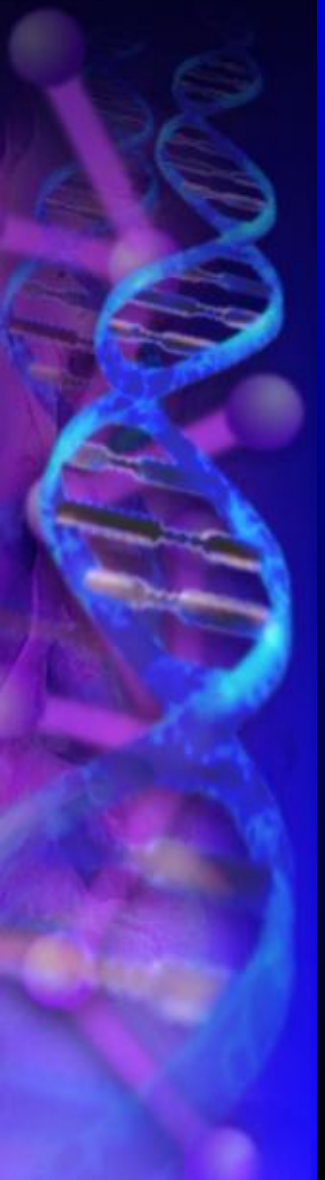
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Optimizing Consumables Reuse for Commercial Therapeutic Protein Production

Darrell Lewis-Sandy

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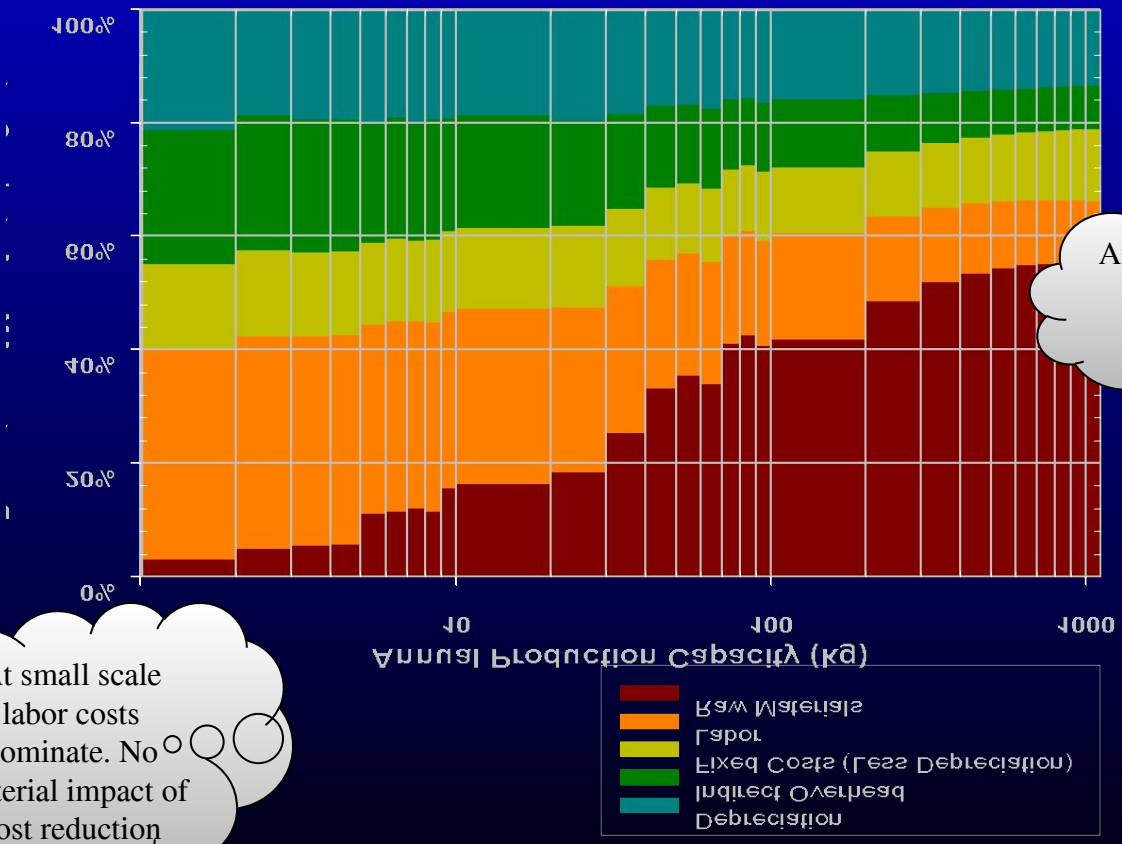
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Overview

Given the high cost chromatography and TFF media, how do we determine the optimal number of reuses to validate for a commercial process? Specifically:

- How may the optimum be calculated?
- When can consumables reuse be neglected?
- What factors influence the location of the optimum?

Example: Dominant Manufacturing Costs for MAb Production as Function of Scale

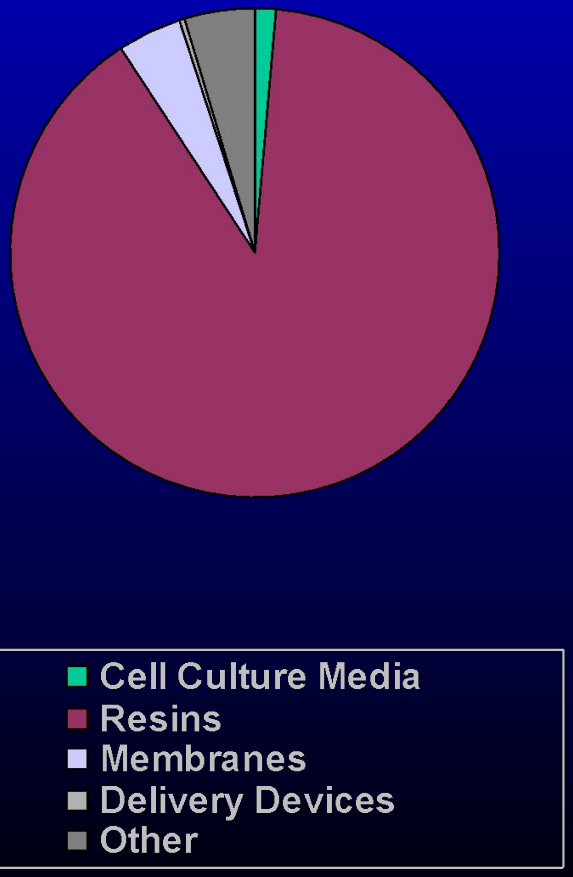


At large scale materials costs dominate

At small scale labor costs dominate. No material impact of cost reduction

Raw Materials Cost Distribution

Generic Mab with single use resins & membranes



RESINS AND MEMBRANES ACCOUNT FOR 95% OF MATERIALS COST

- **Chromatography Media ~90%**
- **TFF Membranes ~5%**
- **Average Mab Scale = 52kg/y***

* P. K. Watler, Vaxgen 5/2002

36% of average MAb manufacturing costs!

