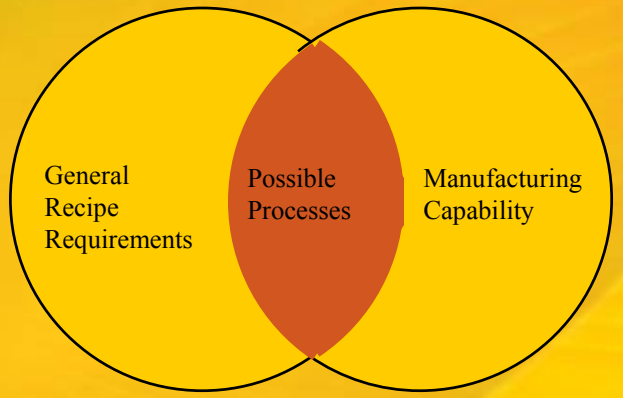


1.(c) Use A General Recipe

- General Recipe is Scale and Equipment Independent
- Defines Process intensive variables
- Rules for equipment and material selection
- Rules for determining scale dependent, extensive responses
- General recipe is used to derive scale dependent recipes

General Recipe Can Be Reused

- General Recipe is a conserved set of process knowledge.
- Scaled Processes are intersection between General Recipe and Manufacturing Capability
- General recipe can be used to forecast requirements for different sets of manufacturing capabilities



Part 2 – Use An Appropriate Valuation Method

a) Choose the right yardstick
b) Use the right accounting principle

Definition of Product Valuation

- An objective and quantitative measure of the economic potential of an investment in a product/production alternative.
- comparison of alternatives requires a consistent method of valuation

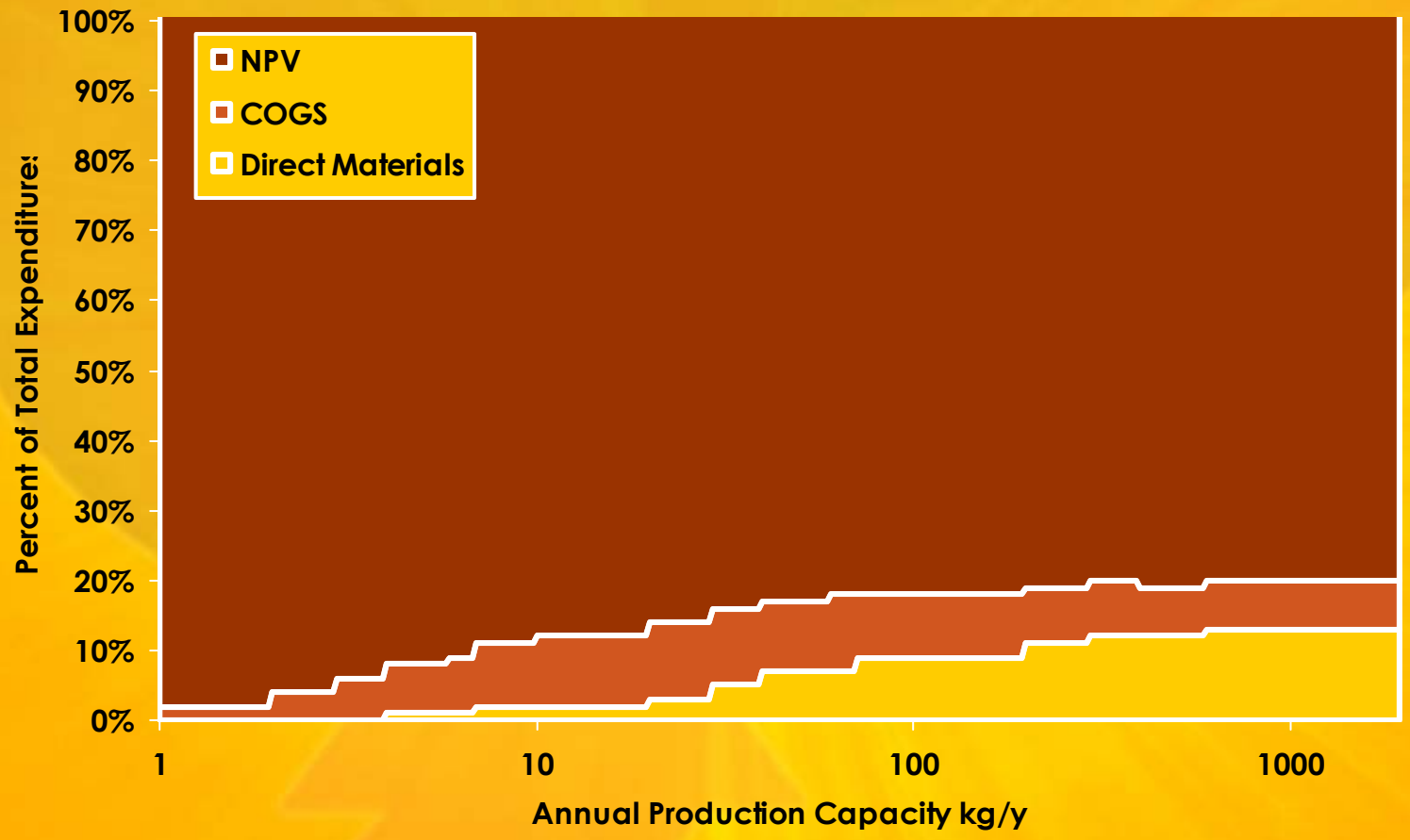
Typical Business Decisions Which Require Product Valuation

