Pharmaceutical supply chains: key issues and strategies for optimisation

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Outline

- Some conclusions
- Background
- The pharmaceutical industry supply and value chains
- Supply chain issues
- Primary manufacturing:
  - Risk management
  - Process development
- Challenges for the future

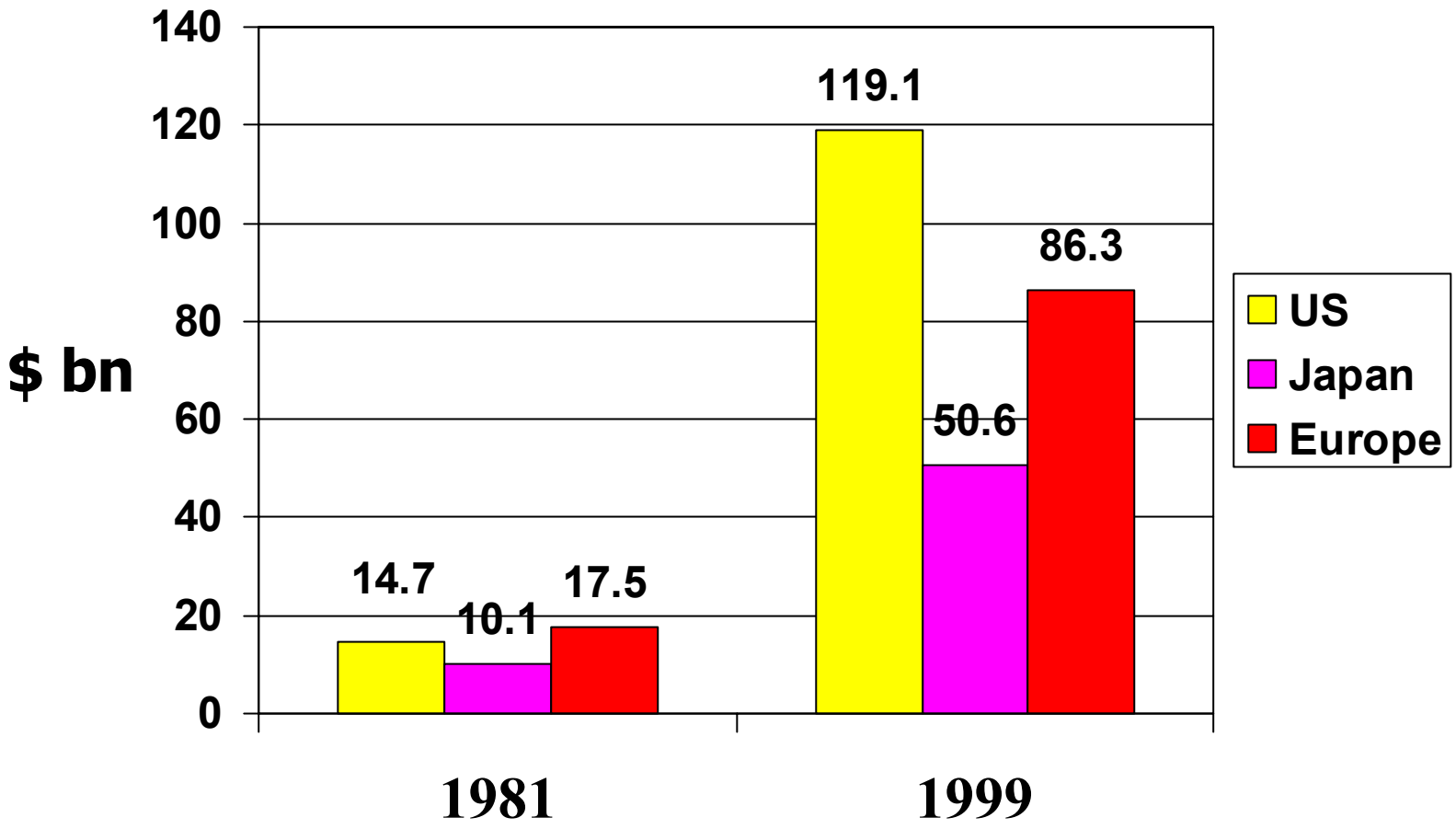
Some conclusions

- The pharmaceutical supply chain is very complex, with many interacting facets
  - Difficult to generate radical improvements quickly
  - Piecemeal approaches (e.g. improved logistics) will generate incremental benefits
- Current process technology is one of the main supply chain bottlenecks
  - Many "built-in" inefficiencies that constrain performance
  - Not a very responsive system
- Current models in the research community are too "company-centric"
  - Future models need to consider a holistic view of an extended supply chain of specialist agents
    - IP generators
    - Testing specialists
    - Contract manufacturers
    - Logistics providers
    - Healthcare providers/consumers

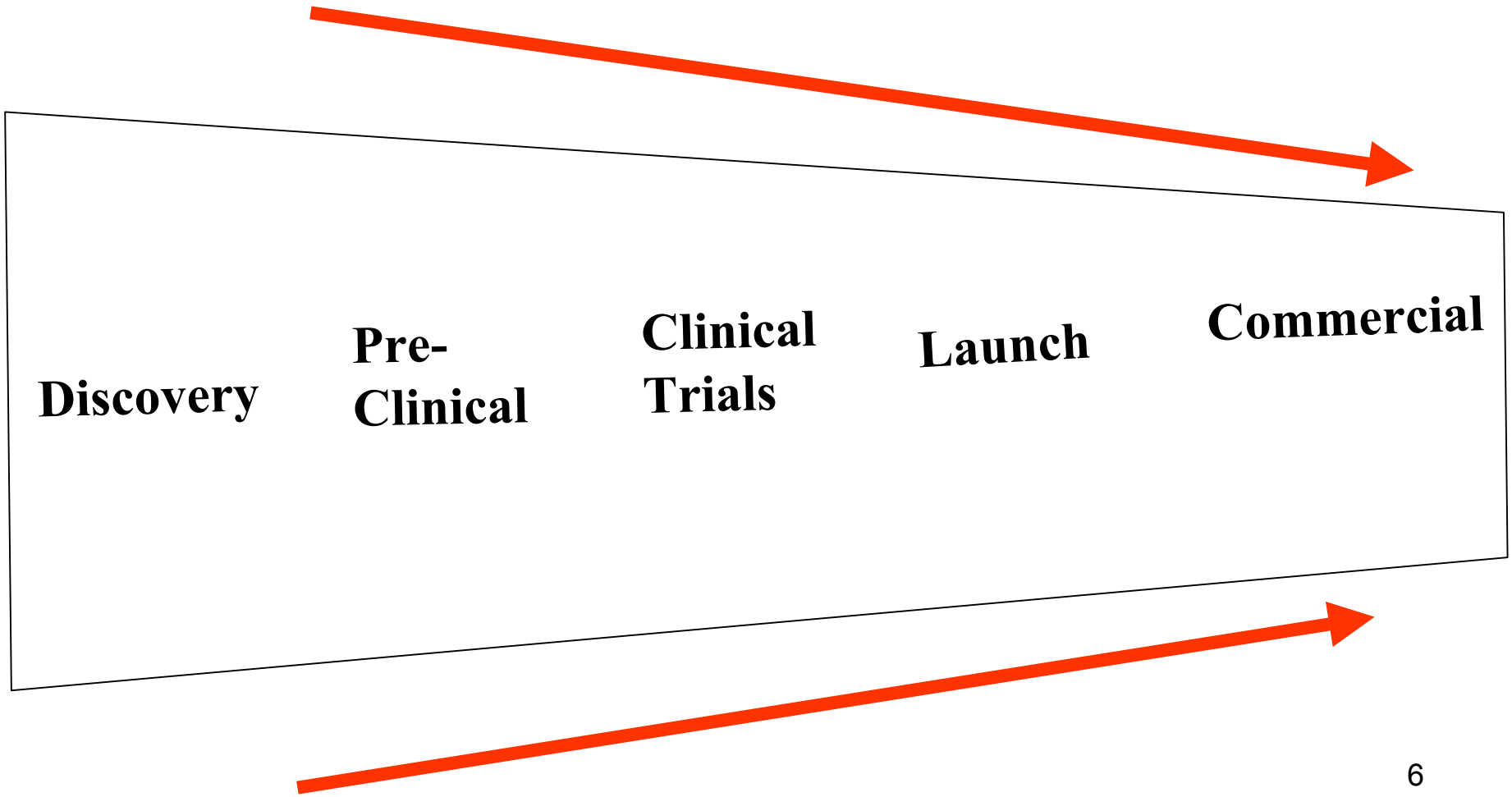
Trends in the pharmaceutical and related industries

- Time to market is the key metric
- R&D productivity (numbers of new chemical entities registered per unit amount of investment) is declining
- effective patent lives are shortening
- even while active, patents provide lower barriers to entry
- many cheaper product substitutes in many therapeutic areas
  - alternative compounds ("me-too drugs")
  - off-patent generics
- payers of healthcare exerting strong price pressure and influencing prescribing practices
- for approval, new drugs must:
  - address new therapeutic areas; or
  - have very significant cost or health benefits over existing treatments.