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Common Misconception of Consumables Reuse

- **TRUE** - Average Cost per cycle is inversely proportional to the number of cycles of use.
- **TRUE** – Costs which occur earlier have more impact on the NPV
- **FALSE** – More validated reuse always defers consumables costs and results in higher NPV.

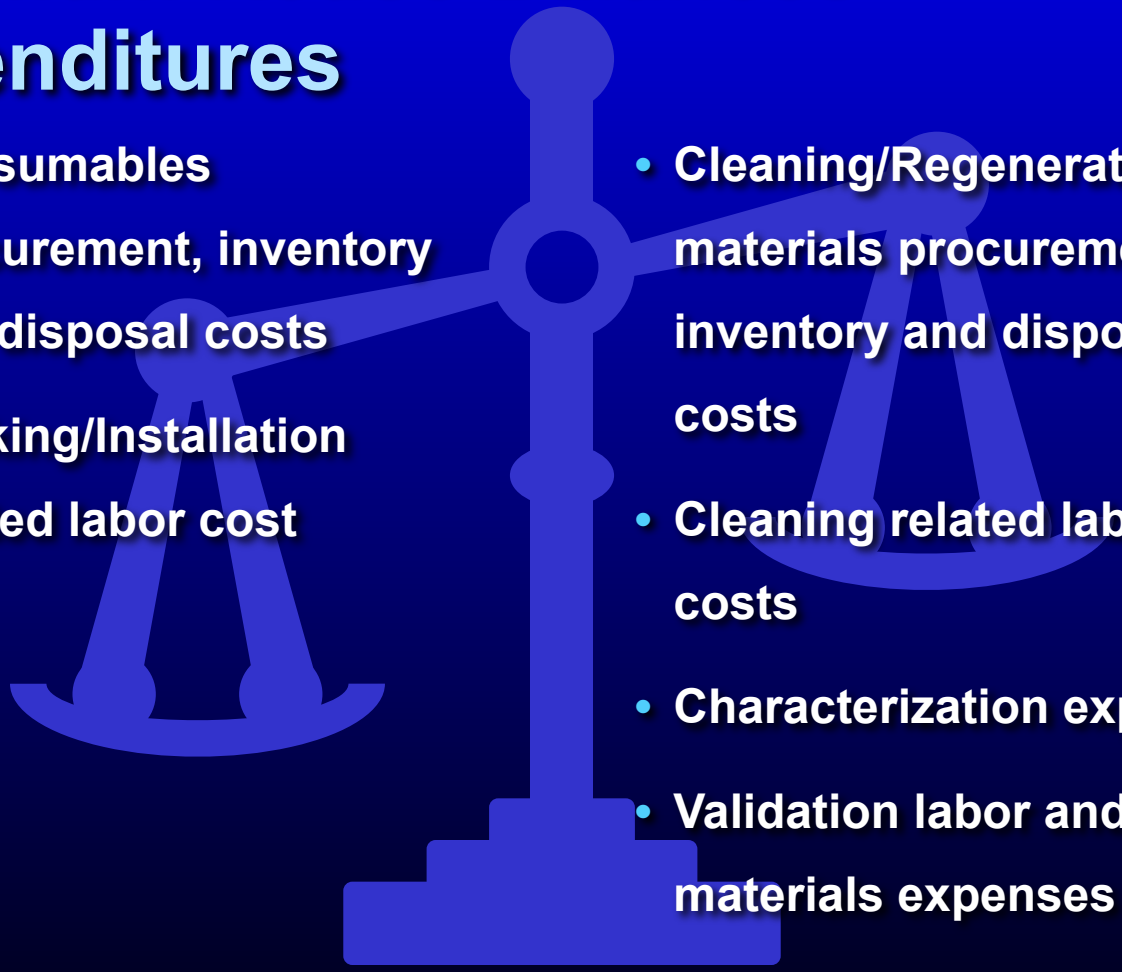
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Why?

- Materials costs are incurred when they are purchased, not when they are used.
- Before first year of production at least two packings for each column and Membrane system are purchased
- Consumables have BOTH use based and time based expiration
- Fewer lots during the early years of sales result in low utilization. THESE COSTS MAY DOMINATE THE NPV.

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Optimum Reuse Balances Expenditures



- Consumables procurement, inventory and disposal costs
- Packing/Installation related labor cost
- Cleaning/Regeneration materials procurement, inventory and disposal costs
- Cleaning related labor costs
- Characterization expense
- Validation labor and materials expenses
- GMP document control overhead

Differences in Lifecycle Cash Flows Captured by this model

Development Expenditures

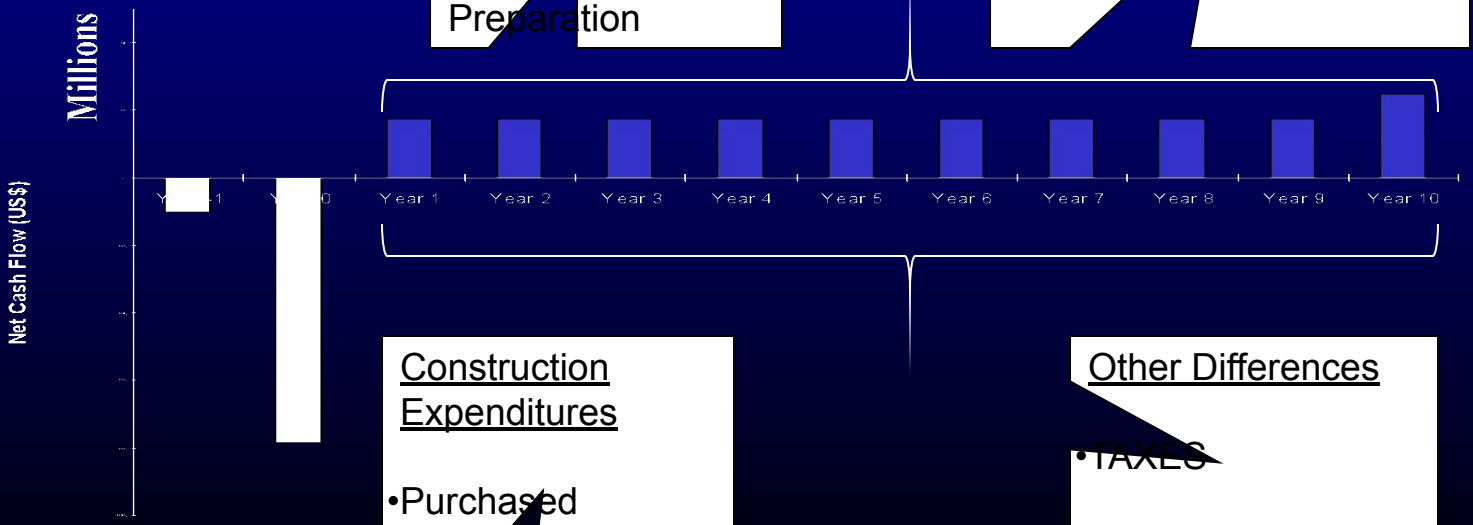
- Characterization Labor & Materials

Startup Expenditure Differences

- Validation Labor & Materials
- Raw Materials Inventory
- GMP Document Preparation

