



Productivity and the Economics of Regulatory Compliance in Pharmaceutical Production

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Declaring a Few Biases

- Business
- Manufacturing
- Systems
- Big pharma



Our Thesis

- The status quo is untenable.
- Pharmaceutical manufacturing - lots of room for improvement.
- Traditional metrics hide poor performance.
- Compliance infrastructures are not economic.
- Technologies are critical enablers - but not in isolation.
- Huge potential for industry & regulators to create a win-win.



Improving the Economics of Compliance



▪ Risk



▪ Compliance effectiveness

Win - regulators & consumers



▪ Cost



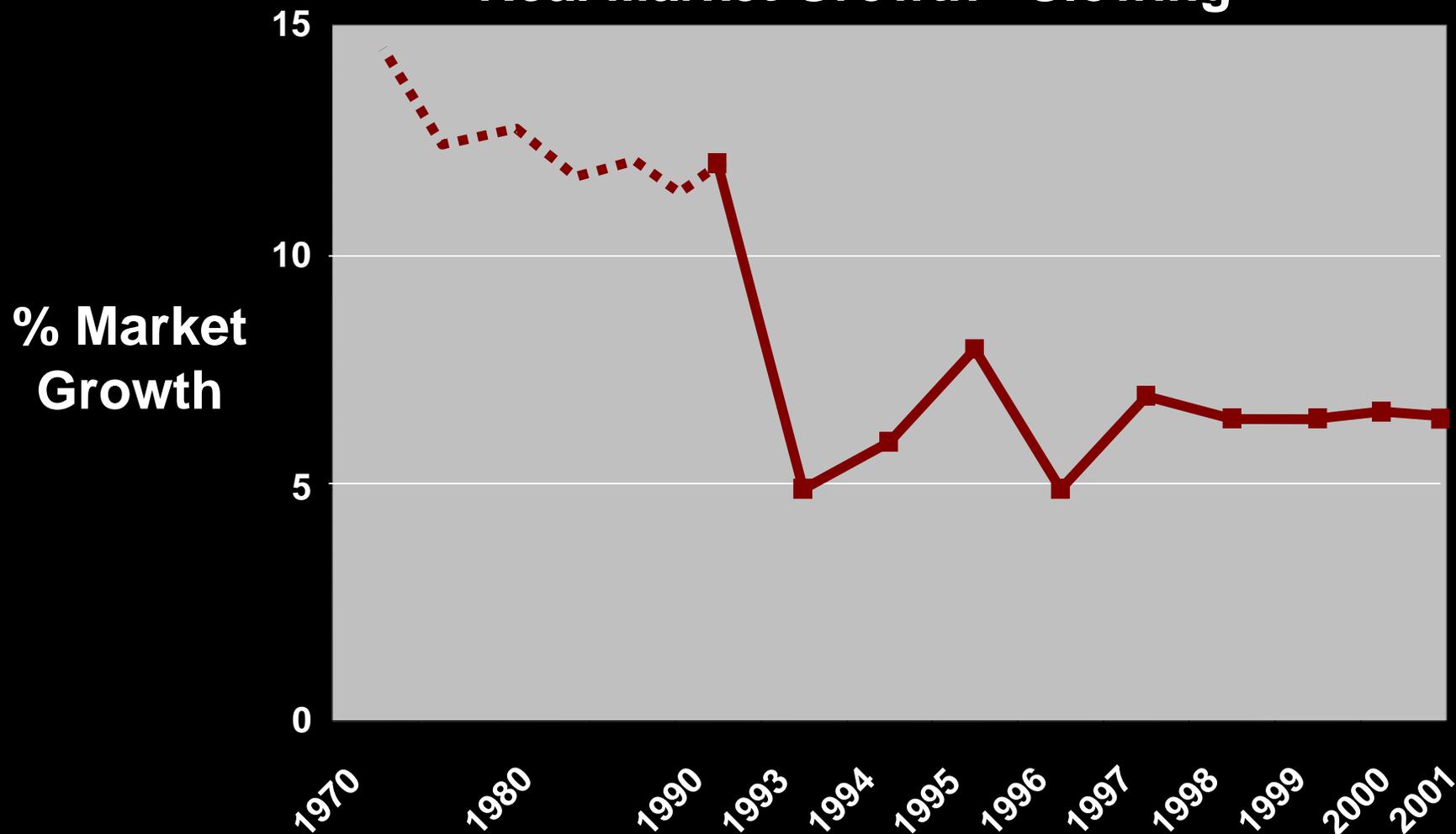
▪ Shareholder returns

Win - business



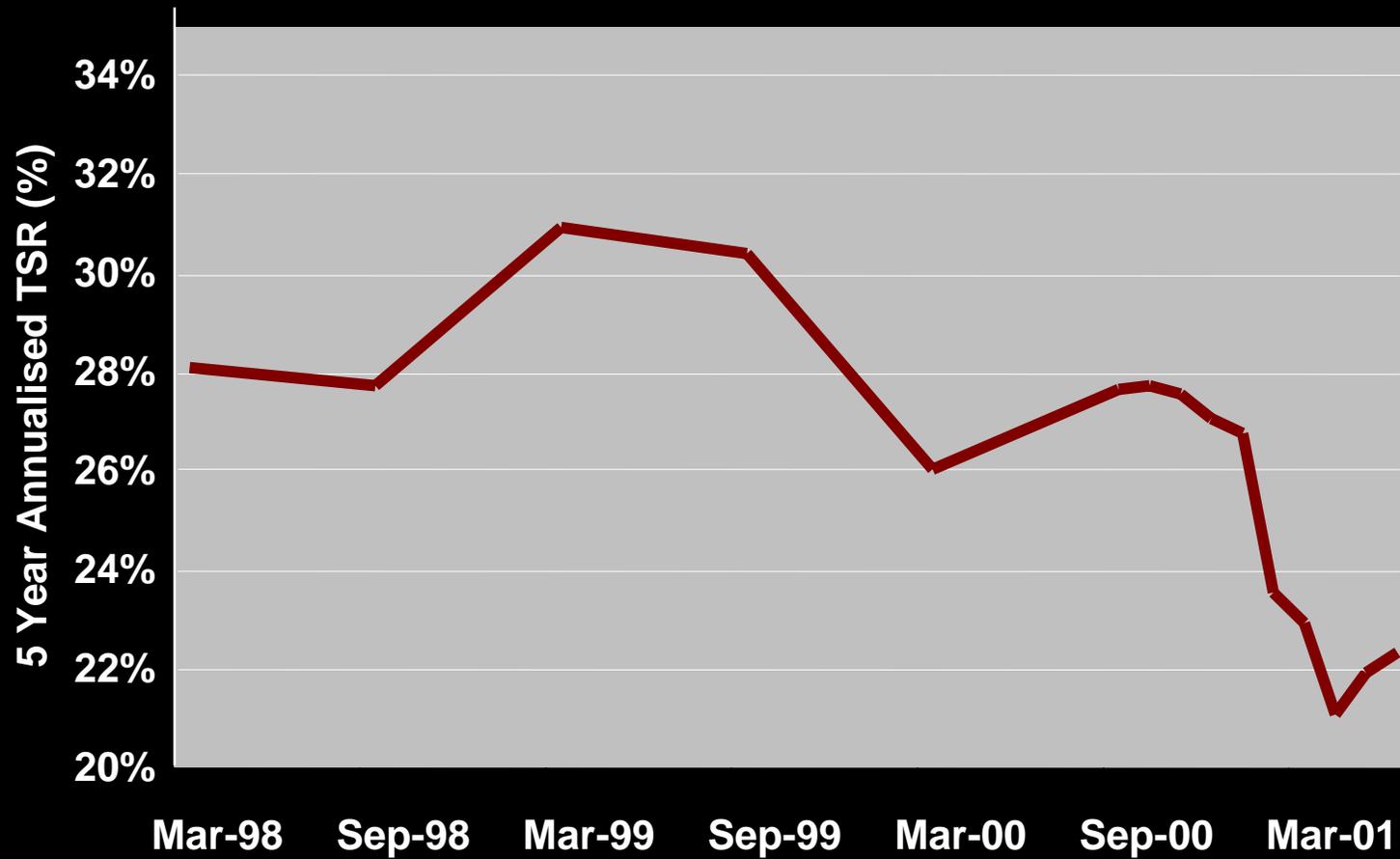
Our Business Environment - Tough & Getting Tougher