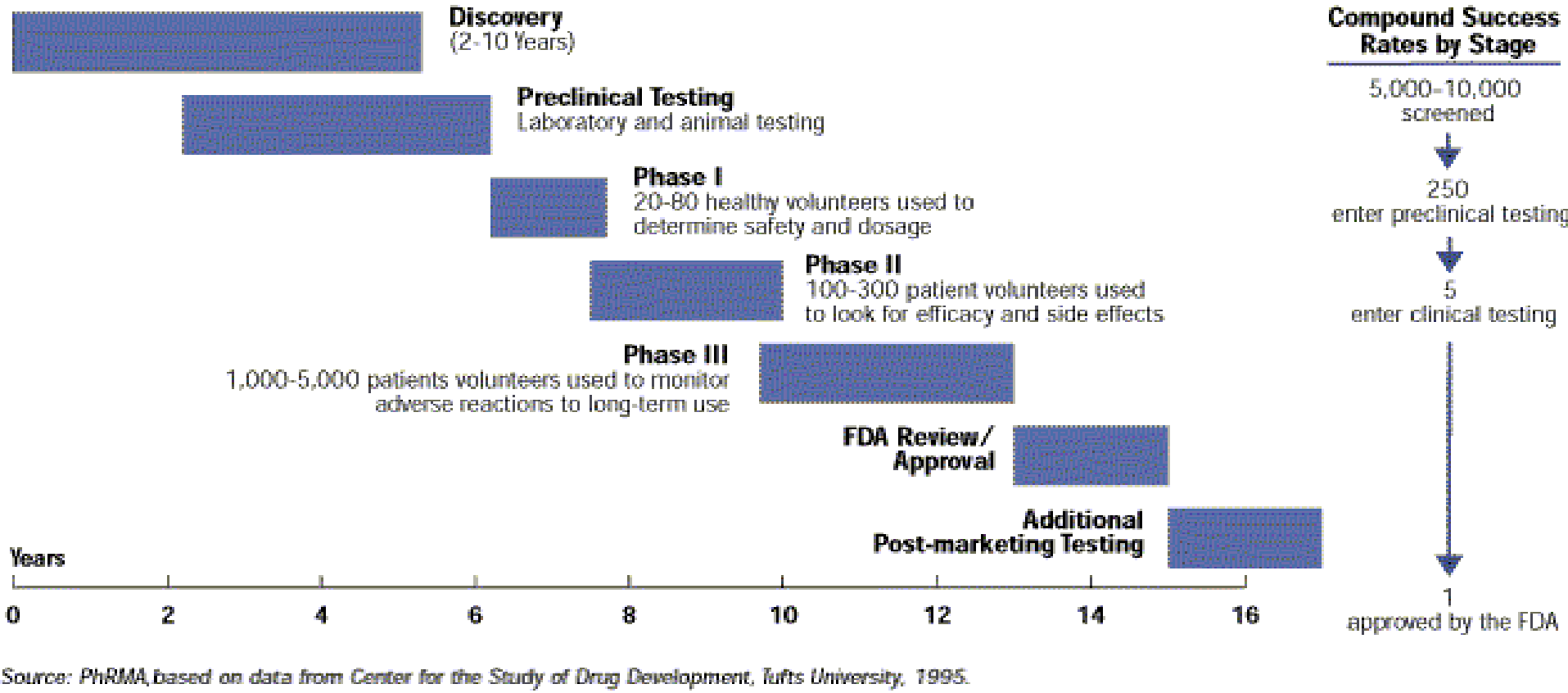
Value growth



Product pipeline

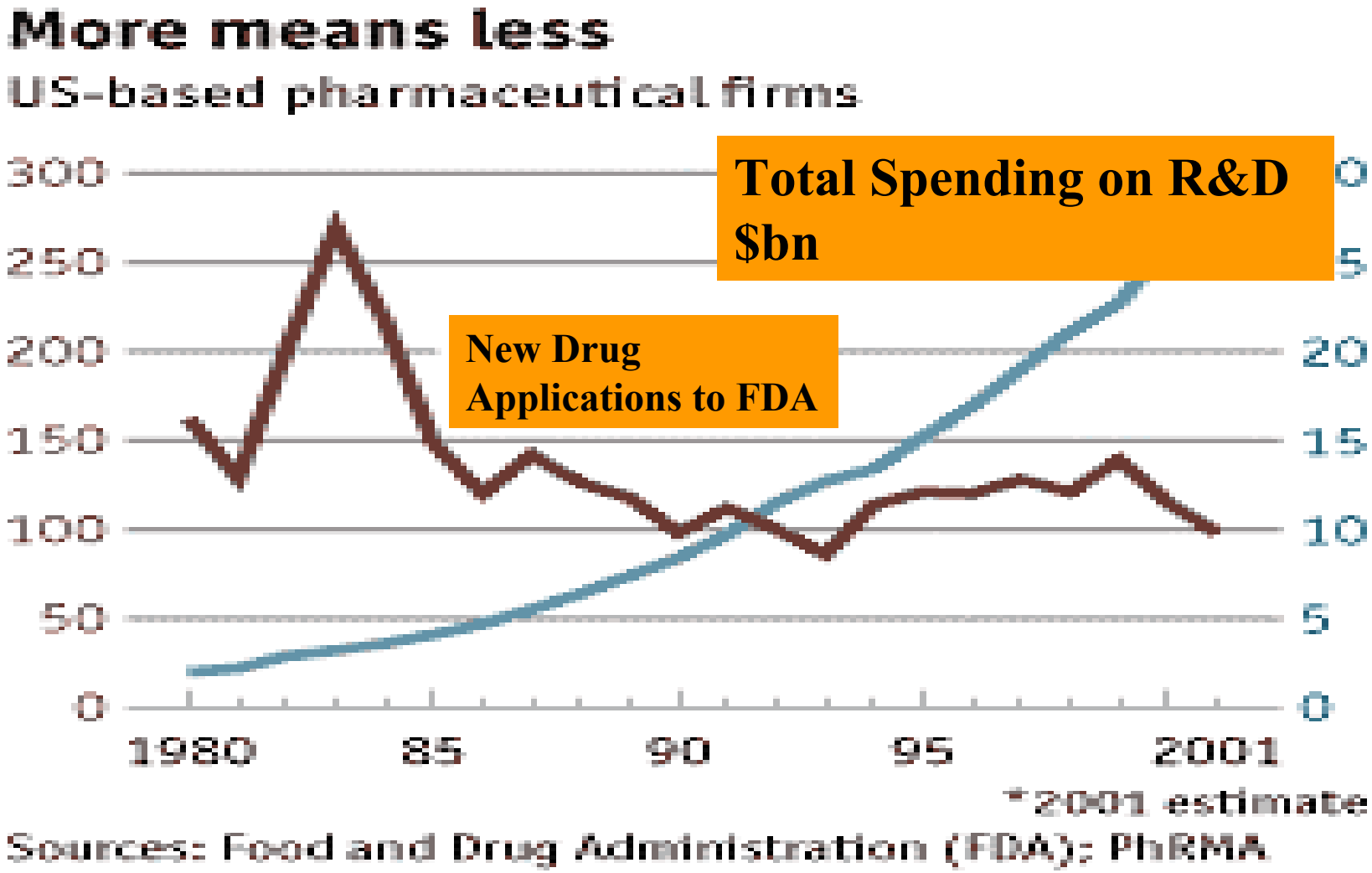


Compound success rates by stages



Source: PhRMA, based on data from Center for the Study of Drug Development, Tufts University, 1995.

Decreasing R&D efficiency



The value chain

- Discovery generates candidate molecules
- Variety of trials evaluates efficacy and safety
- Complex regulation process
- Manufacturing:
  - Primary manufacture of active ingredient (usually 1-2 sites)
  - Secondary manufacture – production of actual doses (up to 20 sites)
  - Often geographically separate for taxation, political etc reasons
  - Complex logistics
- Distribution
  - Supply chains often global
  - Many third parties become involved
    - Distributors, health authorities etc.
- Retail
  - Pharmacies, doctors and hospitals are main outlets for ethical drugs

The "supply chain"

The value chain

Research & development	15%
Primary manufacturing	5 - 10%
Secondary mfg/packaging	15 - 20%
Marketing/distribution	30 - 35%
General administration	5%
Profit	20%
Total	100%