COGM Differences

- Raw Materials
- Disposal
- Manufacturing, Quality, Support, Maintenance & Supervisory Labor
- GMP Document Overhead
- Fixed Charges



Construction Expenditures

- Purchased Equipment

Other Differences

- TAXES

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Objective Function

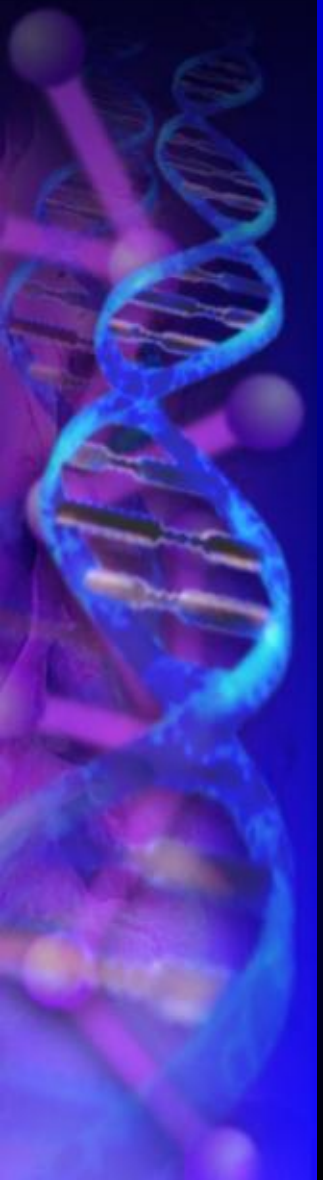
- Maximize Incremental Net Present value
  - $$PV = \sum_{i=0}^{n} \frac{FV_i}{(1+r)^i}$$
  - Monte Carlo Analysis to model uncertainty



  - Nonlinear metahueristic used for

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Generic Process

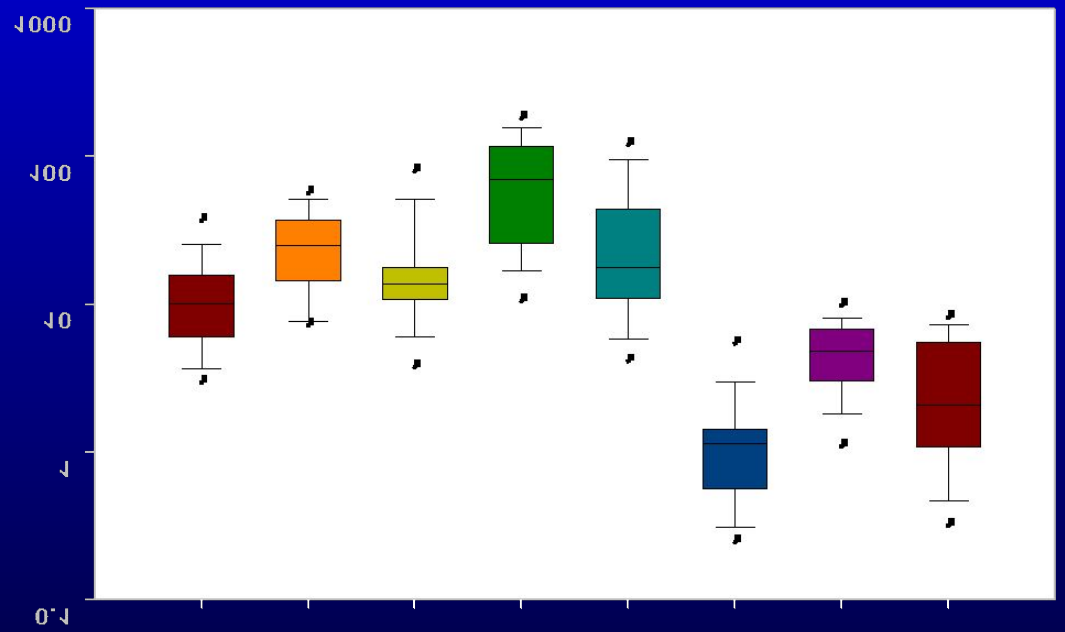


- Seed Train
- Production Cell Culture
- Harvest Centrifugation
- Media Removal TFF @ 95% Recovery
- Chromatography Train 3 steps at 80% Recovery per step
- Viral Filtration
- Bulk Formulation TFF @ 95% Recovery

Base Case Assumptions

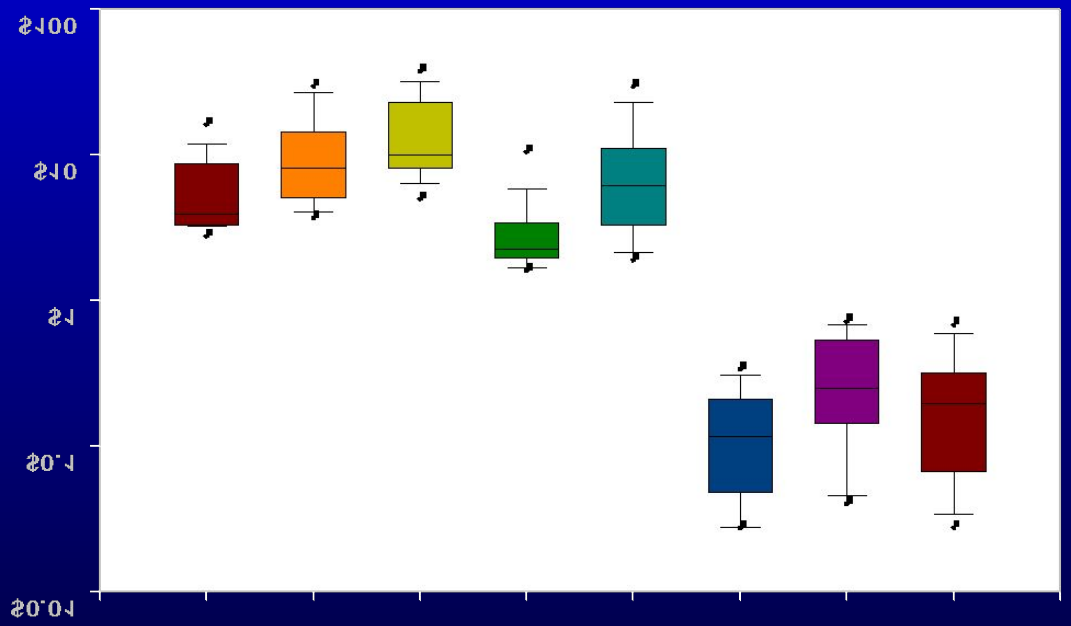
- Titer: 1 g/L
- Bioreactor size: ≤12,000L
- Max 18 lots/bioreactor/year
- Column diameters: ≤2m
- Column cycled if necessary
- Resin/membrane re-uses: 0

