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Pioneering science delivers vital medicines™

The Journey From Good to Great: Process Monitoring Leads to Improving Product Quality

2nd Annual FDA/PQRI Conference

Advancing Product Quality

October 6, 2015

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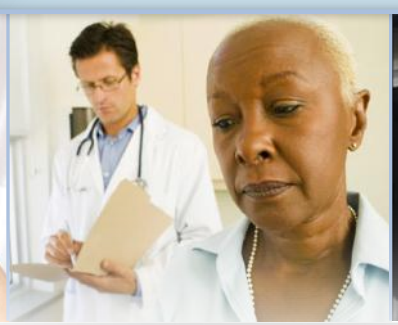
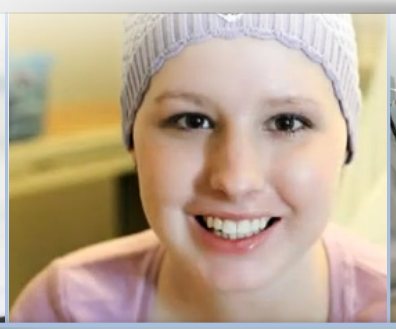


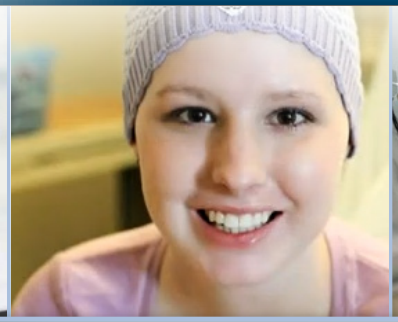
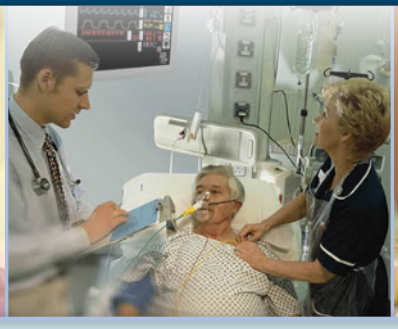

Serving Patients Is a Privilege…






This Privilege Comes with Significant Responsibilities

To Achieve World Class Quality

Mature
Quality Management System
“Quality Beyond Compliance”

Embracing Cultures of
Continuous Improvement
and Quality

Measuring, controlling
and Improving
process capability
6σ

Our Journey Started 10 Years Ago at a Management Review Meeting!

- **Leadership** decided to monitor manufacturing processes and product attributes using process capabilities
- **Leadership** focused on poor performing manufacturing processes and product attributes leading to improvements
- **Leadership** decided that any PpK less than 1.0 required a CAPA to drive continuous improvement

Leadership relentlessly follow-up on these CAPAs at each Management Review Meeting

Results Through 2010 Were Good

QMS

- Reduced Error Rates 90%
- Improved Product Quality
- Good Global Compliance Track Record

Culture

- 3000 trained in OE
- Scrap reduced 54%
- Disposition cycle time reduced 27%

Process Capability

- 65% of Manufacturing Process and Product Parameters were at 6σ Levels

But, to be Great….

Manufacturing processes and product quality must achieve 6 sigma performance!

A Six Sigma Capable Process is Expected to Have No More than 3.4 Defects per Million Opportunities

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Companies That Claim Six Sigma (σ) Capability

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What is Required to Achieve Six Sigma Quality

- Characterize Raw Materials, Manufacturing Processes and Products
- Identify, Tract, Control Variation
- Create Robust Manufacturing Process and Products
- Demand Flawless Execution
- Develop a Robust and Reliable Supply Chain

Now, let me take you through our journey…

Monitoring Process Capabilities, Management Review and Leadership Lead to Improvements

- First introduced Performance Boards
- Second introduction was “5S”
- The third technique introduced was Process Monitoring
- Then a comprehensive Operational Excellence Program was Introduced
- Op Ex was enhanced with Purposeful Presence on the Floor
- The next innovation was Defense-in-Depth
- And there were and will be more enhancements on our journey

“Rome was not built in a day”
It is a journey that requires dedication, effort and persistence

Combining SPC with Process Capability Monitoring Improves Reliability of Supply

- **Apply Statistical Process Control Charts**
  - ✓ In-process & specification parameters
  - ✓ Process performance parameters
  - ✓ Analytical Method Performance
  - ✓ Identify statistically abnormal results
- **Apply Process Capability Index**
  - ✓ In-process & specification parameters
  - ✓ Apply actual process capability index (Ppk)
  - ✓ Identify parameters that are performing poorly compared to specifications or filed limits