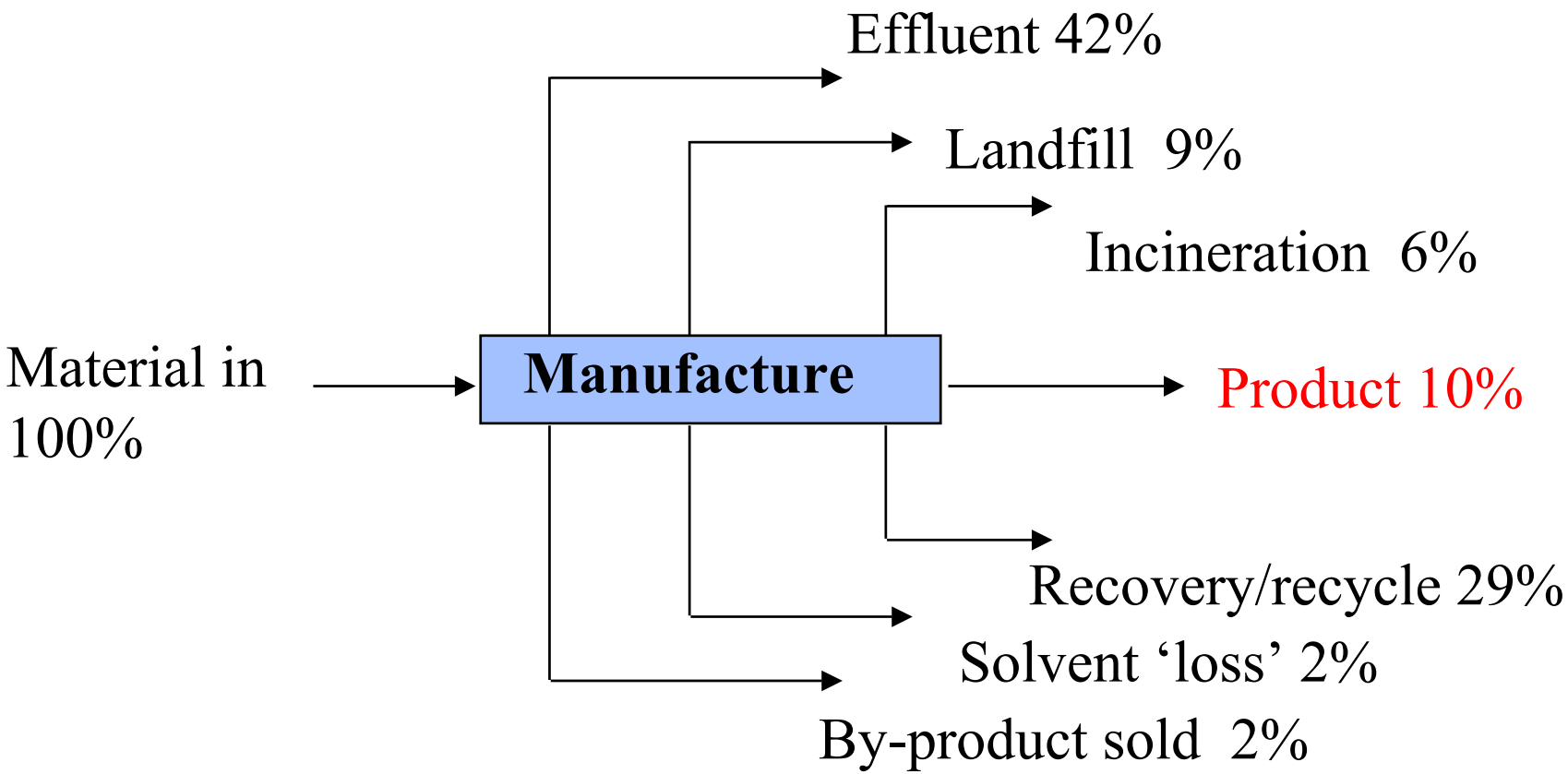
The supply chain

- Difficult to get value from early stage discovery/trials processes (cf. decreasing R&D efficiency, recent mergers)
  - Can Process Systems Engineering techniques help generate more focussed searches/libraries?
- Companies view supply chain differently:
  - was a means of getting product to where it was needed
  - now a means of delivering additional value
- (At least) three interesting problems:
  - Process development and design
  - Planning of trials/testing and capacity under uncertainty
  - "Classical" Supply chain planning and management

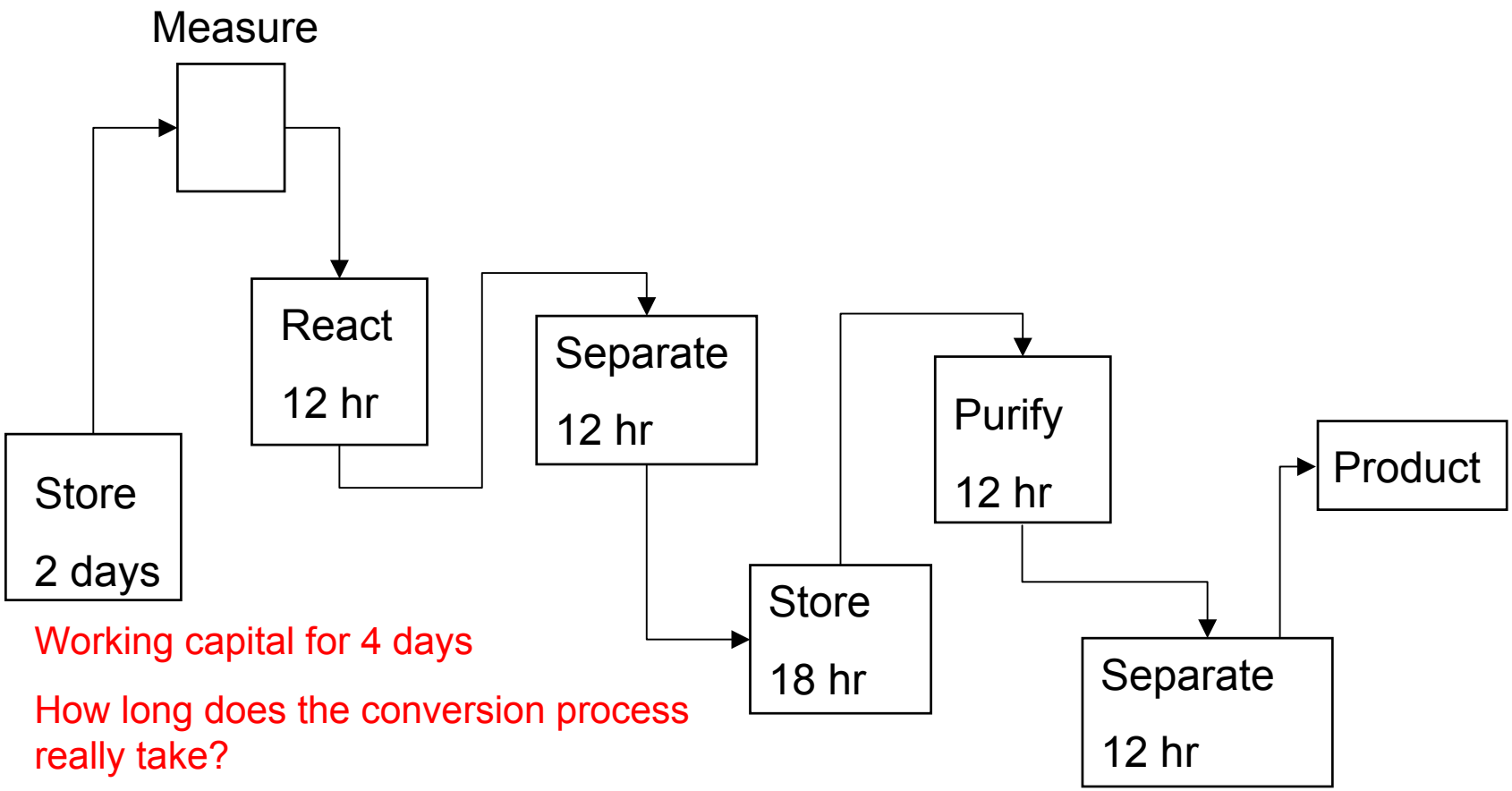
Process development and design

- Problems:
  - Process chemistry, solvent and catalyst choices result in
    - Low material efficiencies (of order 1%)
  - Inefficient, very traditional batch manufacturing processes result in
    - Low velocity ratio or value-added time (of order 1%)
  - Sub-optimal design of drug delivery systems results in
    - Low bio-availability where required (of order 1% for traditional formulations e.g. pills)
- 1mg delivered to target area:
  - may require 10kg of materials overall!
  - ties up a considerable amount of capital!

One stage: typical overall mass balance



Typical batch process

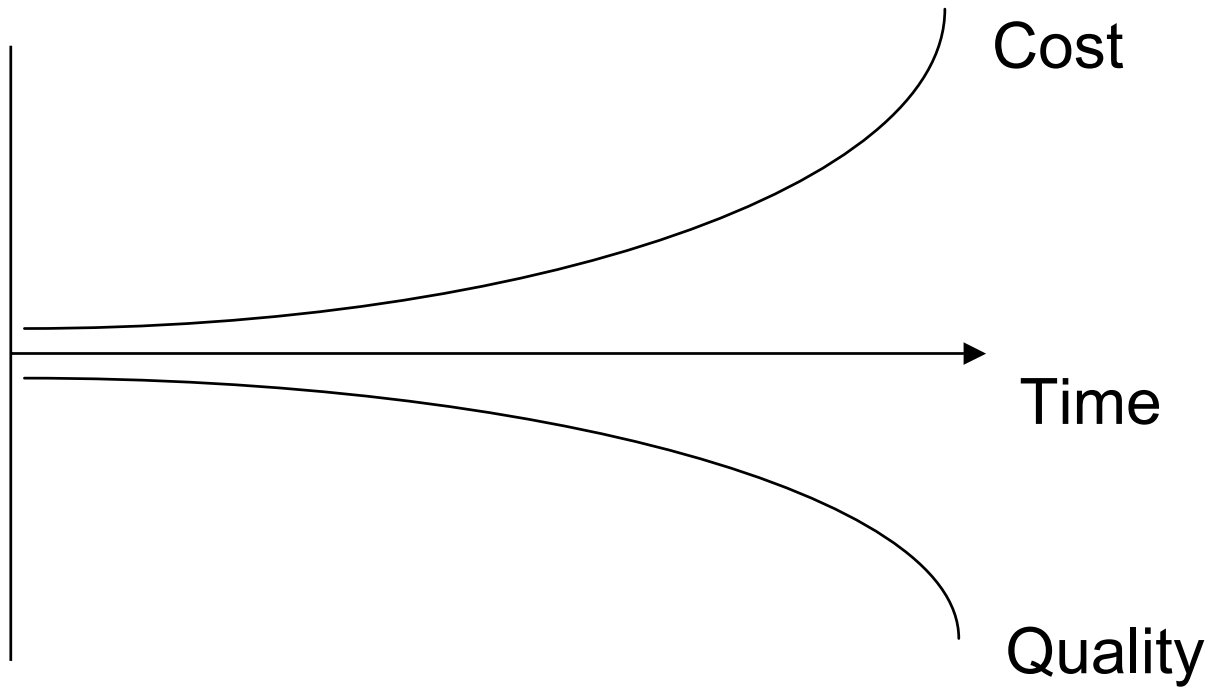


Working capital for 4 days

How long does the conversion process really take?