Consumables Cost Estimation



Pricing based on listed unit cost and loading capacity of 220 surveyed
resins and membranes

Cleaning Cost Estimation





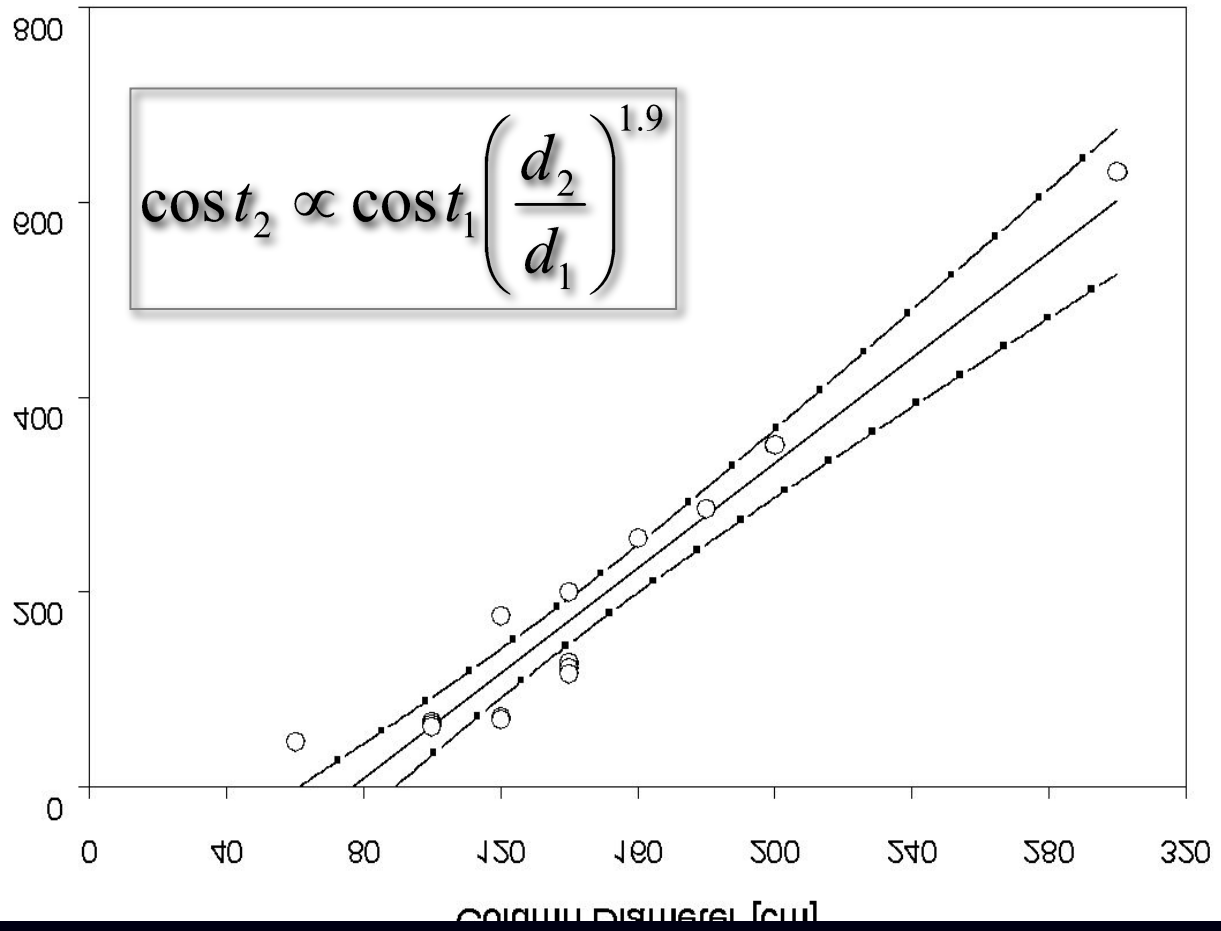
* Cleaning protocols based on Pharmacia Publications 18-1020-90, 18-1022-29 and 18-114-21

** Regent pricing based on Simga Aldrich list pricing

Capital Cost Estimation

Parametric Cost Models

$$\text{cost}_2 \propto \text{cost}_1 \left(\frac{d_2}{d_1} \right)^{1.9}$$



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Estimated Characterization Expenditures

- Characterization at laboratory scale w/ “representative” feedstock
  - ~2 FTE weeks for experimental design & preparation
  - ~2 FTE day per cycle operation and analysis
  - ~2 FTE weeks for reporting
- UP TO 2 YEARS EXPIRATION CHARACTERIZED

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Estimated Validation and GMP Documentation Expenditures

- Validation performed at scale in commercial facility concurrent with production
  - ~2 FTE weeks for protocol development
  - ~4 FTE day per cycle for analysis
  - ~2 FTE weeks for reporting
- GMP document generation
  - ~2 FTE weeks for SOP development
  - ~1 FTE day per year for document management

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Manufacturing Assumptions

- Plant Staffing Level is unaffected by number of re-uses
- Packing and cleaning are off critical manufacturing schedule
- The manufacturing plant is multi-product
- Disposal costs are small compared to other costs

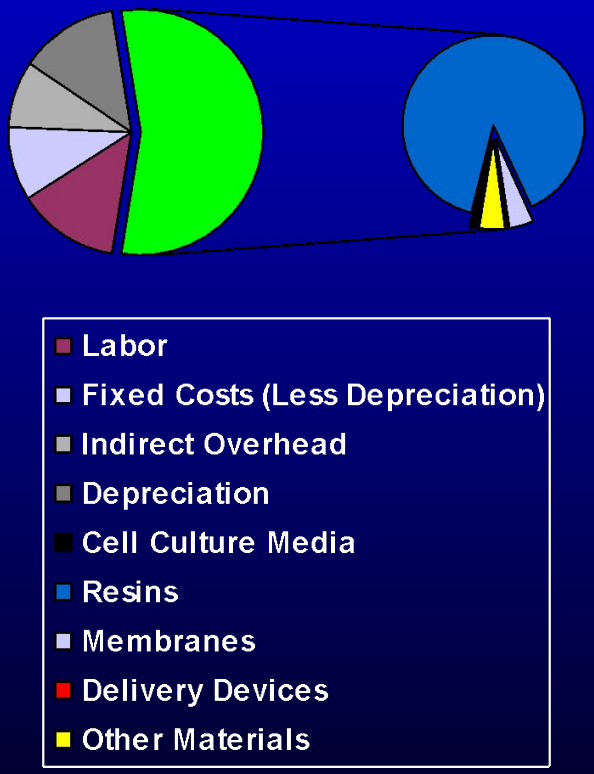
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Sales & Finance Assumptions