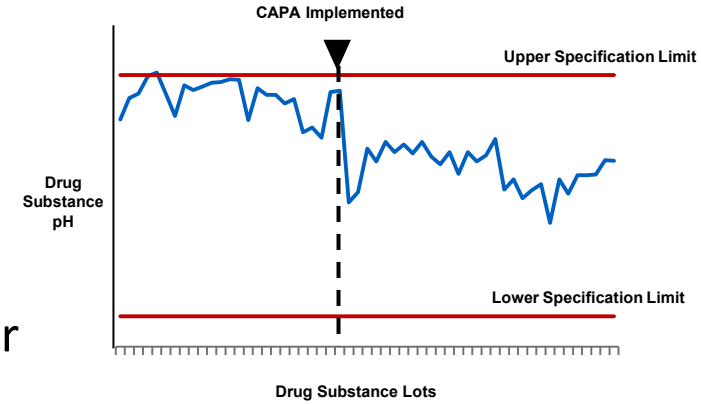
Case 1: Process pH at Upper Specification Limit

- **Opportunity:** pH of a particular Drug Substance was historically trending high with the result closer to the upper specification limit.

- Process monitoring required Amgen to open a CAPA and investigate to determine root cause and implement corrective actions

Improving Performance Increased Reliability

- Process Capability increased from a Ppk of 0.4 to 1.5 (Six Sigma) - decreasing the chance of an OOS from 12% to 0.0007%
  - ✓Eliminated potential loss of a batch
  - ✓Eliminated 3 trend investigations and associated costs
  - ✓Assured more robust product quality over shelf life
  - ✓Assured more reliable supply
  - ✓Drove approval eliminating the Drug Substance pH test in favor of existing buffer pH testing upstream



Less Capable **More Capable**

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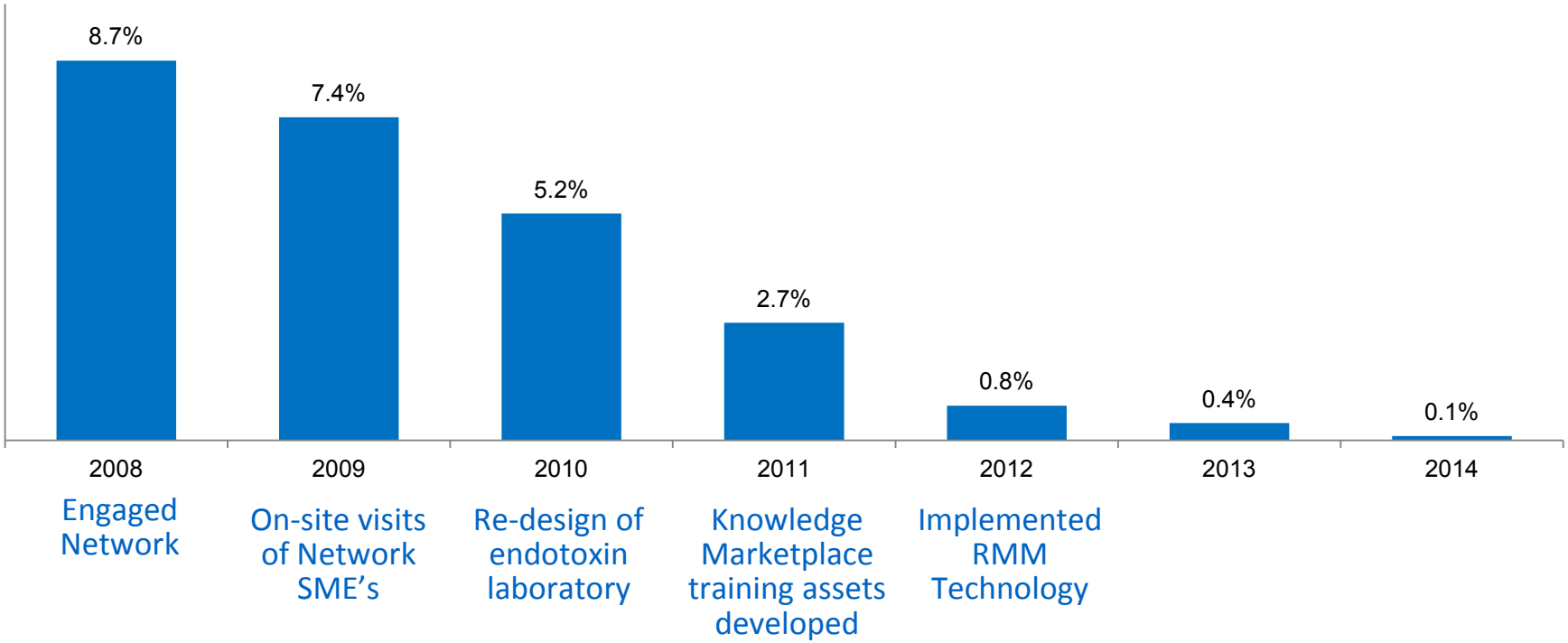
Case Study 2: By Setting Capability Targets for Assays, Required Improving Robustness