- Will this product return its investments?
- Do we buy tanks (US$) or use disposables (US$/lot)?
- Which is more important, minimizing COGs (% revenue) or time to market (years)?
- Do we contract (US$/g) or build capacity (US$)?
- Which is more important, increasing Titer (g/L) or lot success rate (%)?

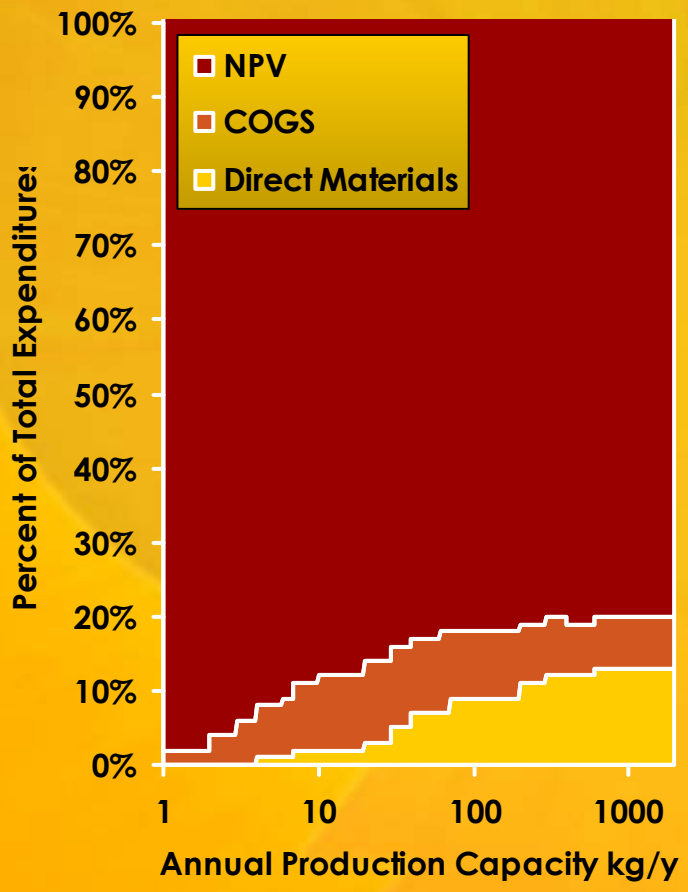
2.(a) Choose the Right Yardstick



Accuracy of Economic metrics for Typical Antibody Process



Accuracy of Economic metrics for Typical Antibody Process



What Are The Big Expenditures?