- Sales Life: 10 years
- Peak Demand: 95 kg/y
- Average Demand: 50 kg/y
- Demand Escalation: 20% of average/year
- Accounting Method: Accrual Based Process Costing
- Discount Rate: 12%

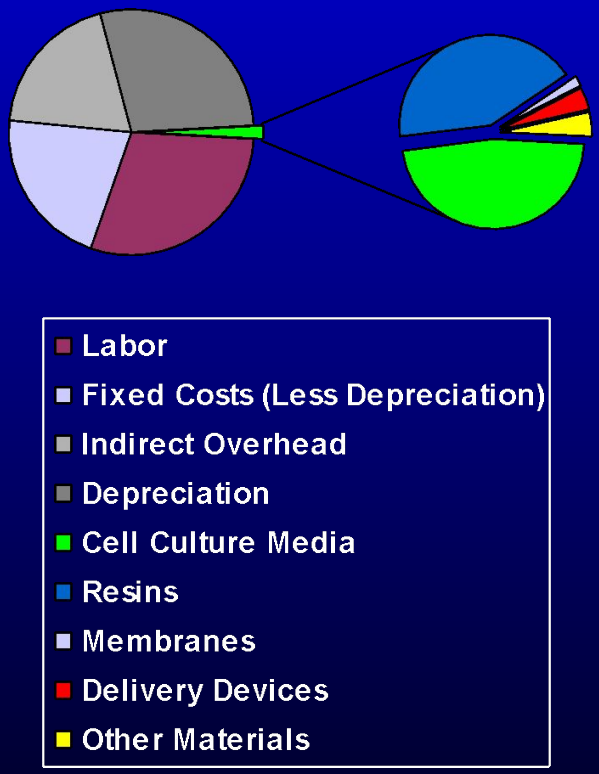
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Base Case Total Manufacturing Expenditures by Cost Center



- Raw Materials are 56% of Total Manufacturing Expenditures
- Resins are largest raw material cost (~50% of total)
- TFF Membranes are much smaller expenditure (~2.5% of total)

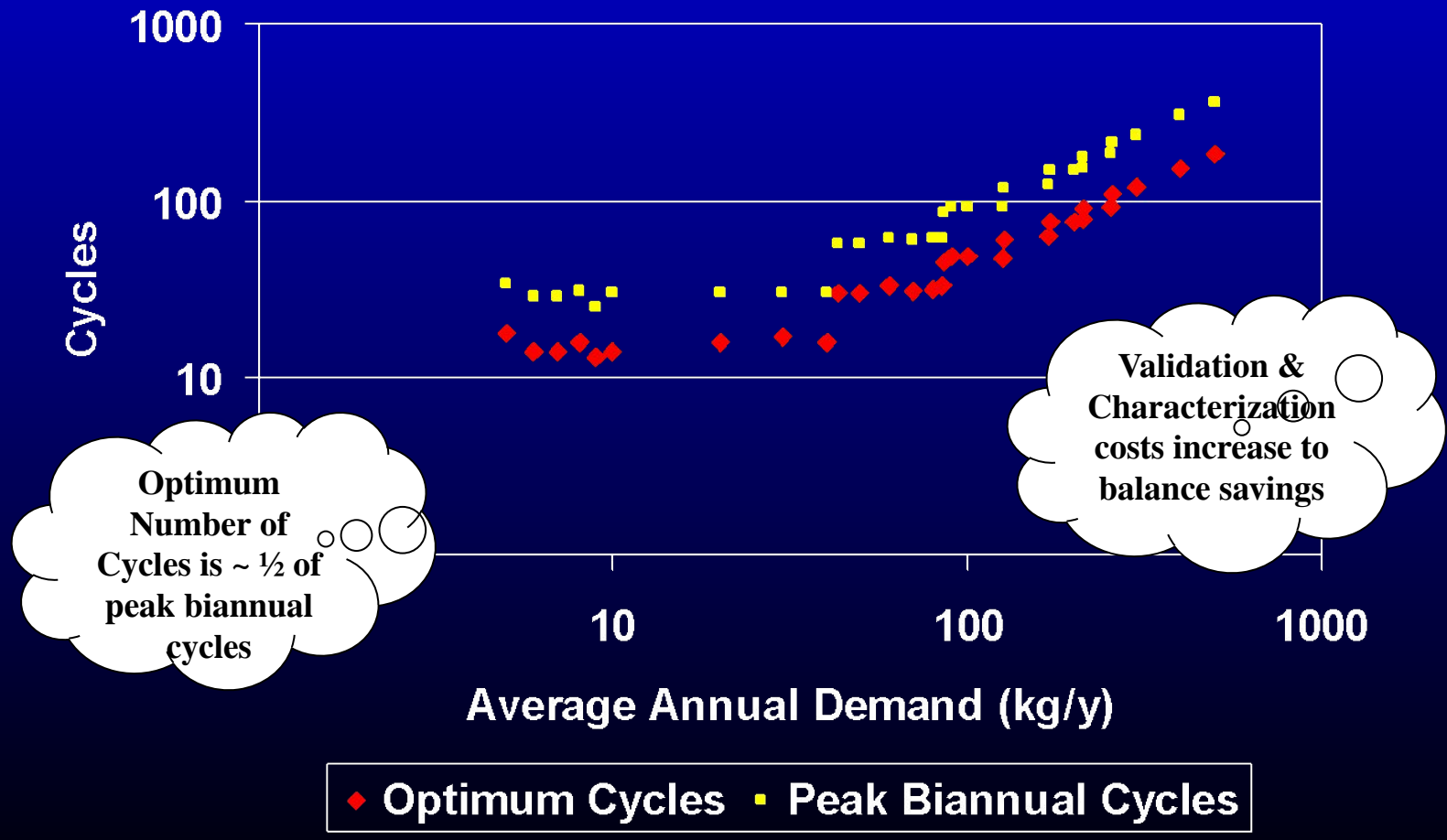
Optimized Total Manufacturing Expenditures by Cost Center