Low value-added time!

Longer time: higher costs and lower quality



Process development and design

- Many research groups now working in relevant fields
- More of a design than operations issue
  - Significant improvements in material efficiencies required
    - Involvement of process (systems) engineering at early stage
      - Model-based design
      - True catalysis rather than stoichiometric reagents
      - Optimise overall material efficiency rather than reaction yields
      - Large reductions in solvents
        - » Need for better heat transfer technology
  - Improve manufacturing performance
    - Run processes as close to intrinsic rates as possible
    - Use small-scale continuous processing where possible
    - Avoid stage-to-stage isolation where possible
    - Cleaning and changeovers! (see later)
  - Improve drug delivery to be more targeted (new field)

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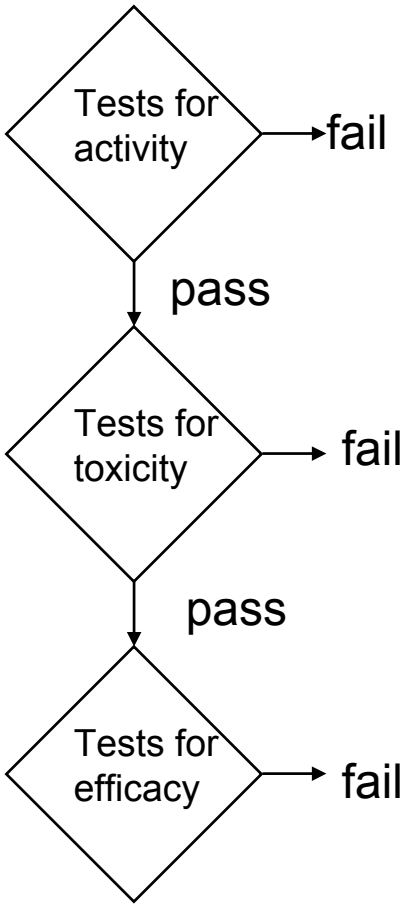
Testing and capacity planning

- "Traditional" sequential approach:



Tests characterised by:

- Duration*
- Cost (in-house or outsourced)*
- Resource requirements*
- Hard precedence constraints
- Soft/conditional precedence constraints
- Probability of success

*may be distributions rather than known

Sequential approach conserves resources, but may increase time to market

Optimised planning of tests

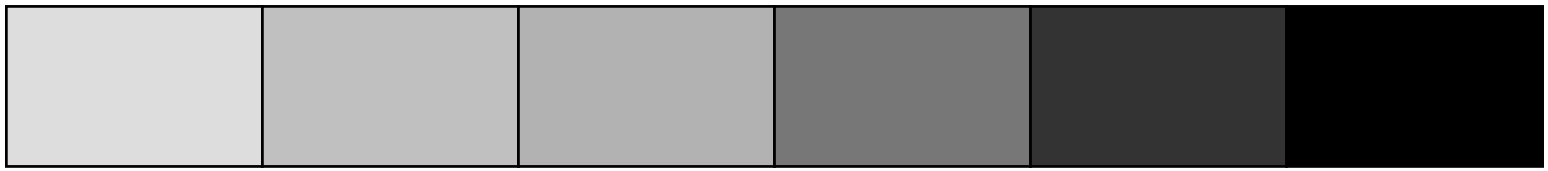
(Grossmann & co-workers, Pekny, Reklaitis and co-workers)

- Rather than follow sequential approach, approach from a resource-constrained scheduling perspective
- Some tasks have conditional dependence
- Degrees of freedom on task precedence
- Optimisation balances:
  - Risk of unnecessary expenditure
  - Potential rewards of coming to market earlier
  - Resource constraints and outsourcing costs
- Resource-constrained stochastic optimisation problem
  - Conservative approaches (always feasible)
  - Hybrid simulation-optimisation approaches

Capacity and portfolio planning under uncertainty

- What technology/capacity, where, when (plant fabrication lead times!), whether to outsource
- Products to prioritise in the R&D pipeline to structure the future portfolio optimally
- Most severe for pharmaceuticals:
  - capacity requirements very dependent on outcome of clinical trials, registration etc.
- Extreme cases
  - pessimistic: no investment and many successful products: severe capacity limitations
  - optimistic: investment $\rightarrow$ plenty of capacity but no new products $\rightarrow$ patent expiry issues
- Need for systematic way to balance risks

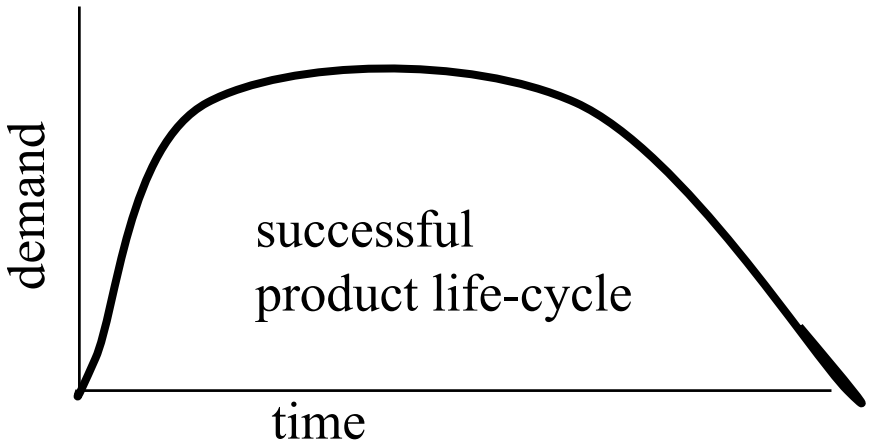
Product Pipeline and Capacity Plans



materials entering CT

promising CT results

current products

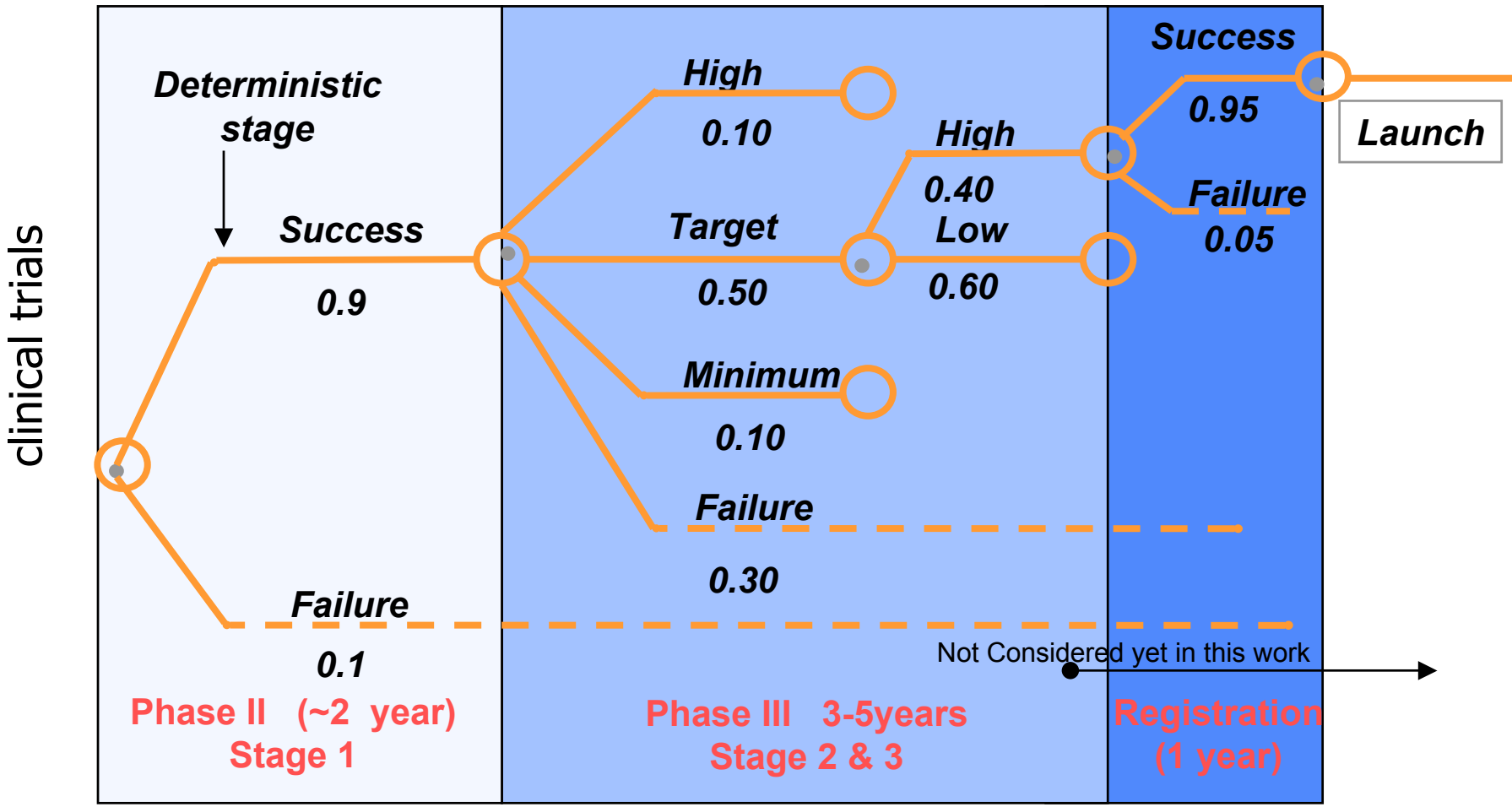


How to:

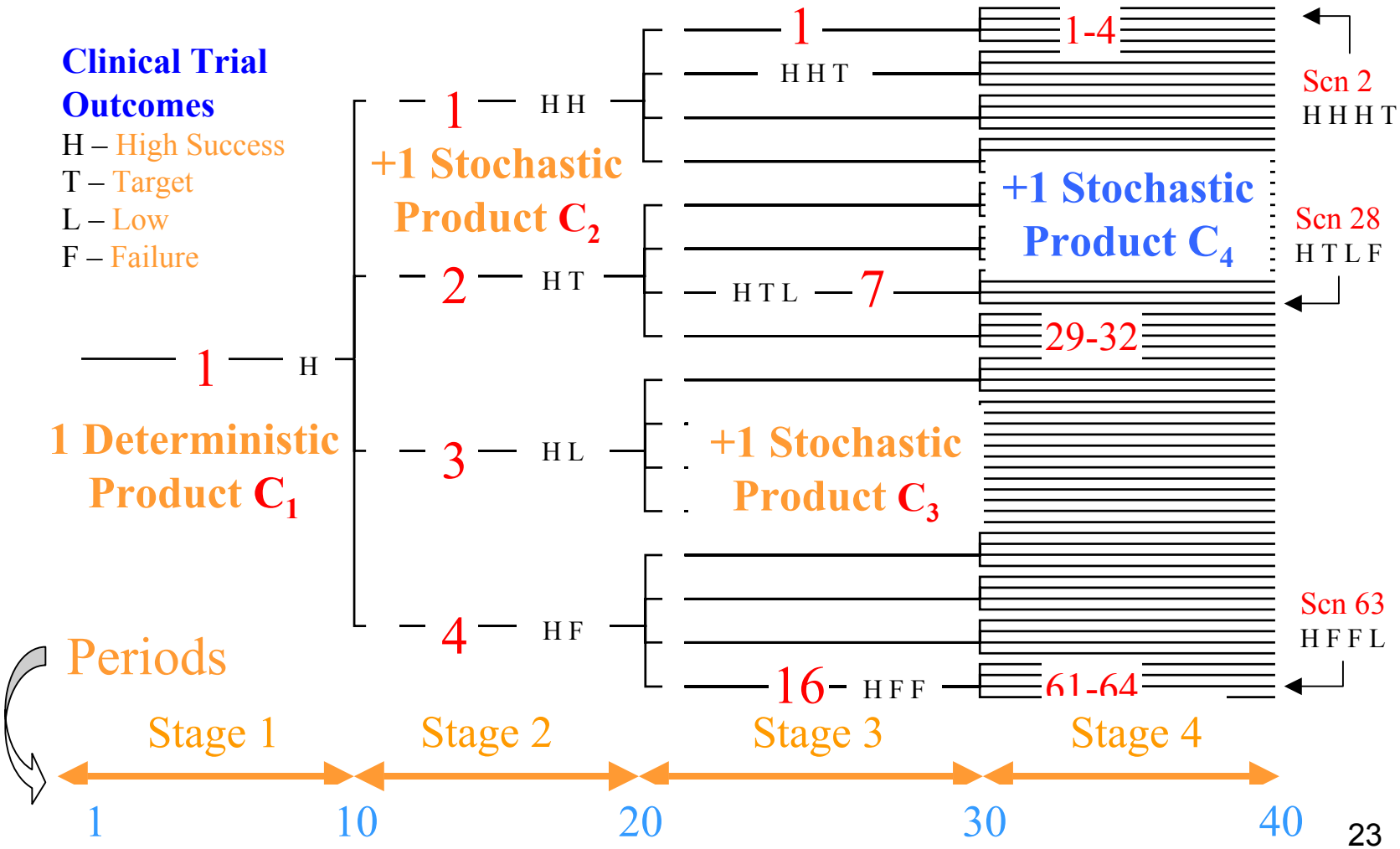
- allocate capacity between products ?
- plan capacity investment ?

Clinical trials

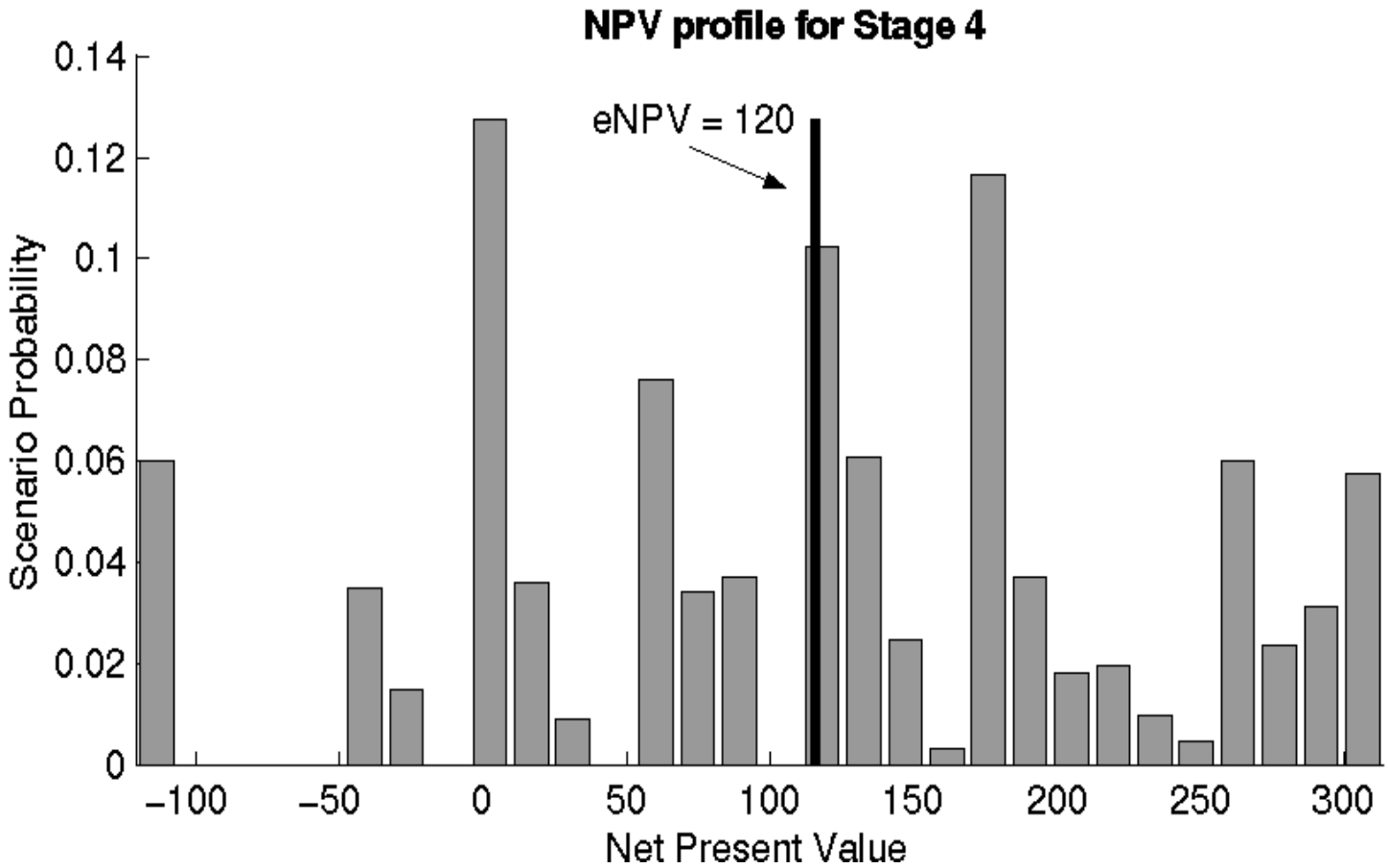
More than two outcomes!