Real Market Growth - Slowing



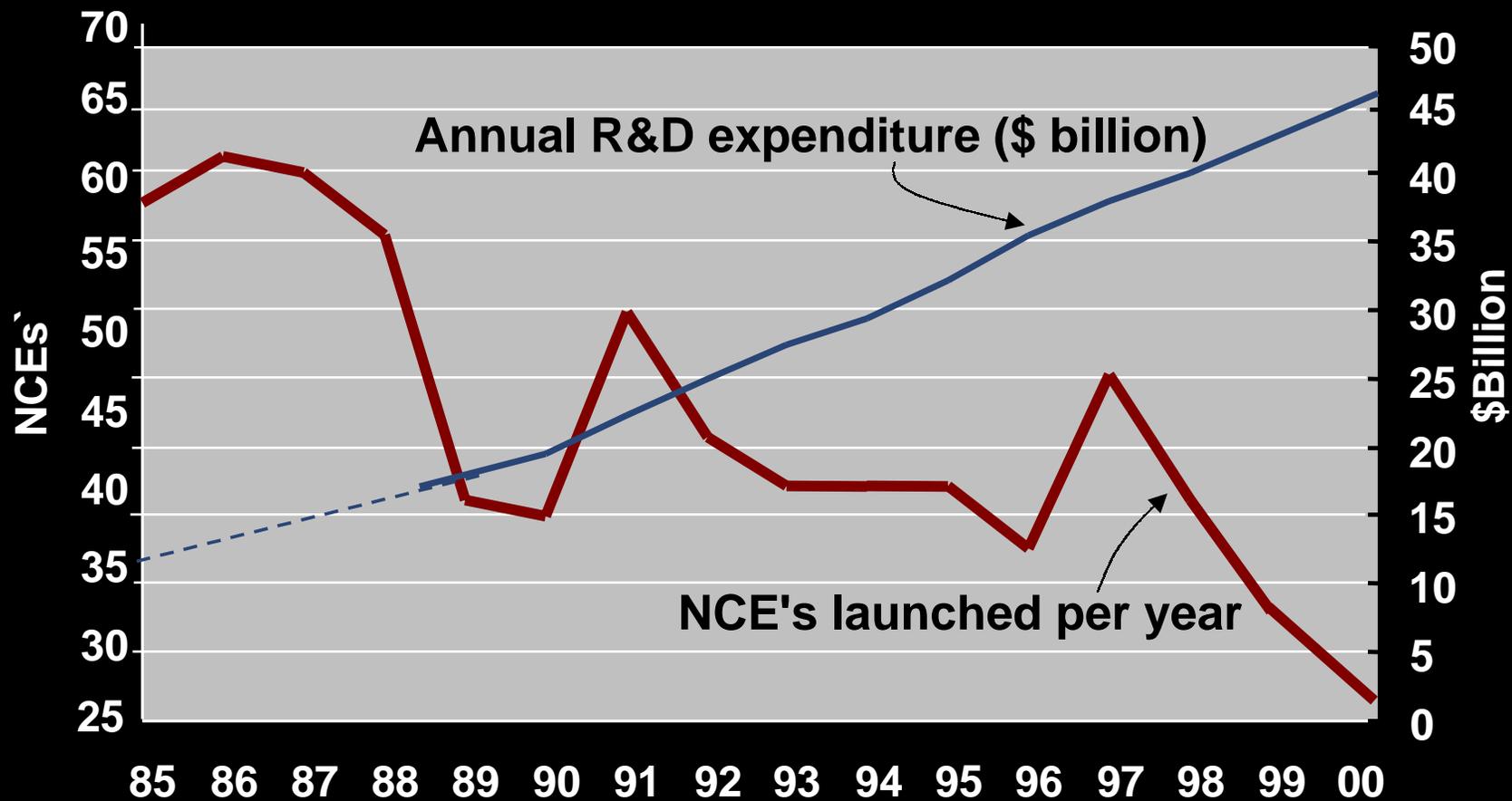


Shareholder Returns - Falling





R&D Productivity - Falling





Window of Exclusivity - Decreasing

Cox-2 Inhibitors 1998/9

Invirase 1995

Recombinate 1992

Difulcan 1990

Mevacor 1987

AZT 1987

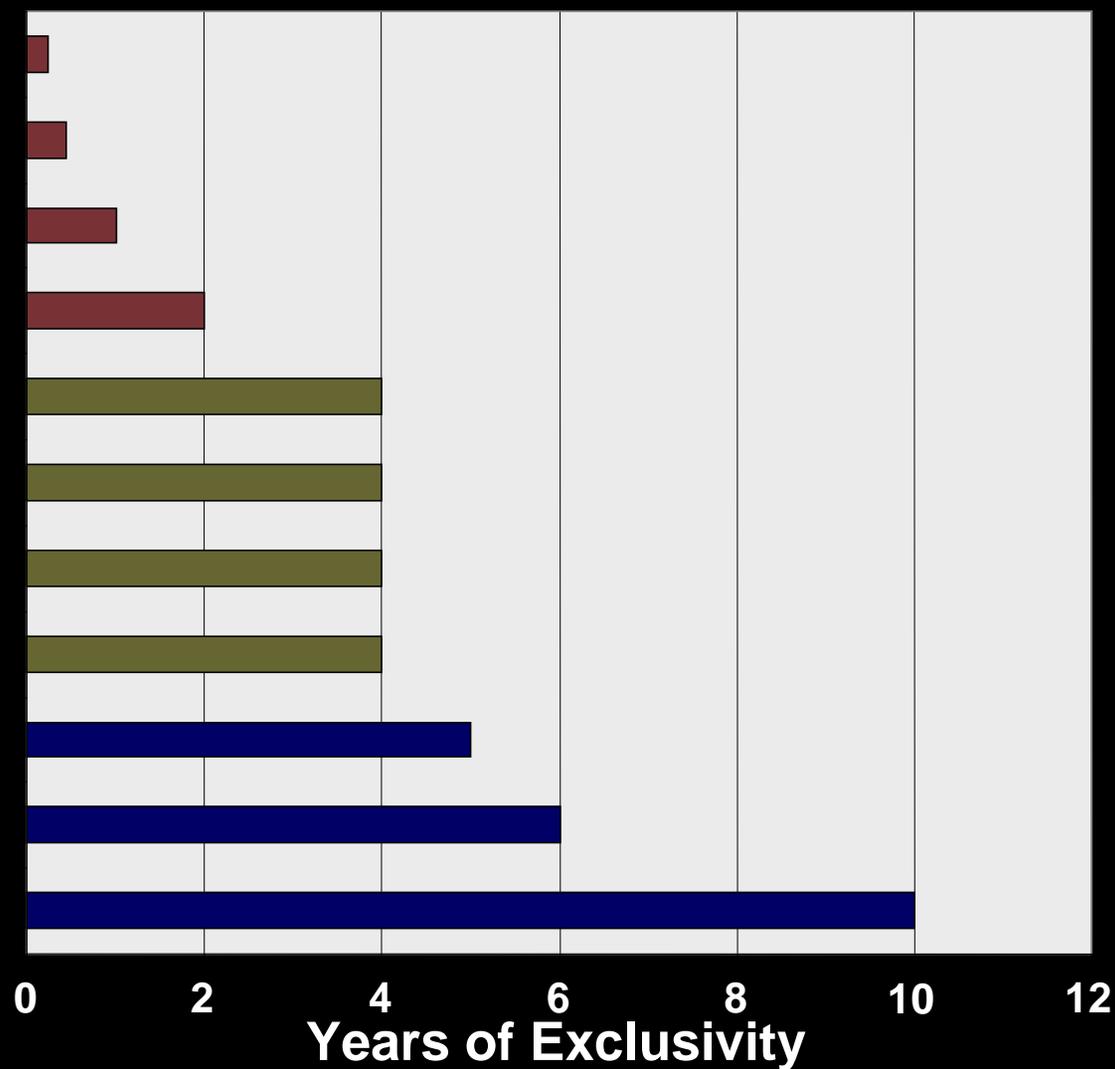
Seldane 1985

Prozac 1985

Capoten 1980

Tagamet 1977

Inderal 1968





Pharma Manufacturing - Unmet Performance Expectations

- Utilisation levels - 15% or less
(but low levels masked).
- Scrap and rework - we plan for 5-10%
(accepted as necessary).
- Time to effectiveness - takes years
(not challenged).
- Costs of quality - in excess of 20%