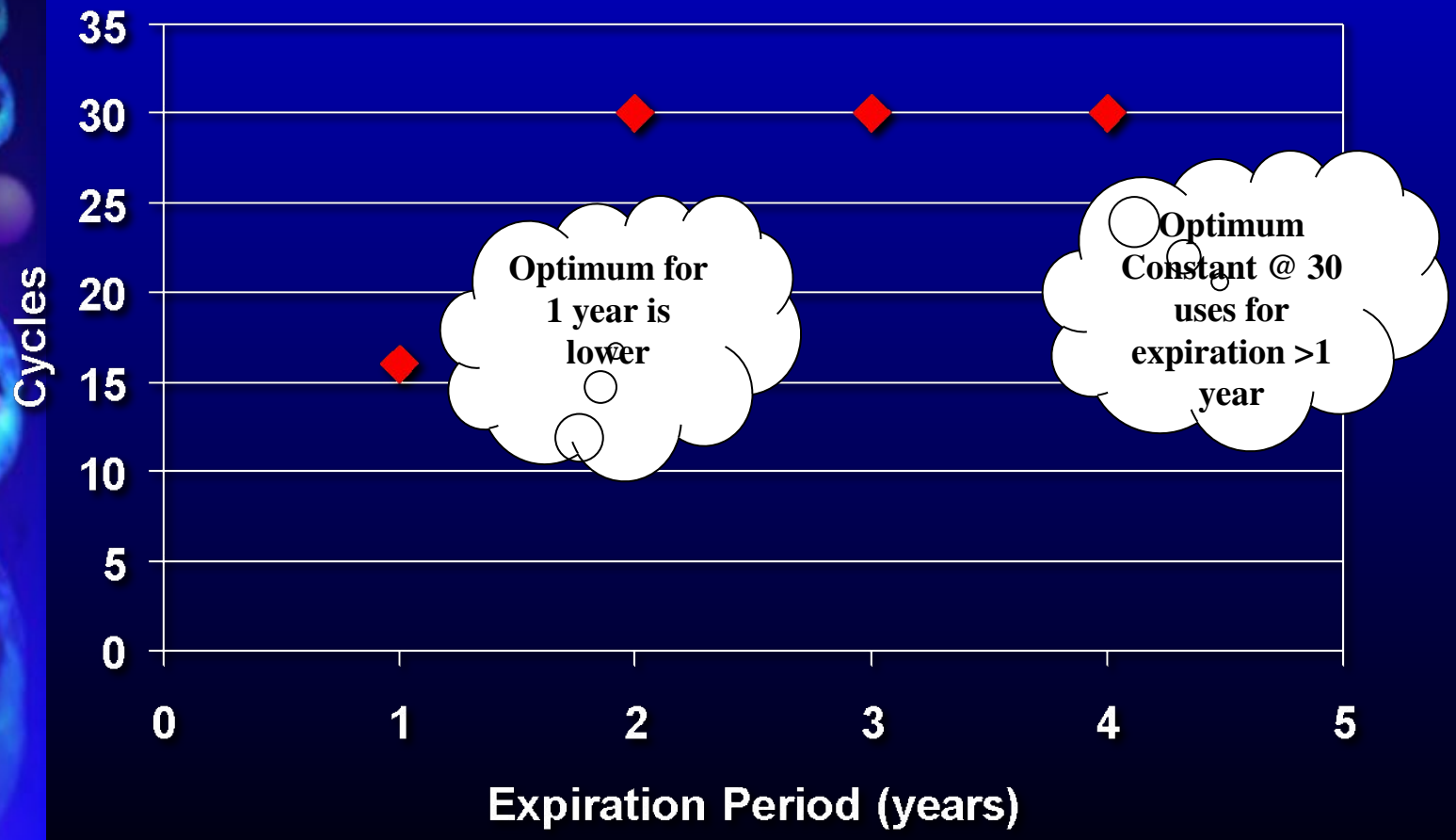
- Optimized Reuse is 30 cycles.
- Results in median NPV improvement of 91%
- Raw Material Cost Reduced to 2% of total Manufacturing Expenditures

Sensitivity of Optimum Number to Annual Production Capacity

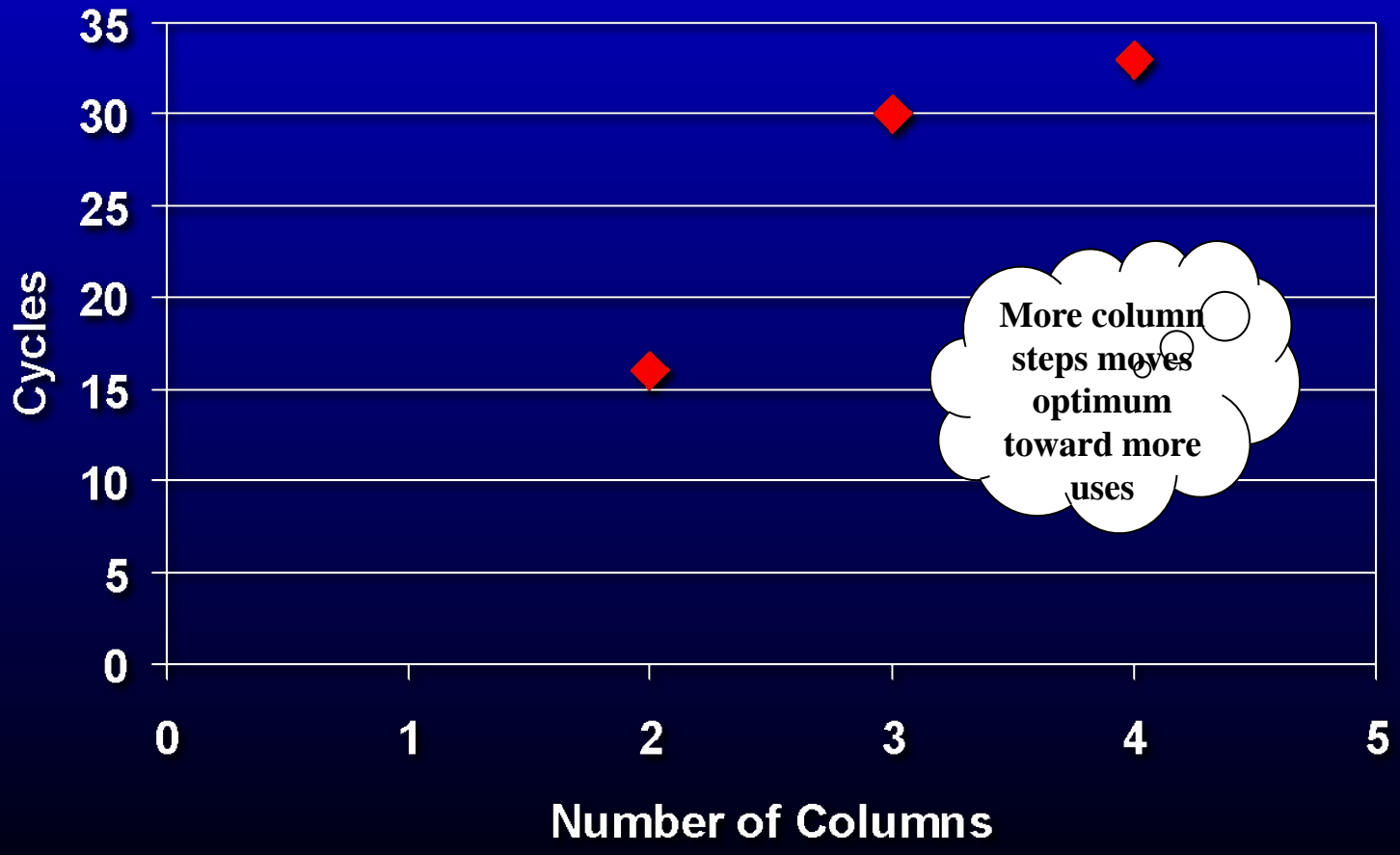
Based on Median Incremental NPV



Sensitivity of Optimum Uses to Number Consumables Expiration Period at 50kg/y average demand