- Apply Industry benchmarks to assay invalid rates
- Review assay performance at Management Review
- Prioritize remediation efforts
- Root cause identified
  - ✓ Method
  - ✓ Equipment
  - ✓ Materials
  - ✓ Procedure
  - ✓ Personnel
- Track effectiveness at Management Review

Use of Network Expertise to Reduce Laboratory Invalids

2013 Invalid Target for Bacterial Endotoxin Testing (BET) = 0.5%
Reduced invalids 8.3% over 5 years to exceed the goal



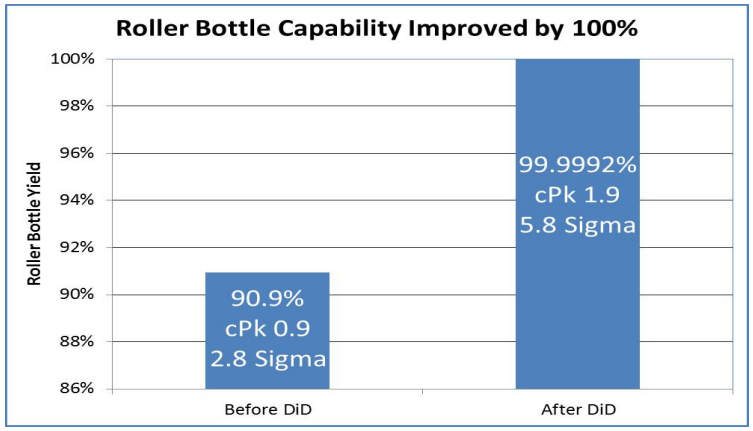
Case 3: Roller Bottle Defense in Depth Implementation

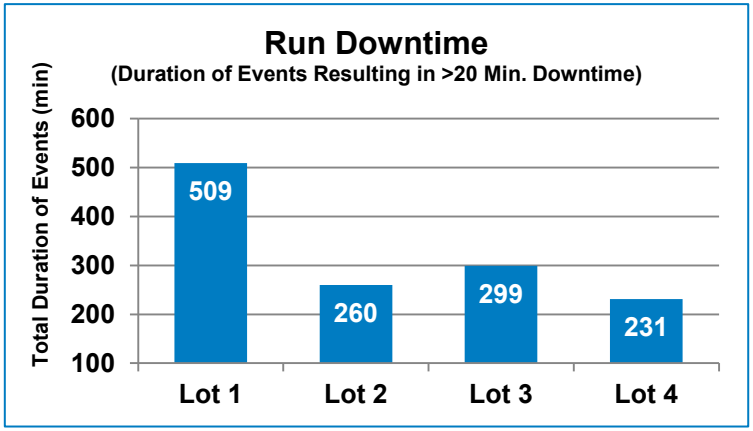
- **Opportunity:** Percentage of roller bottles lost for quality defects was 10% per batch
- Provided ~ 200 improvement recommendations, including:
  - ✓ Improved Design of Process
  - ✓ Improved Reliability of Equipment
  - ✓ Improved equipment maintenance
  - ✓ Focus operator training on critical tasks

DiD is an investment that requires significant investment retrospectively but less if done prospectively

Defense in Depth Delivered Better than Expected Results

- Only 7 roller bottles lost every 1,000,000 processed
- 40% reduction in downtime events
- Saved $1M per lot
- Implemented robust maintenance plans
- Increased staff knowledge and proficiency





Less Capable

More Capable

Case 4: Lyophilizer Defense in Depth Implementation

- **Opportunity:** Average loss of three lyo lots/year and significant non-conformance events.