(that's the way it is).



Conclusions

- Hostile environment.
- Intense competition for resources.
- Manufacturing has to contribute (à la Wheelwright).

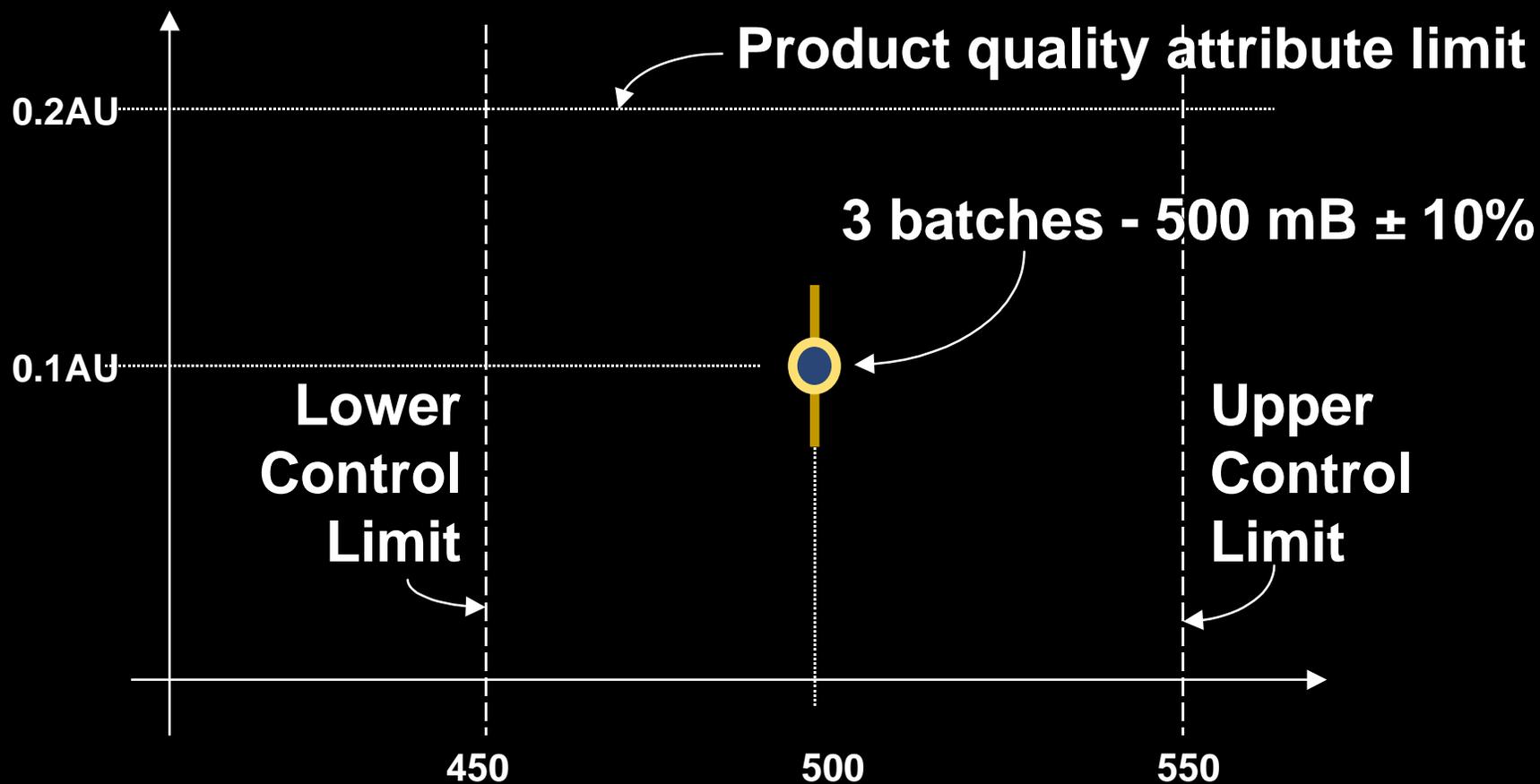


Our Findings - Problems Start in Development

- Processes are transferred that are neither fully understood or capable at commercial scales.
- Lengthy & elaborate new product introduction exercises that generate data but fail to provide critical information.
- 50% of production costs locked in before Phase III begins, process inefficiencies "institutionalized".
- No scientific basis for trading-off time in return for deeper process understanding.