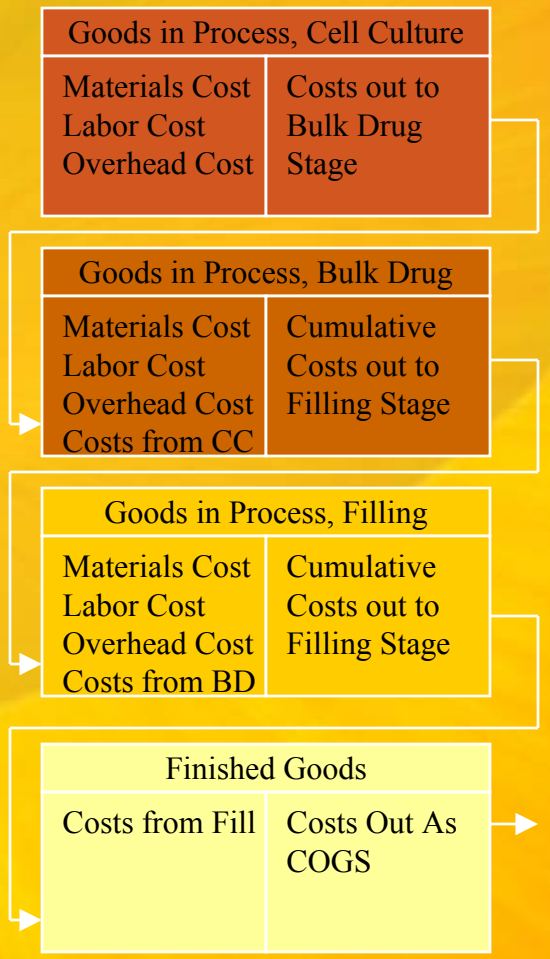
- SG & A - 23% of Revenue[1]
- R & D – 26% of Revenue[1]
- Taxes – 30% of Operating Income[1]
- Pre/Clinical – $366MM[2]

[1] median value of top 5 biotech companies from 2002 annual reports

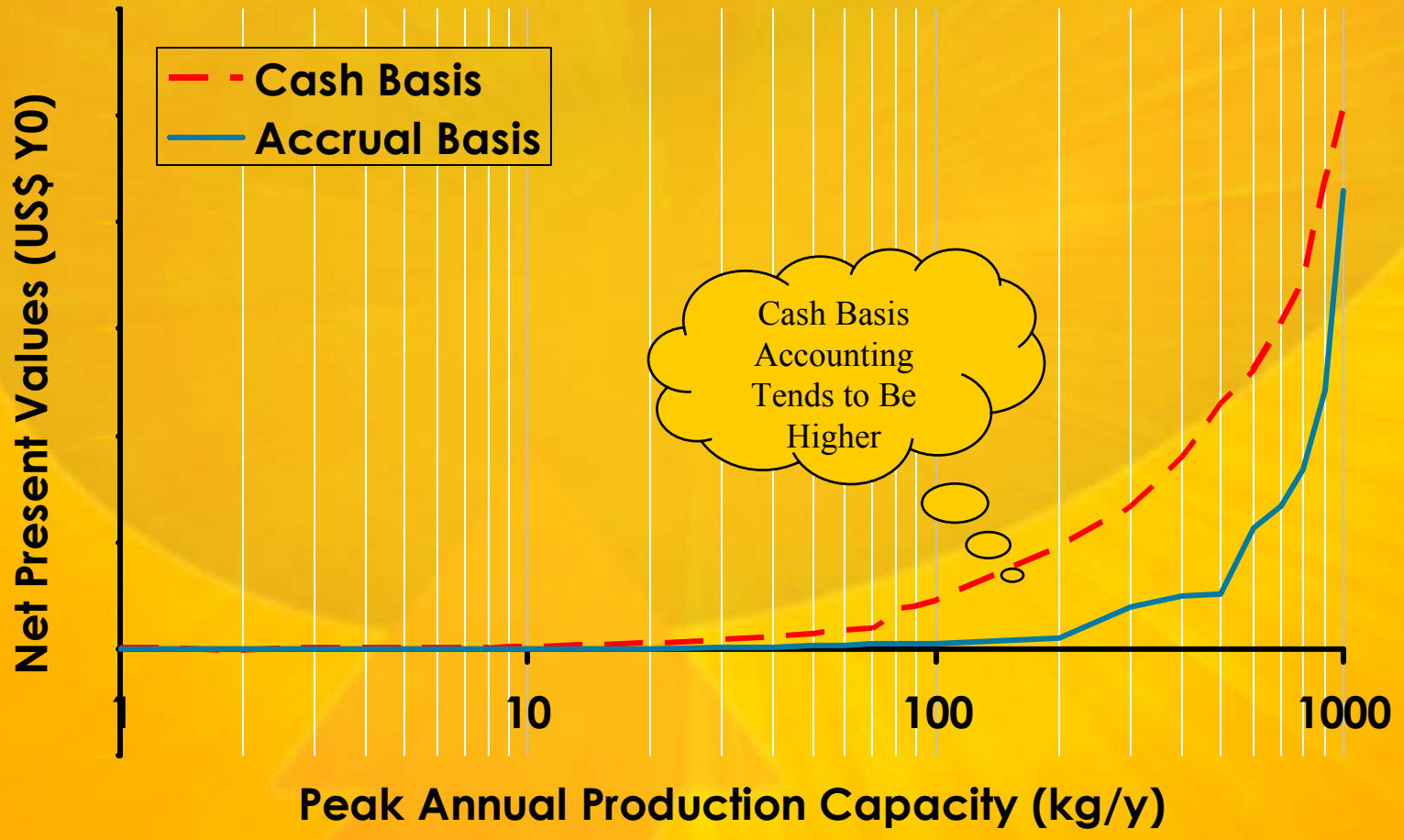
[2] Median value as reported in The BioPharm Guide to Biopharmaceutical Development, 2nd Edition, Avanstar Communications, 2002.