- **Provided ~ 300 improvement recommendations, including:**
  - ✓ Opportunities to strengthen Steam in Place and Clean in Place methods
  - ✓ Closure of maintenance gaps identified during FMEA (e.g., vacuum pumps)
  - ✓ Pre-flight checks to reduce risk of failure during production
  - ✓ Identification of critical steps in SOPs

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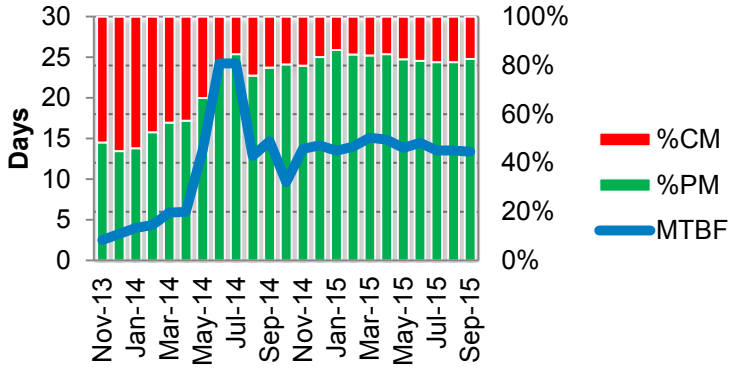
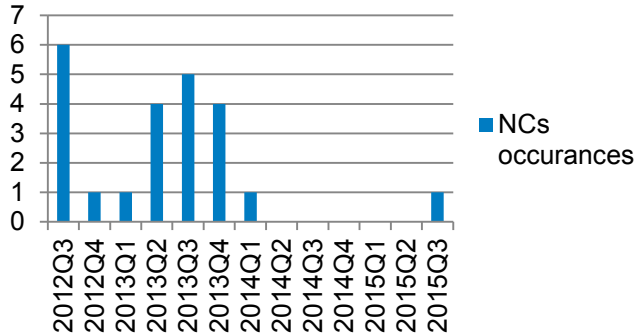
PM2 Lyo Performance
Current Maintenance and Operational Performance

Lyo Metrics	Baseline (Pre - DiD)	Target	Aspirational Stretch	Performance Sept 2015
Mean Time Between Failure	6.5 Days	10 Days	15 Days	13.4 Days
CM:PM Ratio (%)	63:37	40:60	30:70	17:83
Success Rate - # Lyo Related Rejected Batches	3 Per Year	Zero	Zero	Zero
NC's - # Lyo Related Class 2/3 NC's	14 in 2013	25% Reduction	50% Reduction	2 - 86% Reduction
Lyo Cycle Success Rate	88%	95%	98%	99%