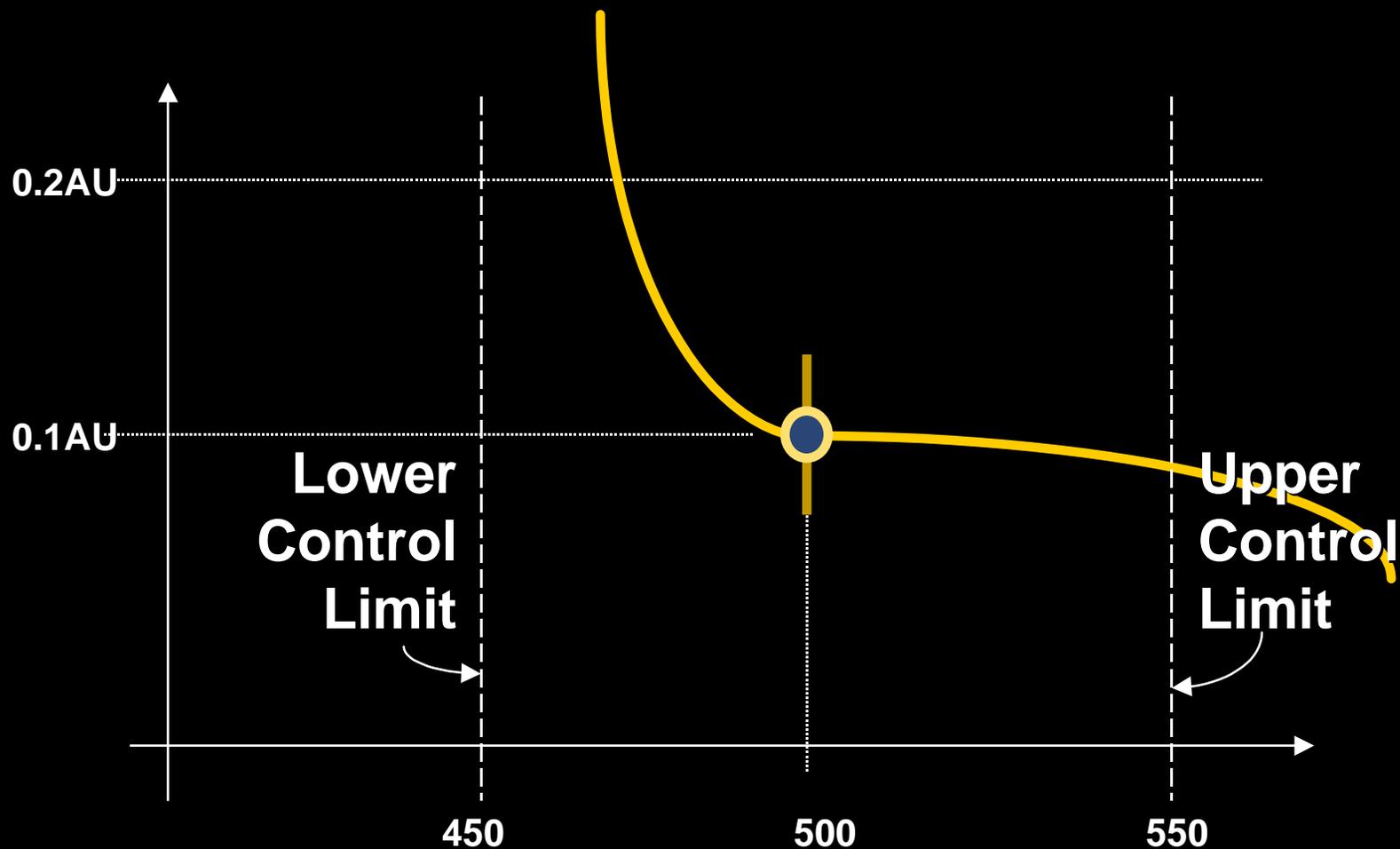


EXAMPLE: Parenteral Emulsion





EXAMPLE: SVP Emulsion



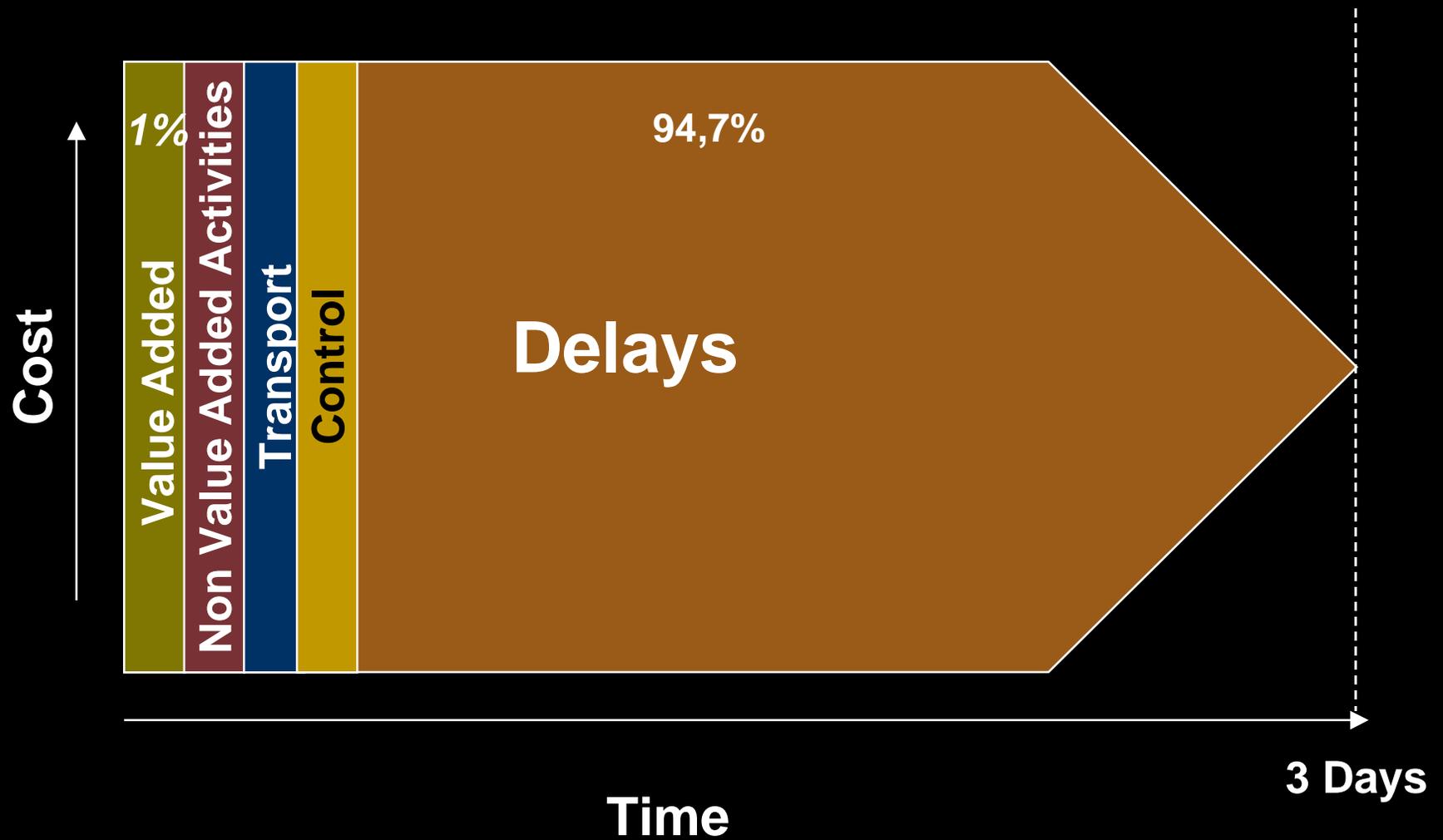


What is the Potential for Improvement?