2(b) Use the Right Accounting Method

- **Accrual Basis Process Cost Accounting**
- Expenditures for Materials, Labor and Overhead are paid when incurred.
- Costs are accrued as inventory assets until the product is sold
- Creates delay between expenditures and tax deduction
- Large inventory times creates longer delay.



Comparison of NPV Forecast for Different Accounting methods for A Generic Antibody



Part 3 – Use Stochastic Models

1) Account for variability
2) Account for risk of failure

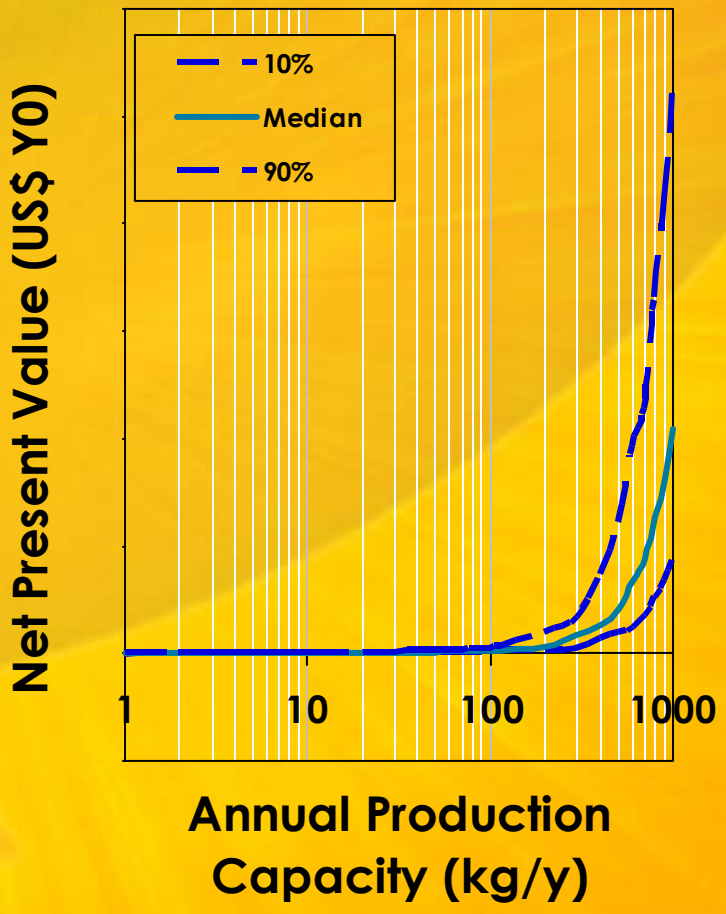
3(a) Account for Variability

- Production Process may not be fully developed/characterized
- Scaled production process may have inherent yield variability
- Dose may not be defined
- Uncertainty in Demand Forecast

All Forecasts are wrong. Quantifying the variance is as important as knowing the expected value.