Performance to Date



Non-Conformances

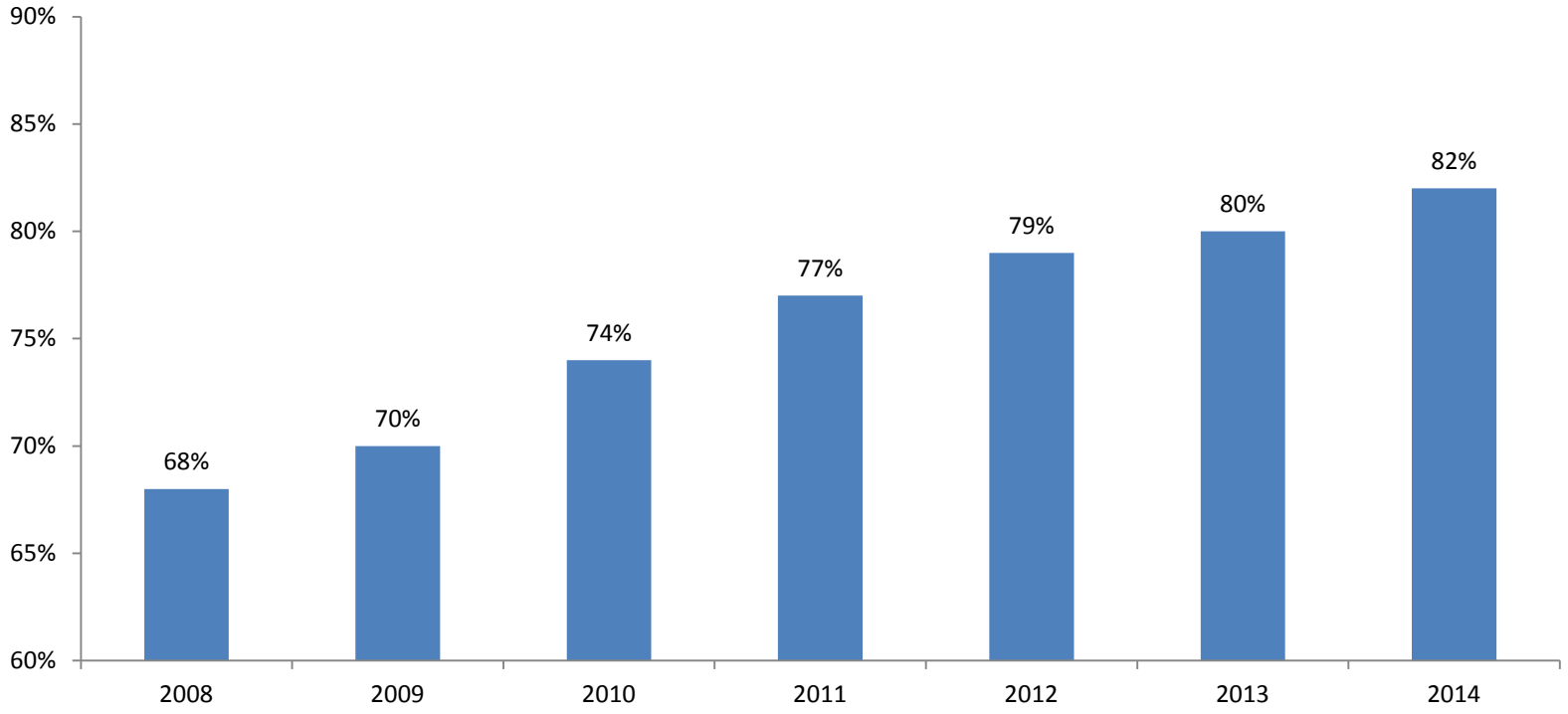


Less Capable

More Capable

Growing 6σ Capability

Since 2007, The Actual Number of Parameters Achieving 6 Sigma has Doubled



At the end of 2014,

- ***82% of the parameters were performing at a 6σ level***
- ***14% of the parameters were performing between 3σ and 6σ levels***
- ***4% of the parameters had CAPA's open to improve performance***

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We Are Also Driving Six Sigma Performance by Applying A Number of Operational Excellence Methods that Directly Reduce Error Rates

Applying “Lean” and “5S” Practices in the Lab
(Sort, Systematic, Shine, Standardize and Sustain)

A place for everything, everything in its place

Less Capable

More Capable

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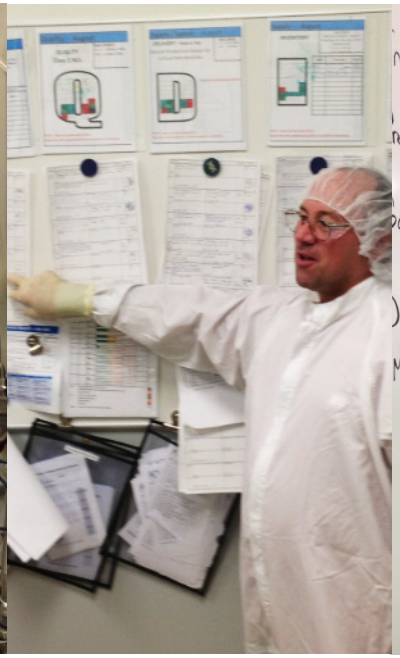
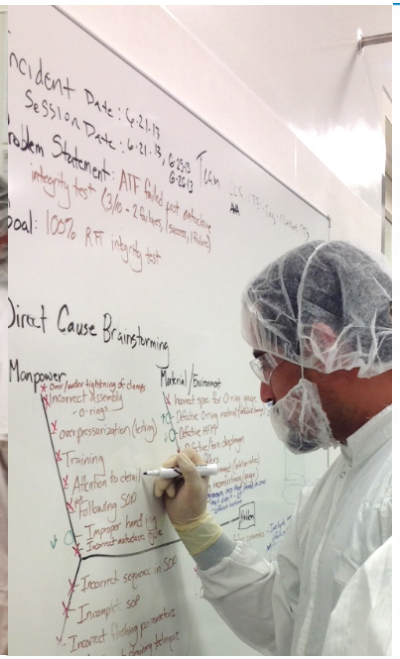
Applying Operational Excellence On the Floor