- Value-added -vs- non value-added activities.
- Measurement for accounting -vs- measurement for productivity
- Ability of a process to be "right first time".

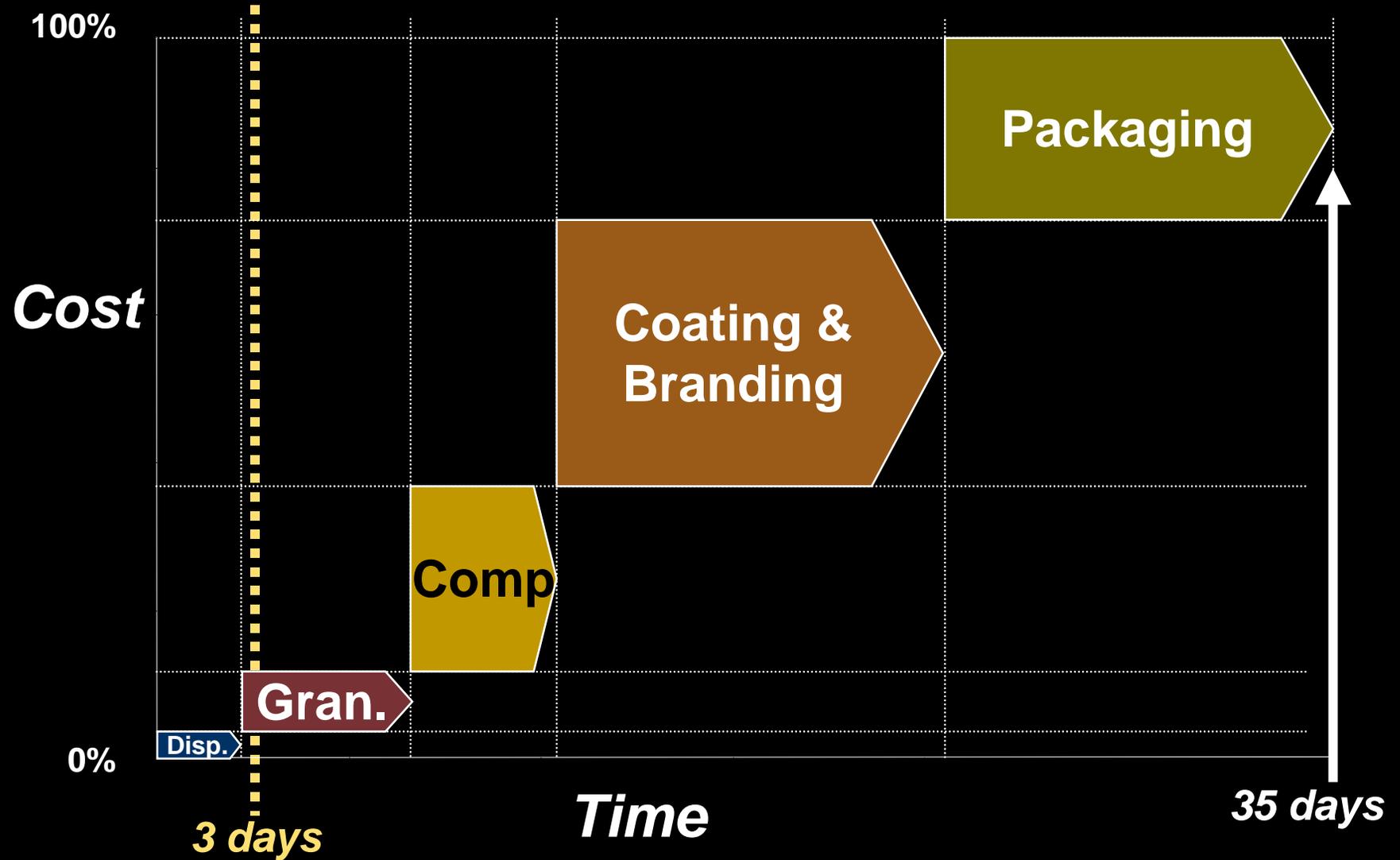


EXAMPLE: Value Added -vs- Non Value Added Process Time



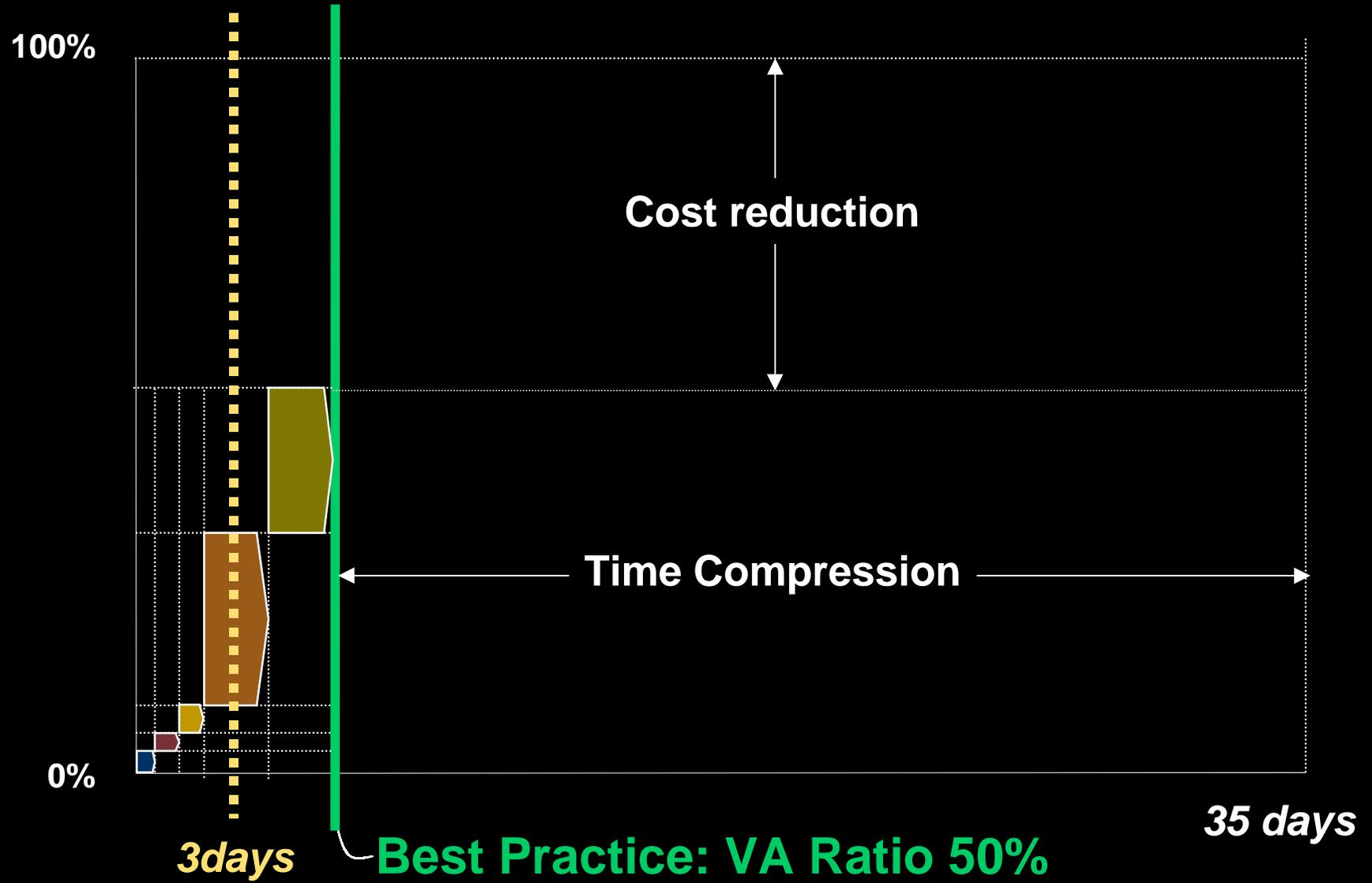


EXAMPLE: See It to Fix It - Value-Added Time Only 3 Days!