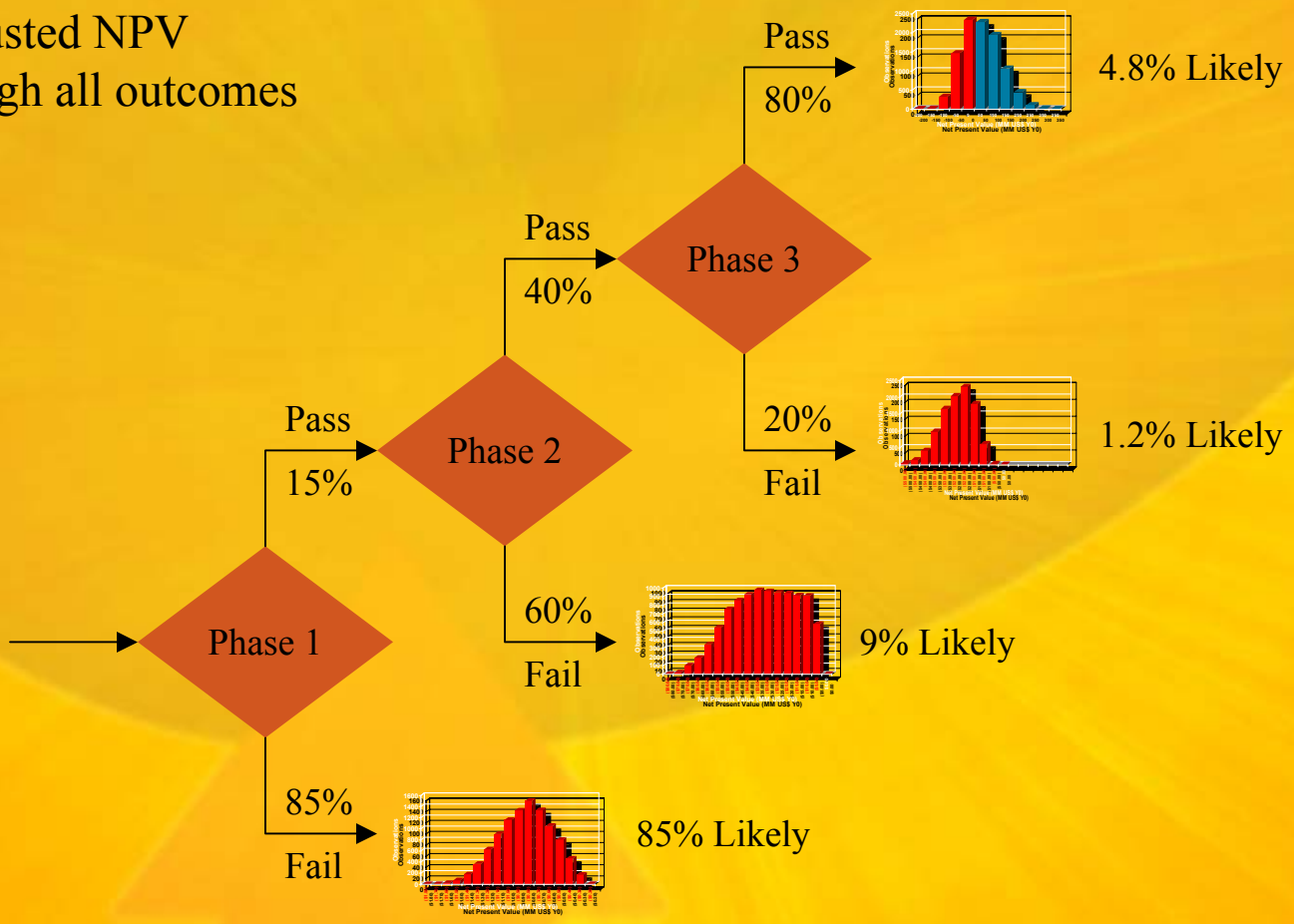
NPV as function of Process scale for generic antibody