Visual Management

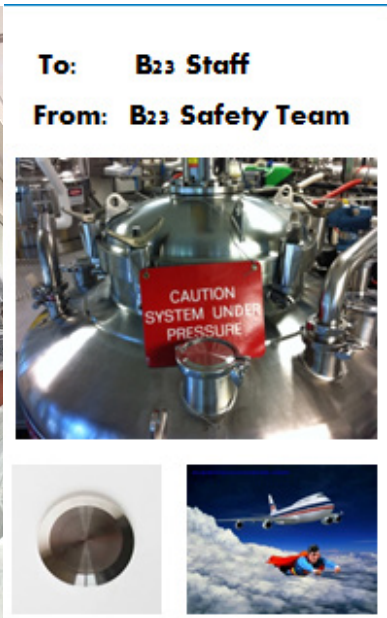
Purposeful Presence



Work Center Teams



Problem Solving



Learning Groups

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And, Other Methods the US Nuclear Navy Used to Implement an Ideal QMS

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This Journey Will Never End…

Mature Quality Management System “Quality Beyond Compliance”	Embracing Cultures of Continuous Improvement and Quality	Measuring, controlling and Improving process capability 6σ

Leadership and hard work has produced results…

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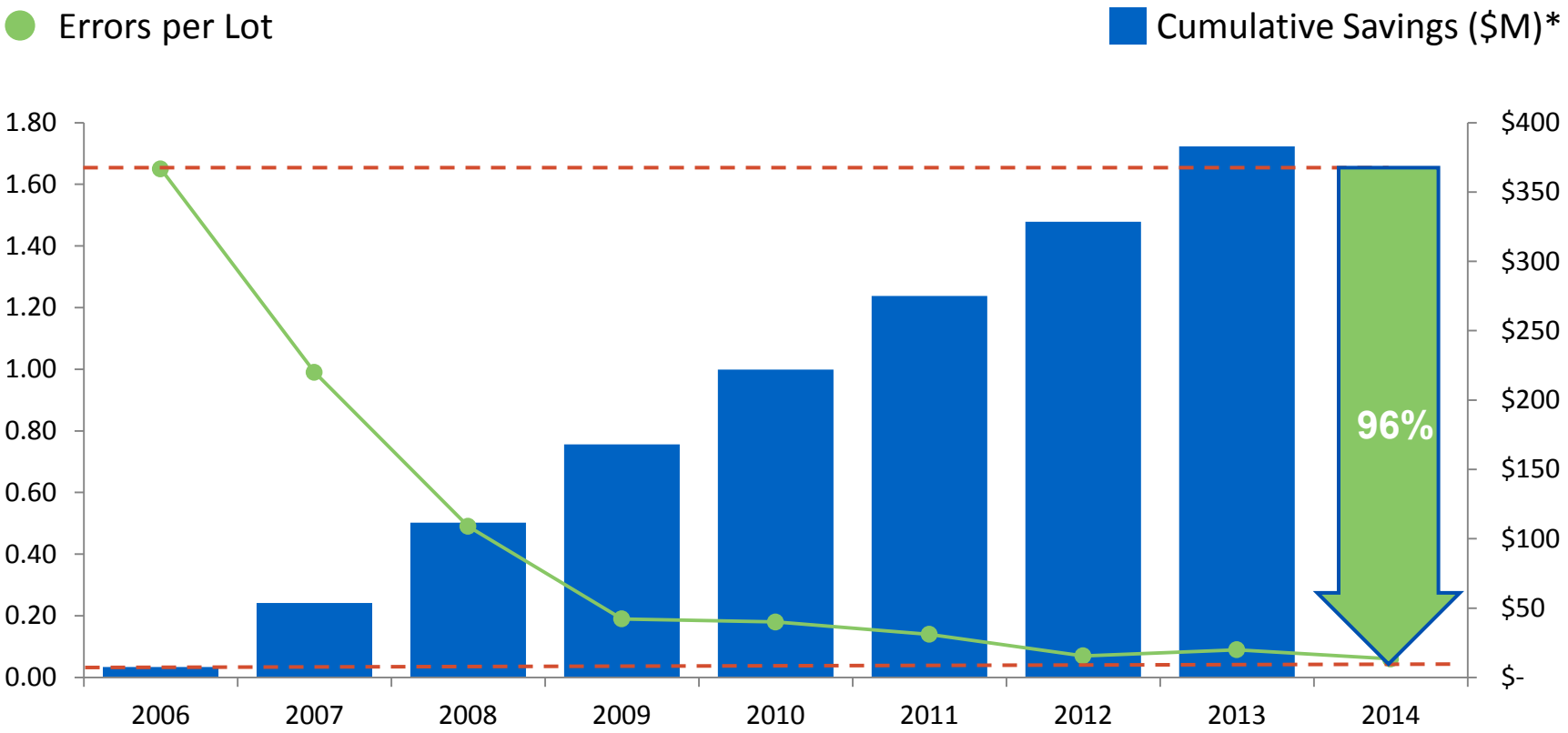
When You Succeed – The Power of Error Reduction