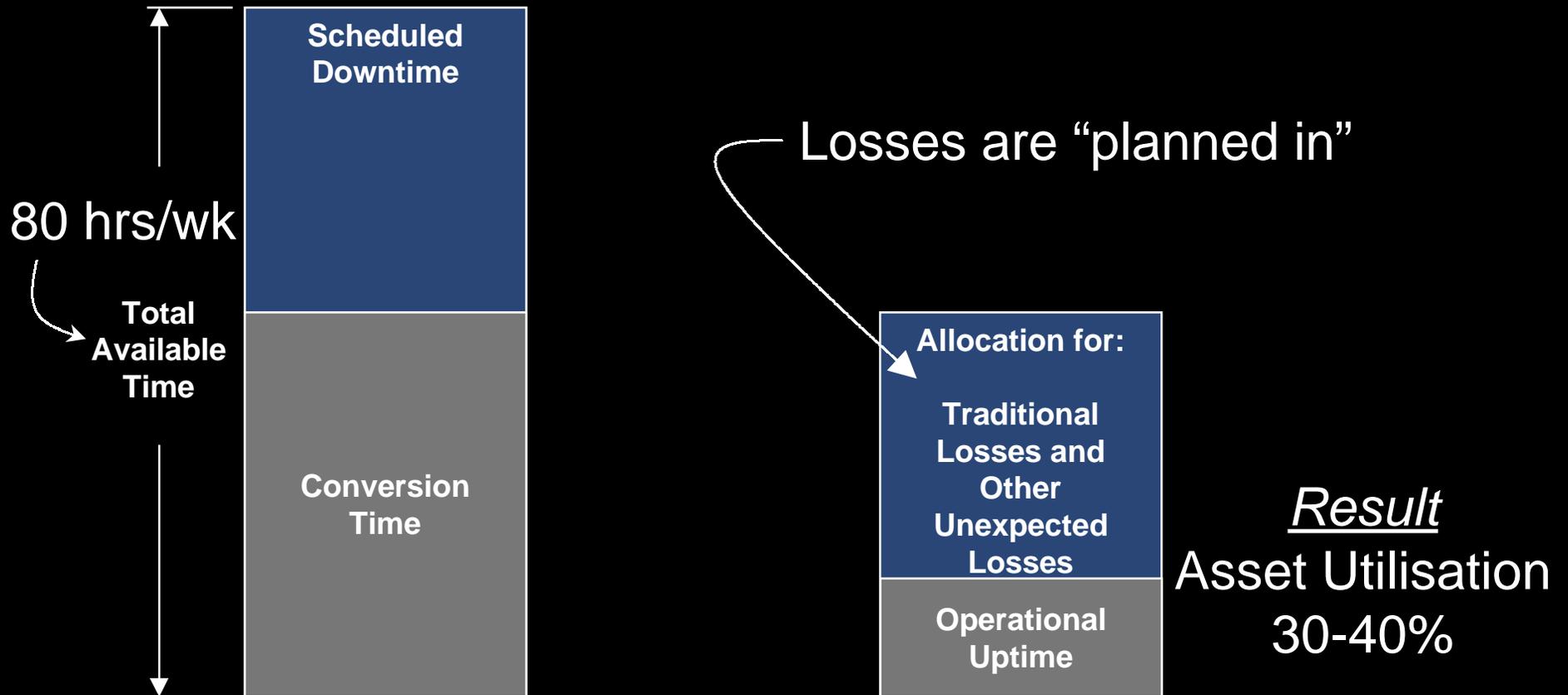


Measurement Shows Potential for Improvement



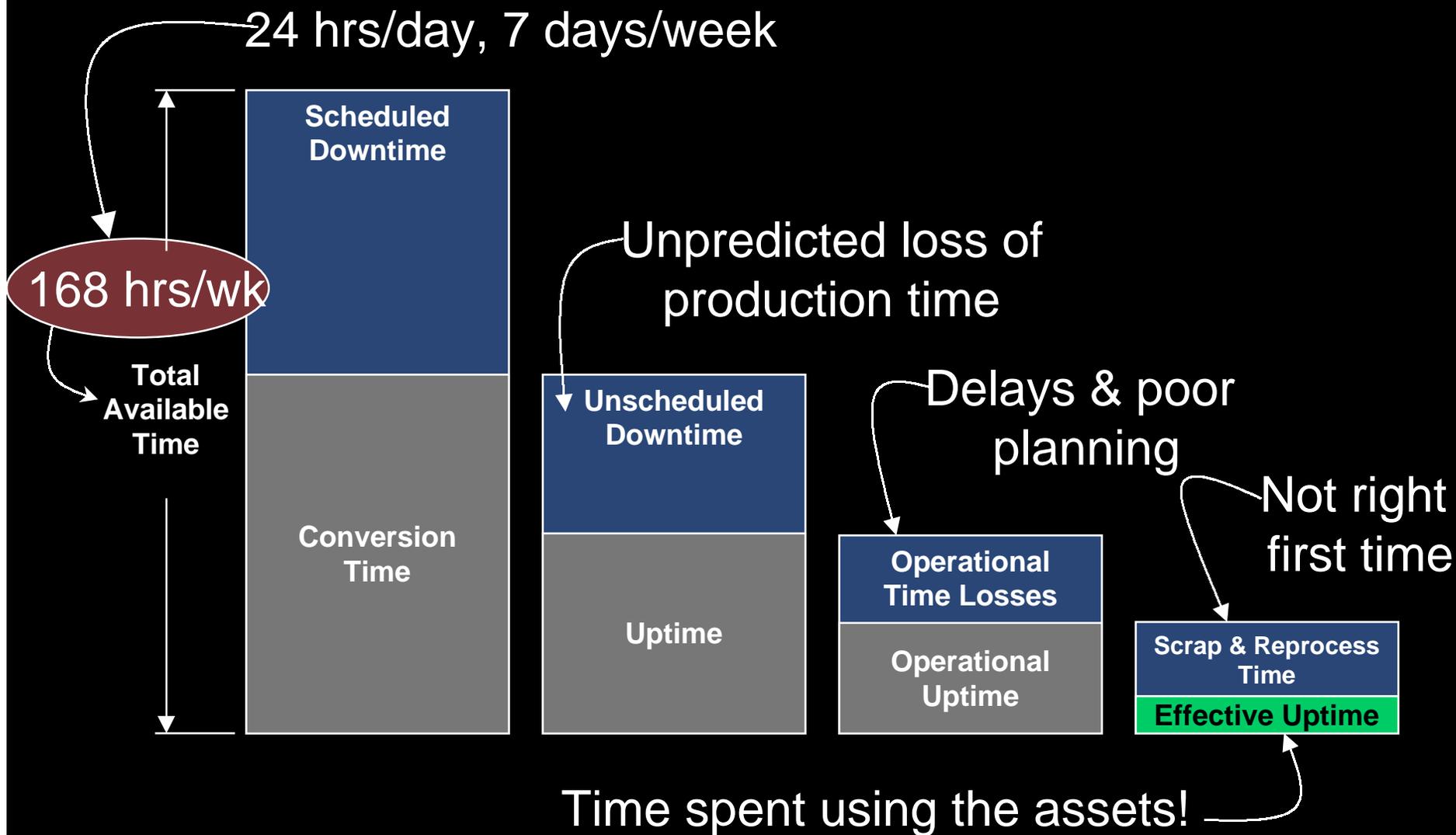


EXAMPLE: Traditional MRP II Measurement - For Accountants.