- Assumptions (Titer, yield, loading capacity, pool volumes, clinical costs, timelines…) varied over historical ranges.
- No Risk
  - 100% Clinical Success Rate
  - Lot Scheduling around median required lots (50th percentile)



3(b) Account for Risk of Failure

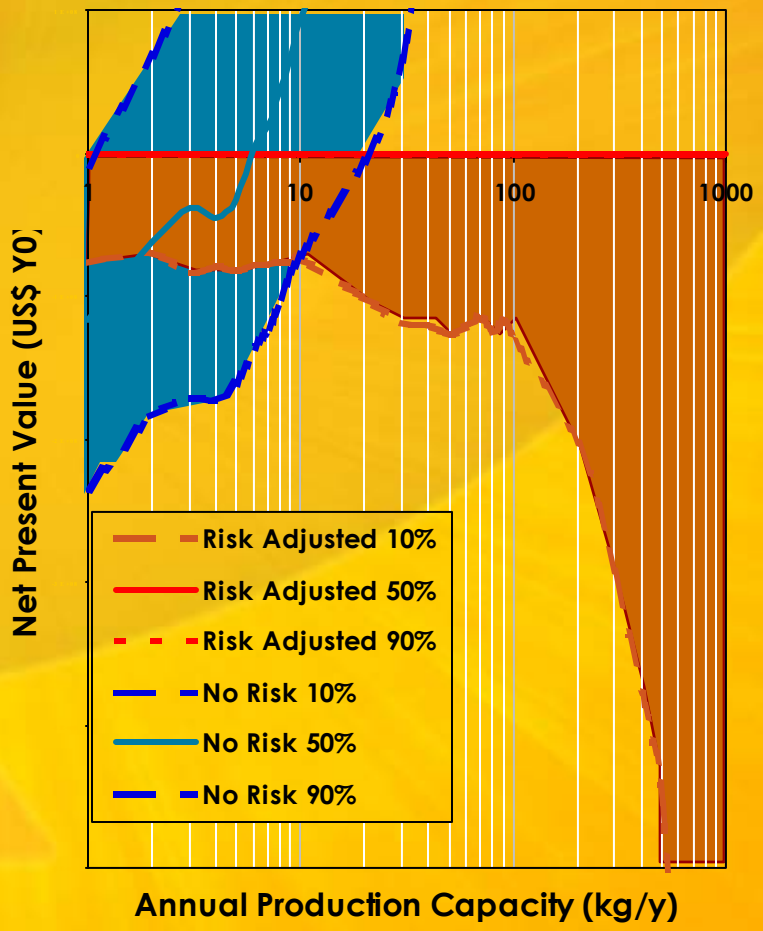
Risk adjusted NPV
must weigh all outcomes



Success Rate Source:"The BioPharm Guide to Biopharmaceutical Development", 2nd Edition

Risk Adjusted NPV as function of Process scale

- Assumes industry average clinical success rate
- Assumes Lot Scheduling around 90th Percentile



Clinical Timeline Source:"The BioPharm Guide to Biopharmaceutical Development", 2nd Edition

My Governing Principles Of Process Modeling

- **Simplicity Principle** – Include only those features necessary generate the desired results.
- **Materiality Principle** – Include only the financial transactions that significantly impact the forecast.
- **Consistency Principle** – Perform all analyses using a single methodology.
- **Accountability Principle** – Assumptions owned by appropriate expert(s).
- **Traceability Principle** – Clearly document all assumptions; analysis and assumptions are inseparable.

Impact of Failing to Use Fundamental Requirements

	Opposite of Requirement	Simplicity	Materiality	Consistency	Accountability	Traceability
1.a	Model at Arbitrary Scale		☹	☹		
1.b	Scale Linearly	☹	☹	☹	☹	
1.c	Don't Use General Recipe			☹		☹
2.a	Use the Wrong Econ. Metric	☹	☹	☹		
2.b	Use the Wrong Accounting Basis	☹	☹	☹		
3.a	Neglect Variability	☹	☹			
3.b	Neglect Risk of Failure	☹	☹			

Concluding Remarks

- Failure to identify the key requirements for your process & economic modeling objectives can impact
  - The accuracy of the analysis
  - The direction of business decisions
  - Your credibility as an analyst
- Defining your guiding principles can be a useful exercise in defining your requirements

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