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More Capable

* Computed using 2014 avg wt NC costs:
C1 $560; C2 $6,700; C3 $86,000

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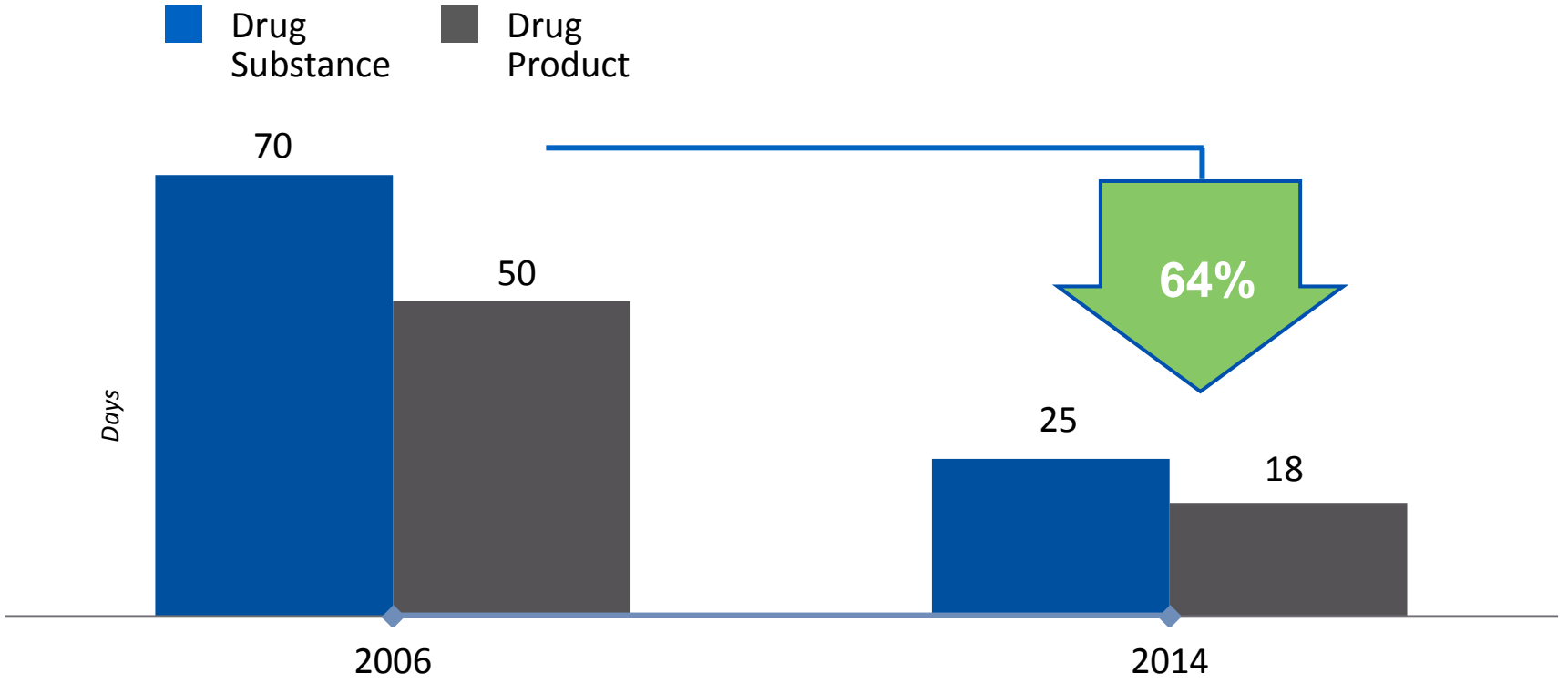
When You Succeed – Faster Cycle Times