EXAMPLE: Measuring for Productivity - Reveals Potential





EXAMPLE: *Sigma* - Getting it Right First Time.

- Quantifies process ability to generate defect-free output.
- Allows comparison of any two processes.
- Higher sigma values indicate better processes.
- Should be the scientific basis for process transfer.

Pharma

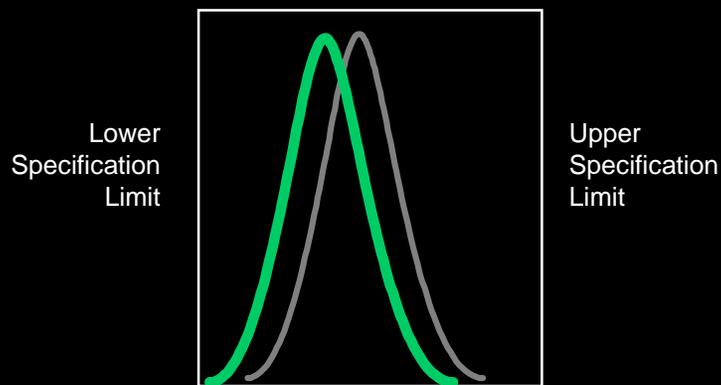
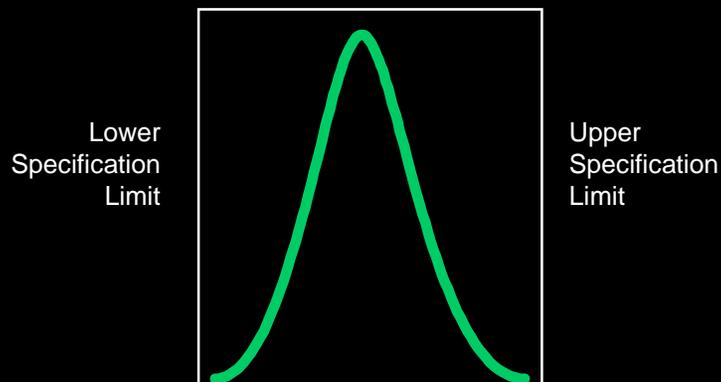
Semicon

Sigma	ppm Defects	Yield	Cost of Quality
2 σ	308,537	69.2%	25-35%
3 σ	66,807	93.3%	20-25%
4 σ	6,210	99.4%	12-18%
5 σ	233	99.98%	4-8%
6 σ	3.4	99.99966%	1-3%



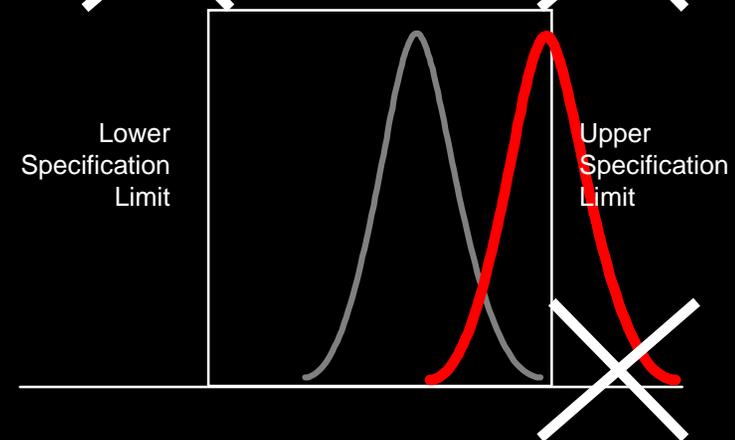
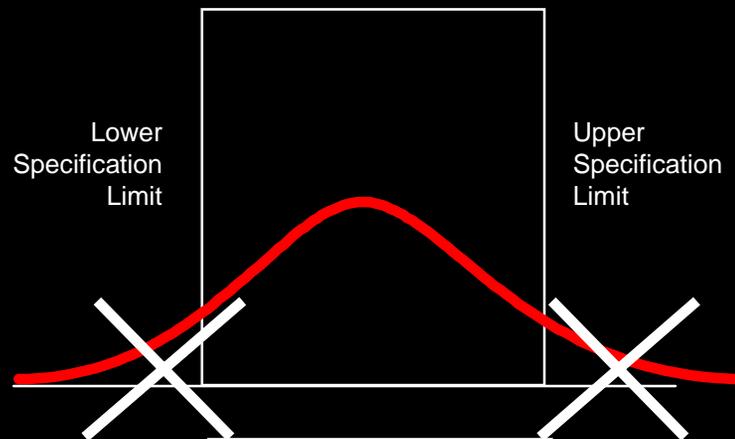
Measure Spread & Variability

GOOD: High Capability



This process is capable

BAD: Low Capability



This process is not capable



Calculating The Purely Business Benefits

Decrease by scrap reduction.

Reduce cost of compliance.
Eliminate non-value add activity.

$$\downarrow \text{Unit Cost} = \left(\frac{\text{Material Cost} + \text{Period Cost}}{\text{Efficiency} \times \text{Planned Volume}} \right) \downarrow$$

Increase by raising process yield.

Raise process capacity.