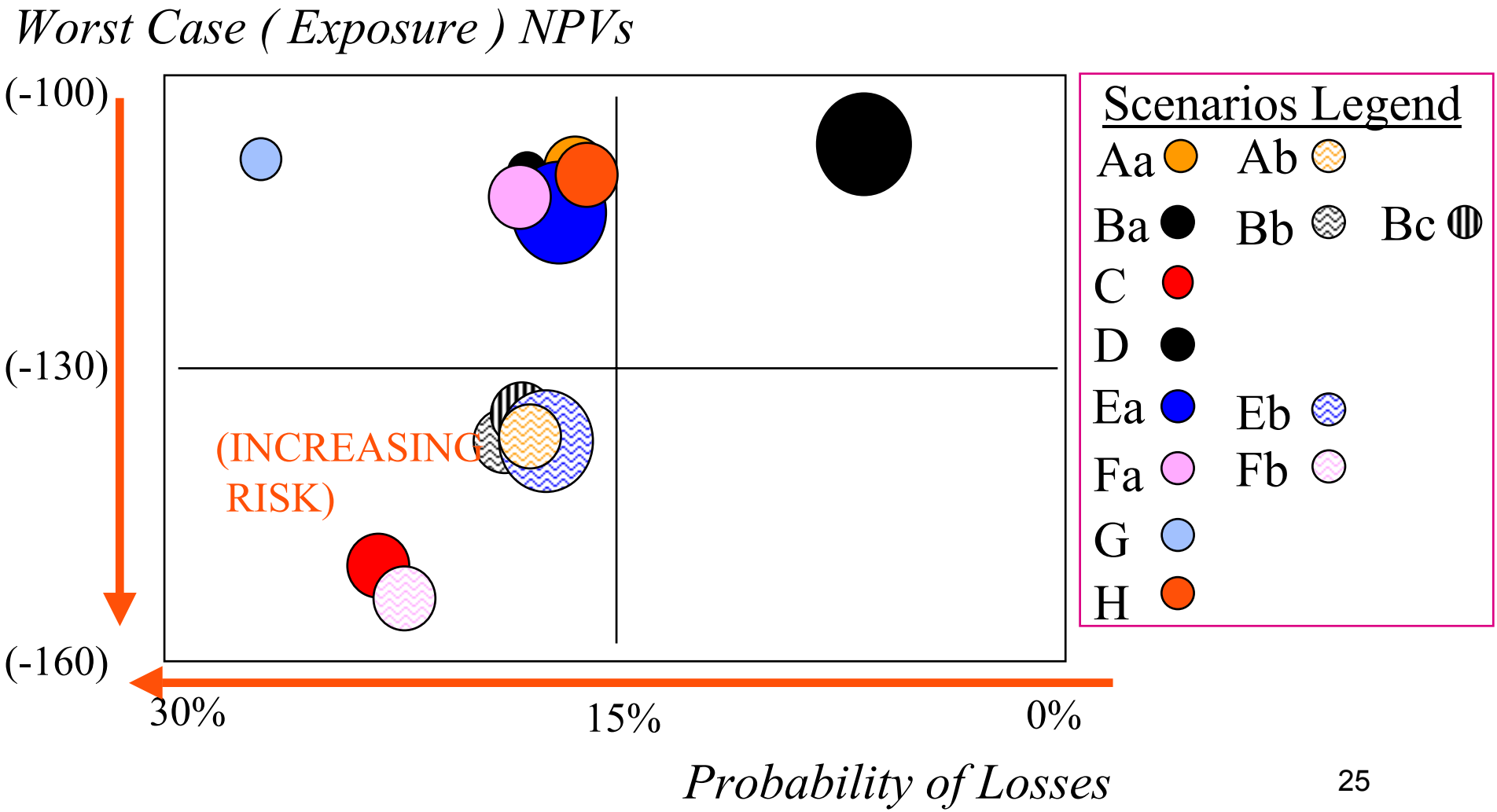
Scenario Tree & Clinical Trial Outcomes



Results
NPV profile



Strategy matrix: risk analysis



Combined testing and capacity planning
(Grossmann and co-workers)

- Interesting way forward
  - Holistic analysis of value chain
    - Better synchronisation leads to material being ready if tests are successful
  - Avoid shortage of material for clinical trials
- Basis for future work; extensions:
  - Management of risk is a key feature
    - Real options techniques should be relevant
  - Needs to take account of global trading structures
  - Needs to include creative possibilities in model
    - e.g. placing of low-commitment options with subcontractors
  - Needs to take more extended view of supply chain

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“Classical” supply chain planning and management

- Some performance measures
  - Pipeline stocks may be 30-110% of annual demand
  - Finished good stocks 10-50% (4-26 weeks) of annual demand
  - Supply chain cycle times of order 1000s of hours
  - Value added times 0.3-5% of cycle times
  - Supply chain costs overtaking R&D costs

- What can better operations deliver?
  - 30% stock reduction
  - 30% increase in value-added time
  - 7% reduction in supply chain costs

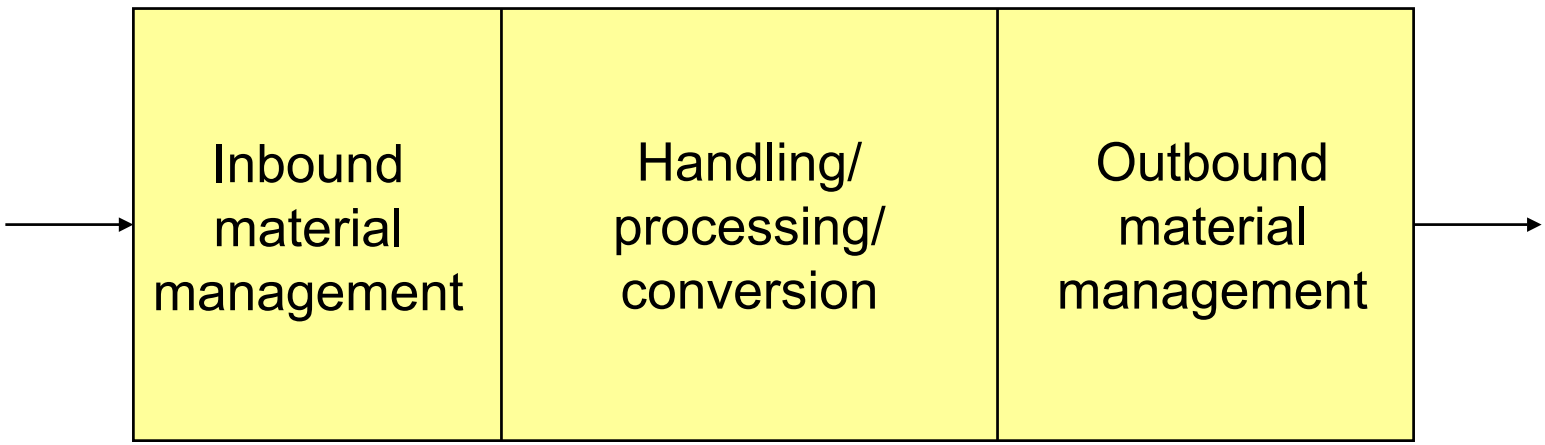
- Benefits of improved operation for one large drug:
  - $30m one-off
  - $8-16m p.a.

Issues/Structure

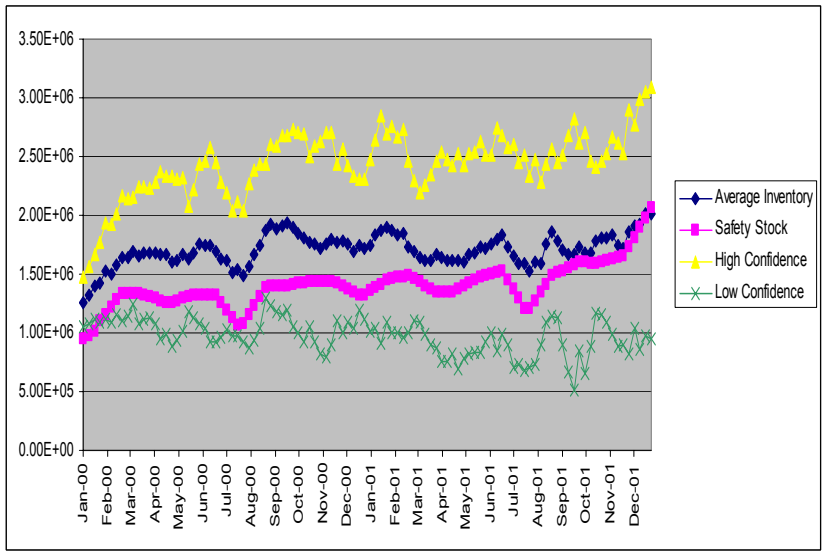
- Primary production processes usually "slow" and "unresponsive"
  - lowish yield
  - labour- and time-intensive
  - can take 30-200 days from end to end
  - many QA steps along the way
  - long changeovers (one to four weeks) force campaign operation
- Secondary processing often geographically separate from primary
  - transportation lags, but sensible use of API storage can mitigate
- Secondary processing sometimes serves market directly, but more commonly:
  - regional storage locations/wholesalers and other agents
- Long supply chain cycle times (60-300 days)
  - Many delays in process
  - poor responsiveness to changes in demands
  - High service levels required $\rightarrow$ high stocks

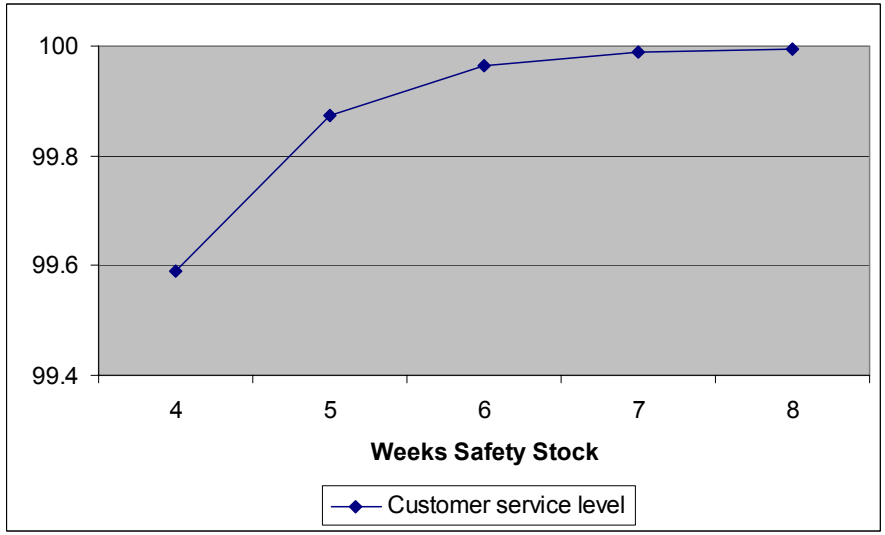
Dynamic supply chain analysis

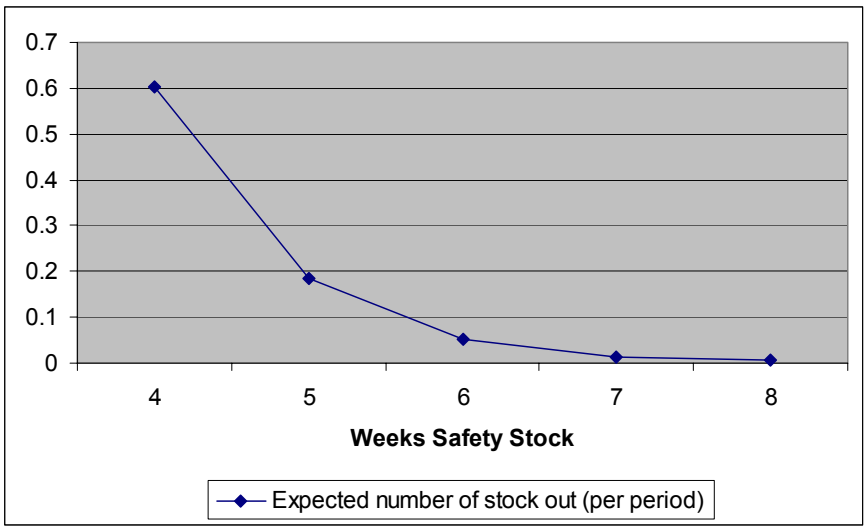
- Dynamic analysis of existing supply chains generates considerable insight
  - Understand relationship between policies/parameters and performance measures
- Use a generic modelling approach which captures physical and business processes
- Library of supply chain objects based on generic node:

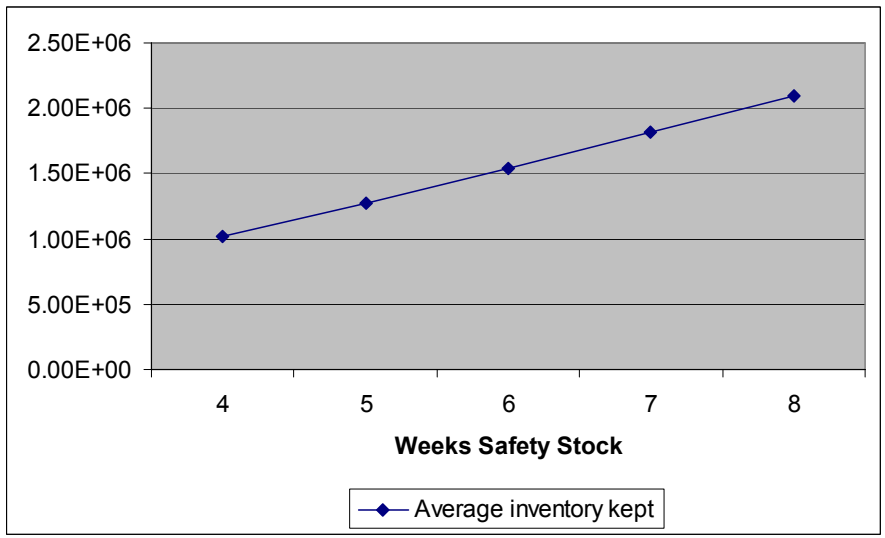


One SKU: forward look





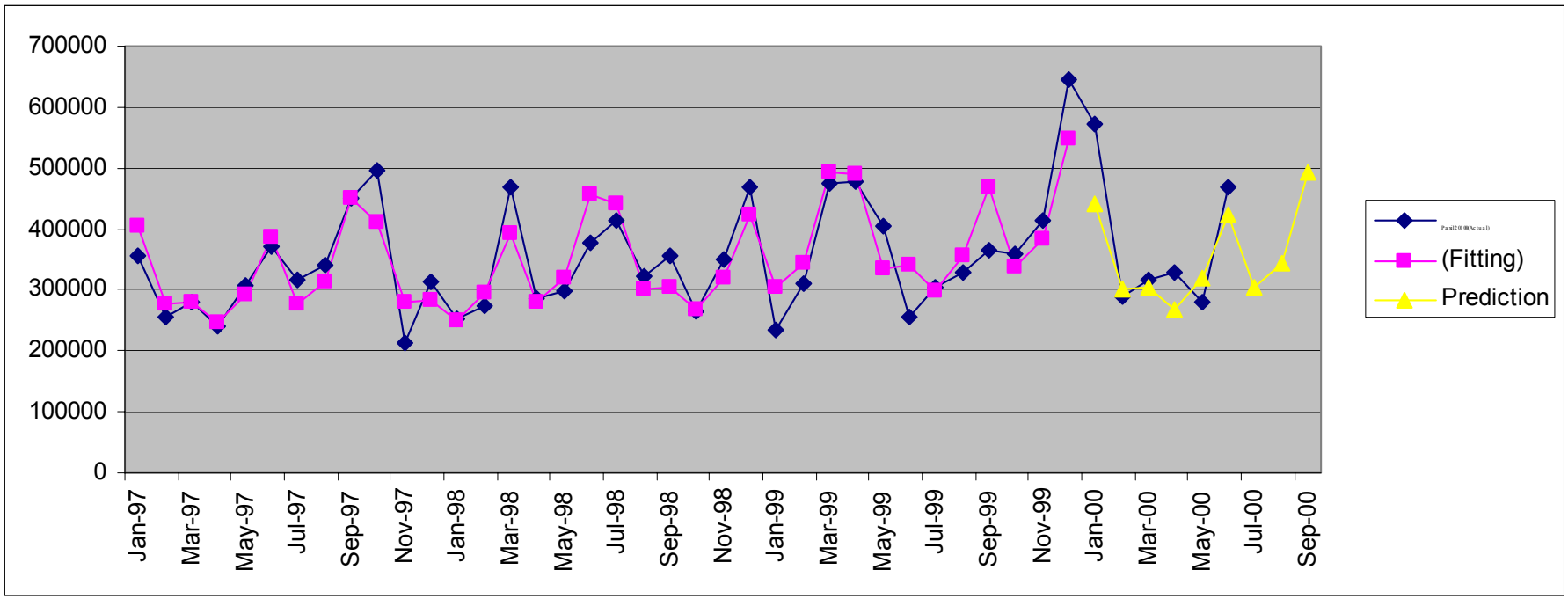




A particular market

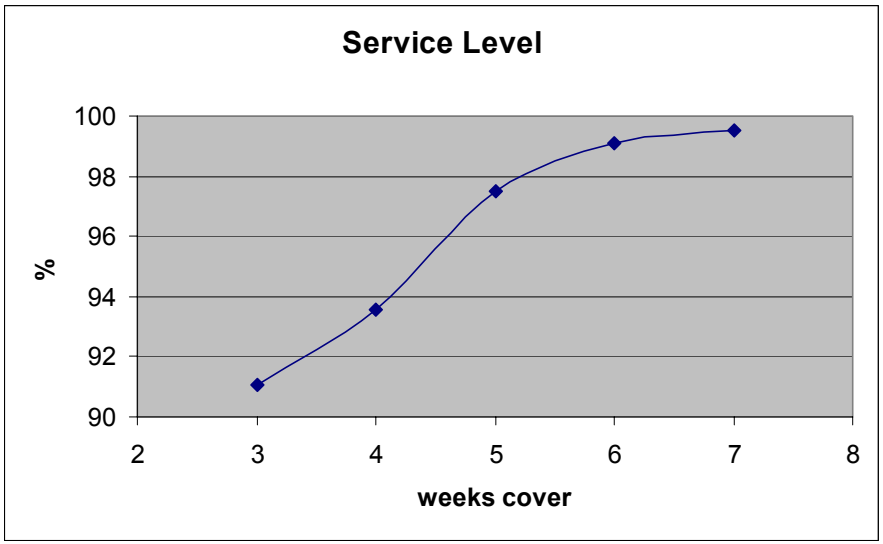
- End-user demand fairly steady, but
- Internal processes create additional dynamics
- Need for high safety stocks to buffer
- Aim for high service levels – high perceived opportunity cost
- What if demand was more in line with end-use ?