Less Capable

More Capable

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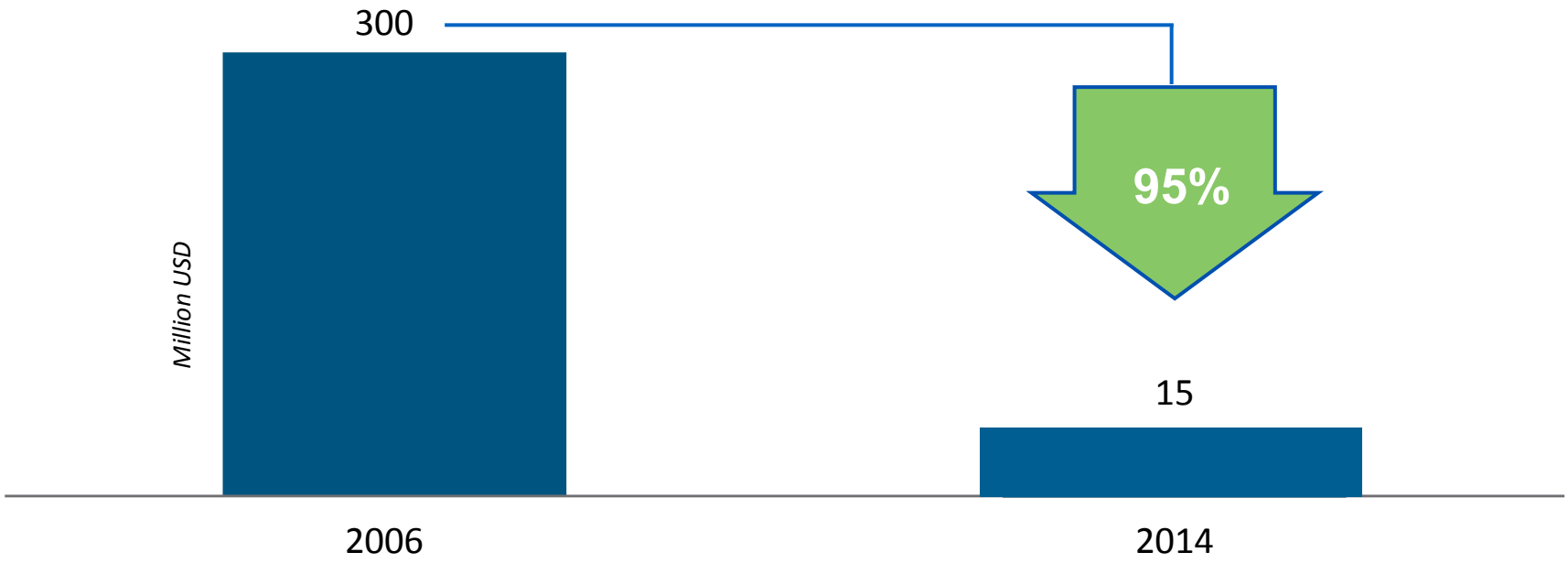
When You Succeed - Reduced Scrap



Less Capable

More Capable

The Effort has a Positive Business Impact

But Most Importantly Our Efforts
Enable Us to Serving Every Patient, Every Time


Thank
You
Merci
Gracias
Danke
Spacibo
Arigatò
Hvala
KamSahHamnida
Xièxie
Mèsi
Grazie
Takk
aDank
Buznyg
ThintKo
Blagodaram
Rahmat
TerimaKasih
Dakujem
Taiku
Mercé
Malondo
Gràcies
Faleminderit
Efharisto
NäjisTuke
Grandmercé
Tanemirt
Tenki
Aabhar
BarakAllahuFiik
Dziakuju
Kiitos
Chokrane
Mauruuru
GratiasAgimus
Barkal
Ačiū
Dankie
Tak
TänanVäga
Chnorakaloutioun
Gratzias
GratiasAgo
Gracie
KopKhunKha
Sagolun
Motashakkeram
CámOn
Multumesc
Saha
Salamat
Obrigado
Bayarlalaa
Nirringrazzjak
Takk
Murakoze
Köszönöm
TapadhLeat
WaadMahadsantahay
Grazzi