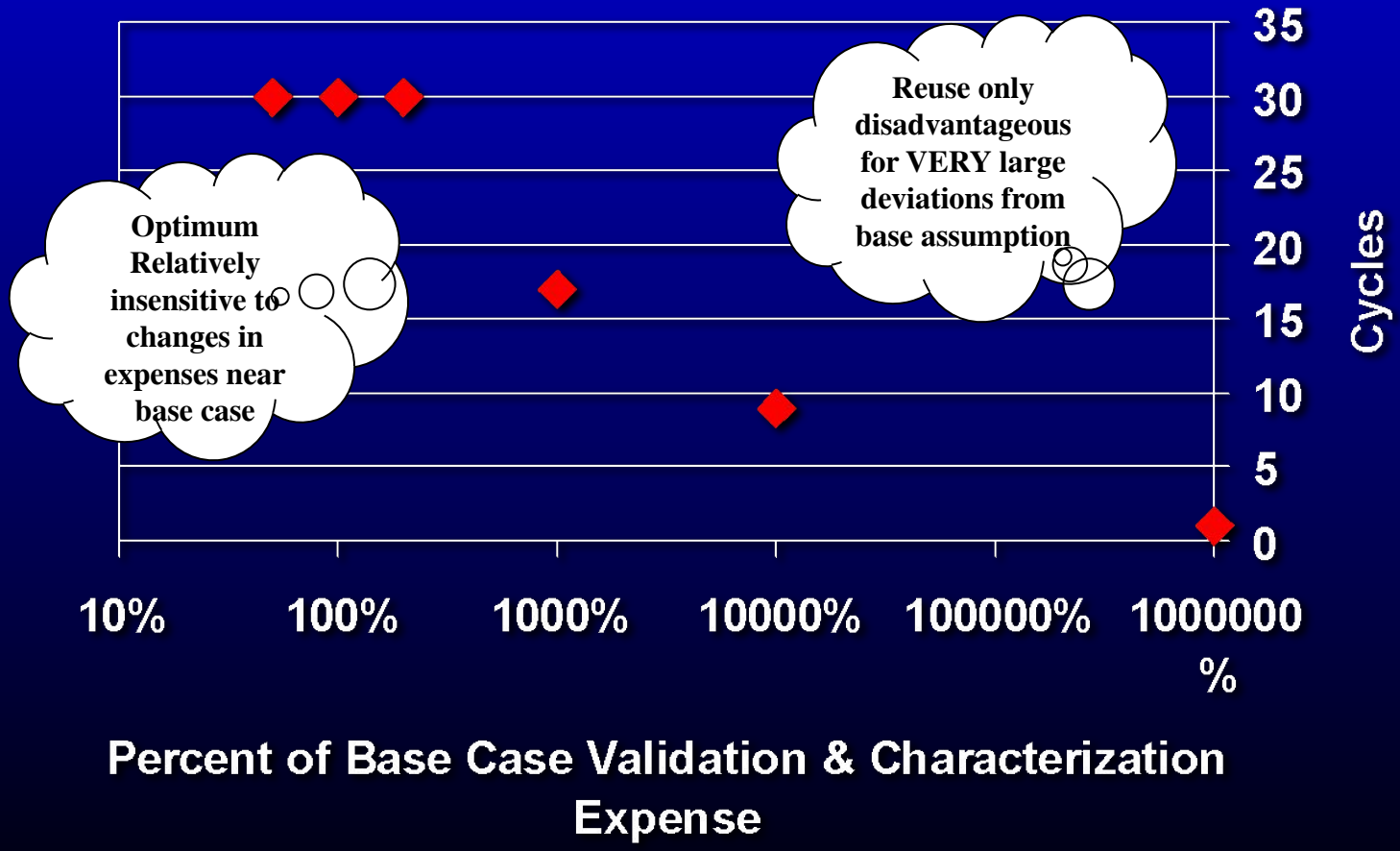


Sensitivity of Optimum Uses to Number of Column Steps in Process at 50kg/y average demand