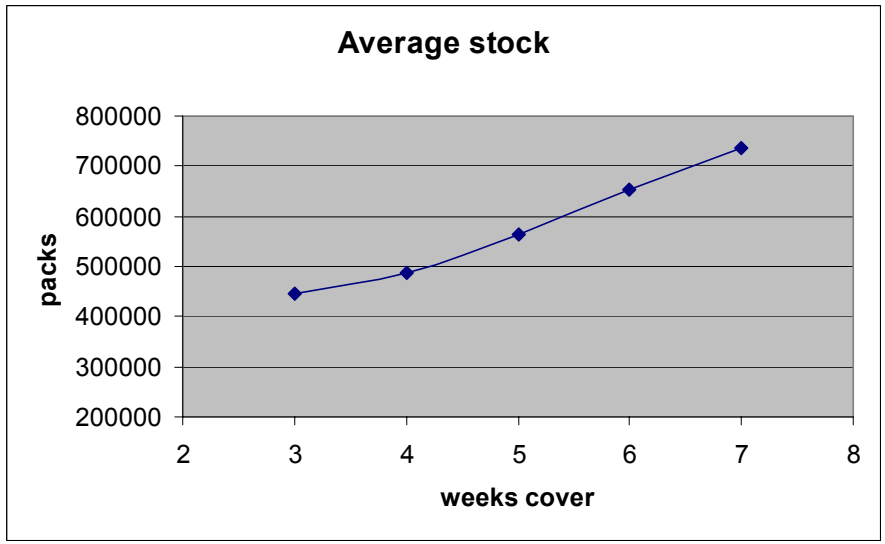
Demand profiles



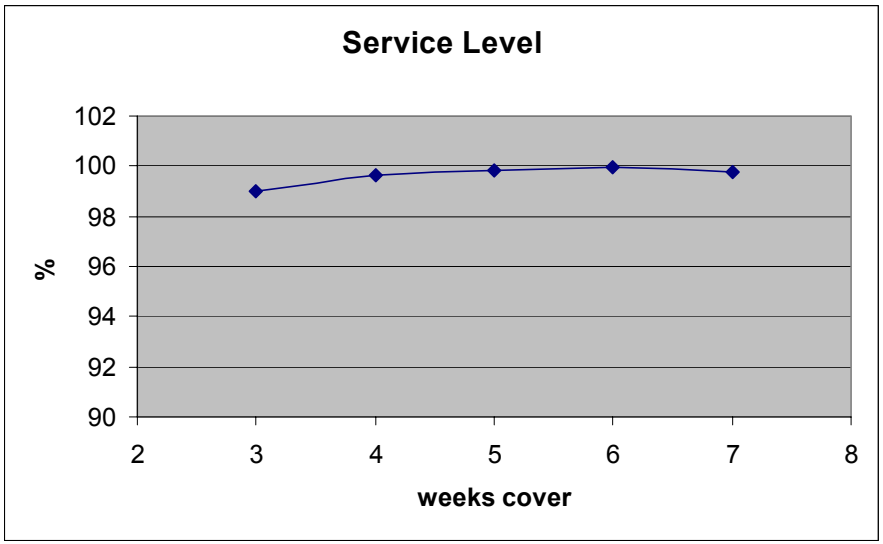
includes our forecasting algorithms for future forecasts – these pick up key dynamics

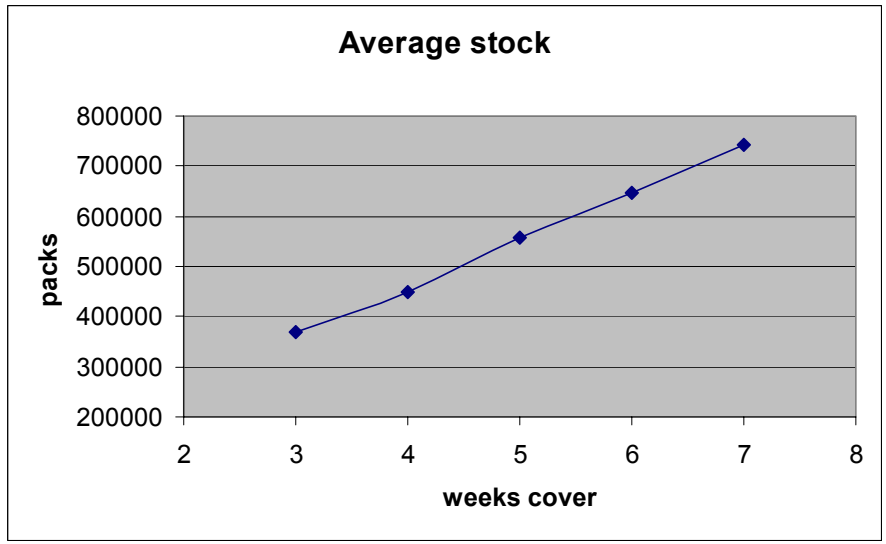
Current policy: performance





Smoothed performance

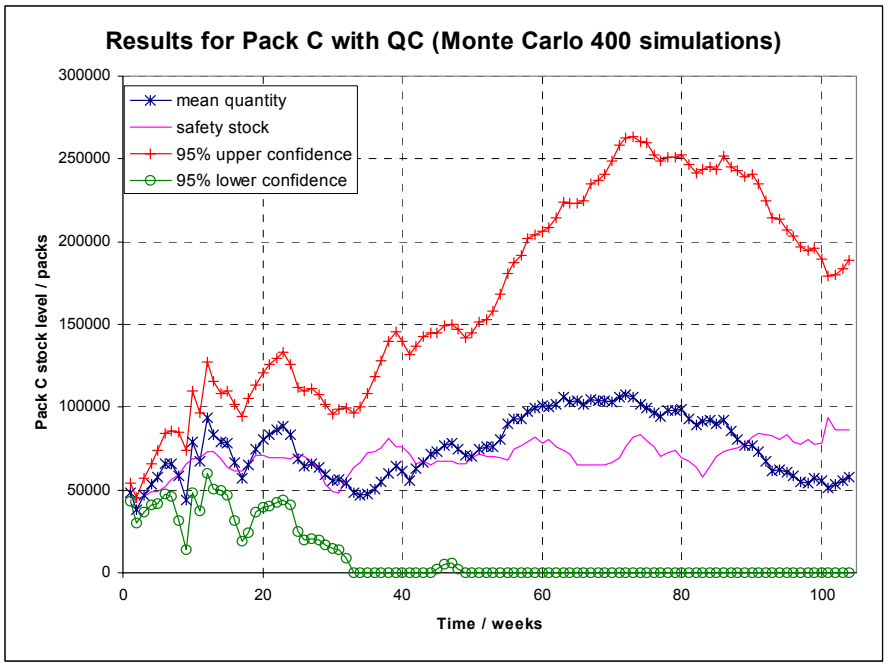




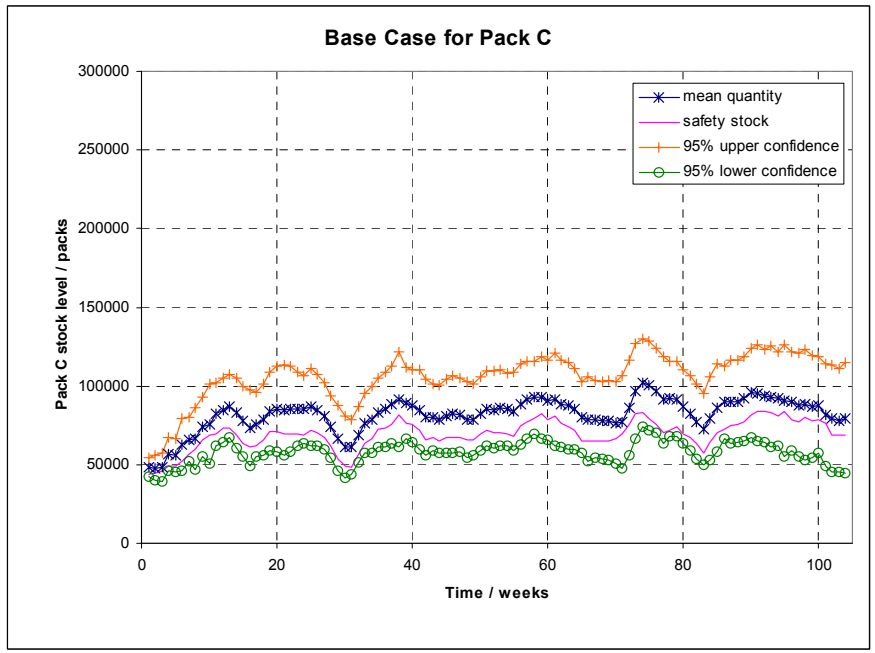
Comparison of two supply chain responses

- Pharmaceutical process
  - primary production has five synthesis stages
  - two secondary manufacturing sites
- Two different process principles
  - Case A: QC at the end of each synthesis stage and the final products
  - Case B: QC for the product of the primary process (AI), and the final product

Inventory variation for one SKU



Case A



Case B

SCM more generally…

- Re-emphasise need for better process technology for 1^0 manufacture
- Currently push-based at back-end of supply chain:
  - hard to be responsive
  - complicated dynamics
  - can't exploit short-term opportunities (e.g. tenders)
- aim for much faster processes
- avoid too many quality control interventions and isolations
- aim for easy to clean/reconfigure (disposable?) plants
  - Move towards short-term scheduling
- Interim:
  - optimise campaign planning (cf. literature of 1980s!)
  - optimise changeovers using SMED concepts

SCM more generally (cont'd) …

- Current SCM methodologies involve a degree of decentralisation
  - Regional demand management
  - Primary or secondary planning
  - Subcontractors
  - Robust, but built-in inefficiencies
- Need for more integrated, seamless planning
  - Very large-scale multi-site problems with large geographical span
  - Looser alliances may arise (e.g. semiconductors, computers)
    - Increased co-ordination problems
  - Tailored optimisation algorithms will be required
  - Need to build in robustness (*cf.* work of Maranas and co-workers, Sahinidis and co-workers)

Some conclusions

- The pharmaceutical supply chain is very complex, with many interacting facets
  - Difficult to generate radical improvements quickly
  - Piecemeal approaches (e.g. improved logistics) will generate incremental benefits
- Current process technology is one of the main supply chain bottlenecks
  - Many "built-in" inefficiencies that constrain performance
  - Not a very responsive system
- Current models in the research community are too "company-centric"
  - Future models need to consider a holistic view of an extended supply chain of specialist agents
    - IP generators
    - Testing specialists
    - Contract manufacturers
    - Logistics providers
    - Healthcare providers/consumers

Future perspectives

- Industry
  - at crossroads?
    - "Big is beautiful" v. alliances of specialists
    - Latter will need next generation of supply chain tools
- Products
  - More complex, more synthesis stages, more chiral, more active, smaller lot-sizes
  - Better drug delivery mechanisms
    - Smaller dosages
  - Likely to become more specialised
    - Local solutions to local problems
    - Genetic research leading to target sub-populations
    - Current manufacturing and supply chain poorly suited to this
      - Economies of scale 1-2 orders of magnitude out
  - Rapid response vaccines (civilian and military)
  - More crop-derived products – new supply chains

Acknowledgements

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