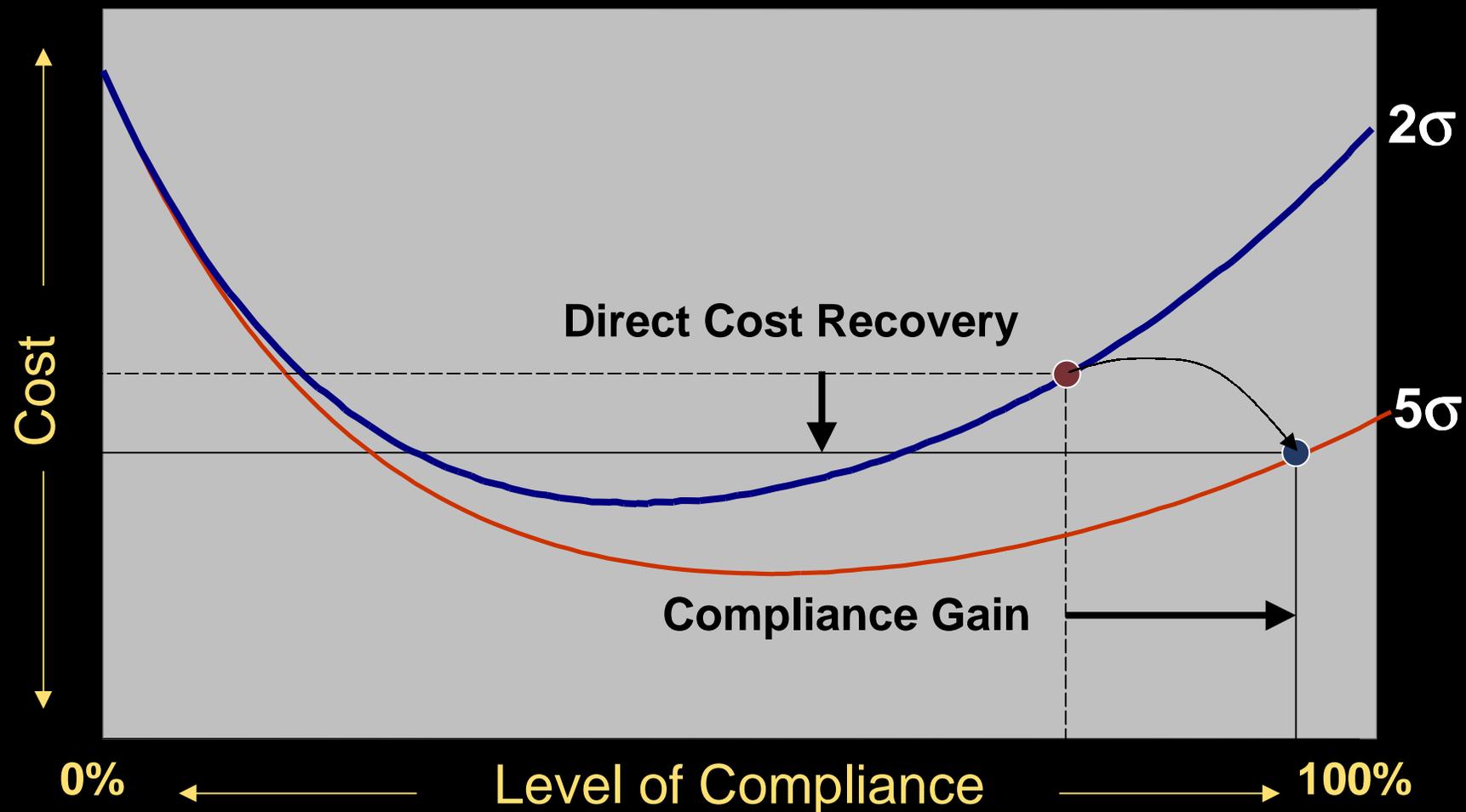


A Thought Experiment - 5 Sigma Pharmaceutical Production

- Cost of quality & compliance - 3% of period costs.
- Unit cost of production 60% lower than 2.5 sigma competition.
- Cycle time - 5 days (down from 30).
- Newly introduced processes immediately effective.
- Key enablers:
 - ◆ *Process understanding*
 - ◆ *Parametric profiling of production processes.*
 - ◆ *Process capability hurdle levels governing development promotion*
 - ◆ *NIR analysis for raw materials and in-process control.*
 - ◆ *Continuous high-volume microwave sterilization.*
 - ◆ *On-line measurement supported by sigma tools..*
 - ◆ *Enterprise Manufacturing Execution System with EBR capability.*
 - ◆ *Enterprise Document Management System, shared with R&D.*

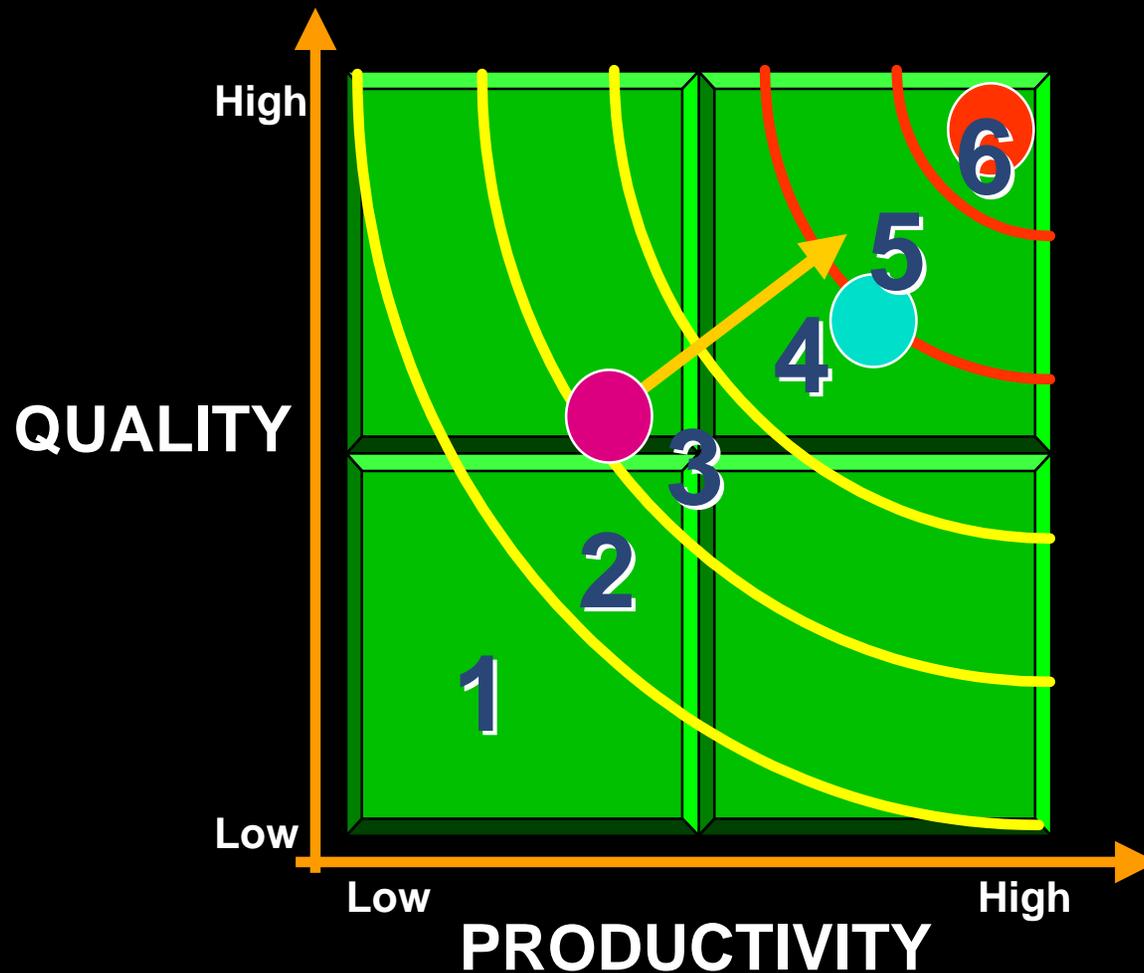


Benefits - Increased Effectiveness of Compliance Infrastructure





How this is a Win-Win



- 6 σ - World Class
- 5 σ - Superior
- 4 σ - Healthy
- 3 σ - Average
- 2 σ - Not Capable
- 1 σ - Not Competitive