Sensitivity of Optimum Cycles to Characterization and Validation Expense

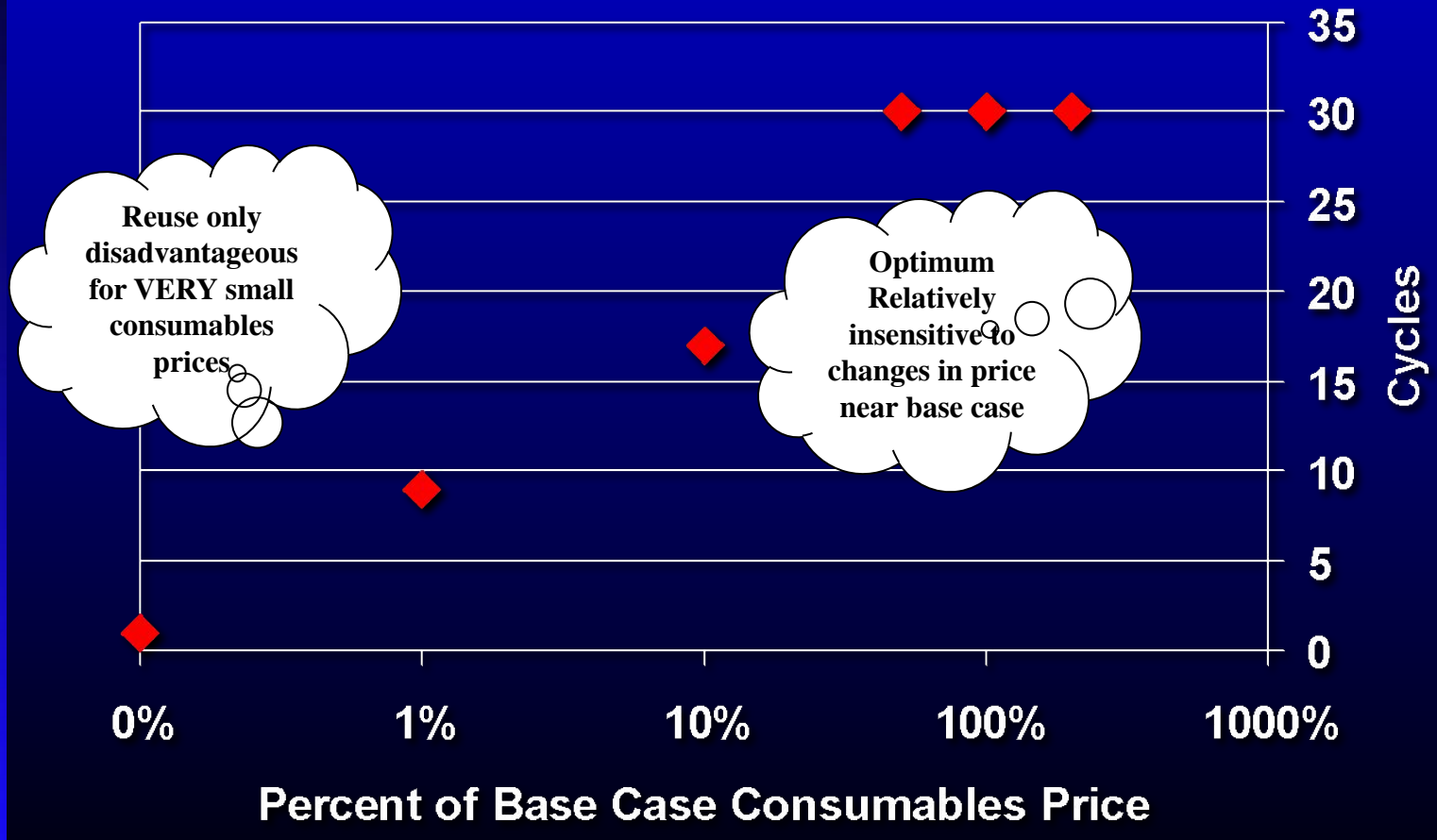
at 50kg/y average demand



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Sensitivity of Optimum Cycles to Consumables Price

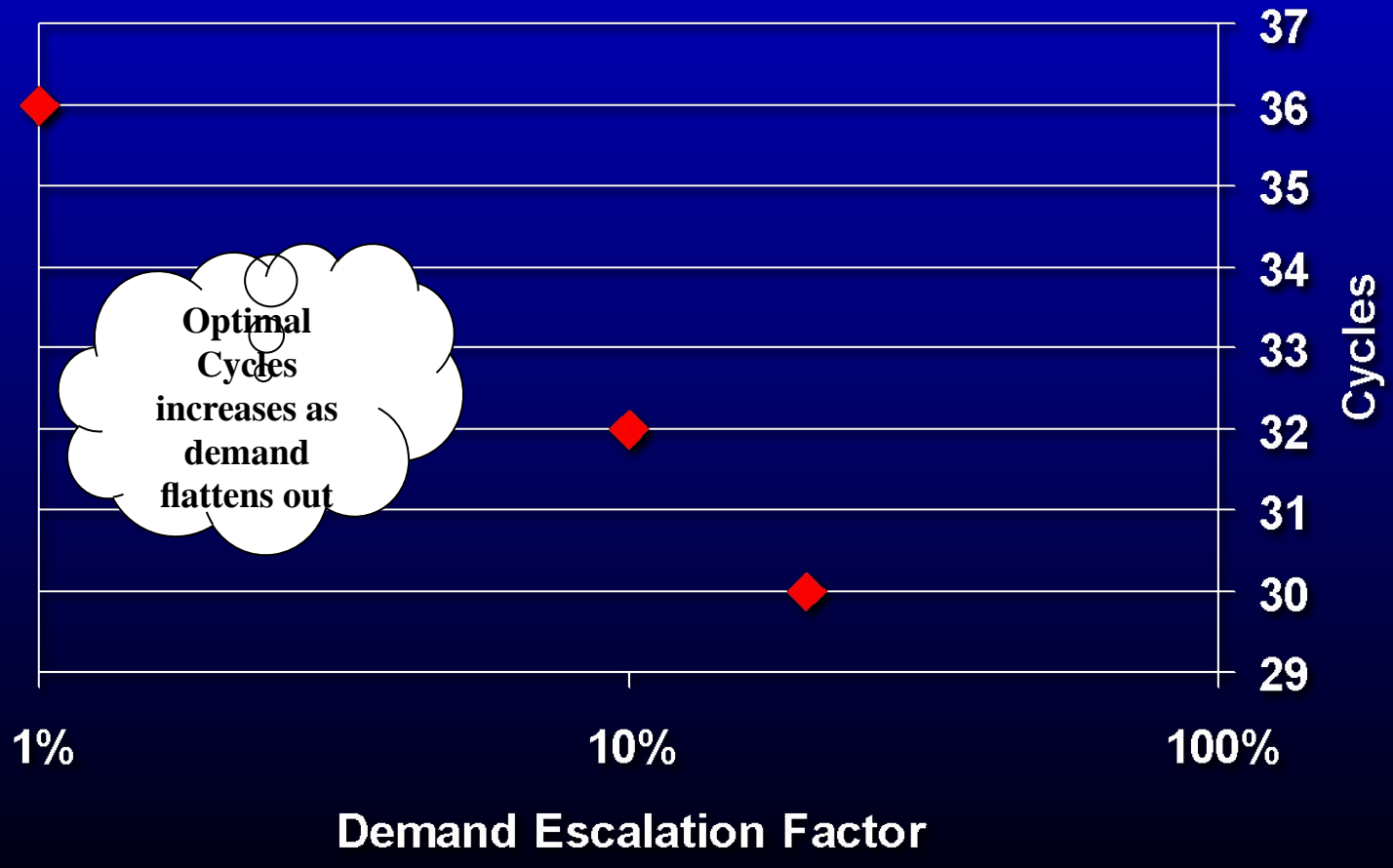
at 50kg/y average demand



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Sensitivity of Optimum Cycles to Demand Escalation Factor

at 95kg/y peak demand (Constant Plant Size)



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Conclusions

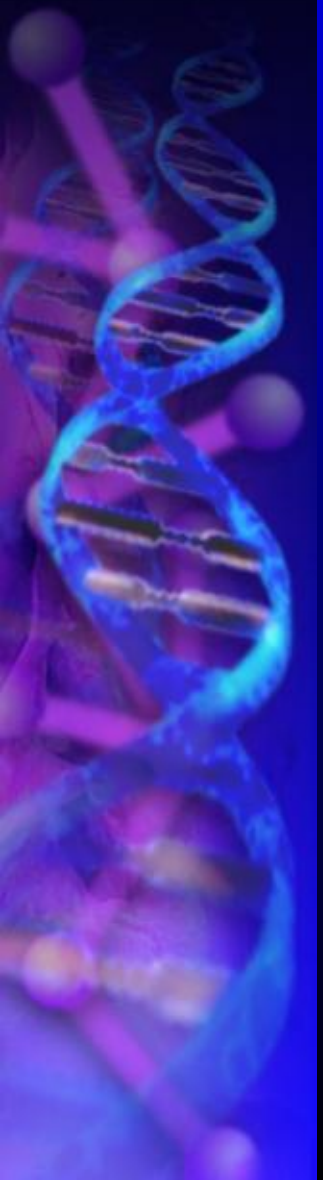
- Reuse of resins and membranes can dramatically improve NPV
- The Optimum reuses balances cash flows occurring over the life cycle.
- Optimum NPV does not always occur with the maximum number of reuses
- Optimum should be evaluated with process specifics.

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Conclusions (continued)

- Factors which increase the optimum number of cycles include:
  - Higher demand
  - Longer expiration period
  - Higher number of chromatography steps
  - Higher resin/membrane costs
  - Lower reuse related validation expenses
  - Lower sales escalation rate

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