CMC Activities for Commercialization: PAI, QMS, and BLA/NDA

"Advancing from Clinical to Commercial – The Commercialization Roadmap"

NEPDA Dinner Meeting
Cambridge, MA
16 May 2018

Learning objectives

1- ***Q(M)S***

2- ***BLA/NDA***

3- ***PAI***

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QUALITY (MANAGEMENT) SYSTEM

The Future of QS/Manufacturing, Data Integrity and Automation

- Biogen's new Swiss Luterbach facility (144,000 L)
  - "Manufacturing 4.0"
  - Seamless integration of data from production floor, to QC, to QA
  - Automation and data closely tied to quality system (QS)
  - Exceptions automatically generate an investigation that starts immediately
  - Lots released by exception
  - Real time release
    - PAT- Process Analytic Technology
  - All of the above significantly reduces COGS
    - Less labor
    - Fewer deviations and investigations
    - Low capital in inventory

"4.0"

Interoperability: Connect and communicate
Information transparency: Aggregation of raw sensor data to higher-value context information.
Technical assistance: Comprehensible information for making informed decisions and solving urgent problems on short notice. Conducting a range of tasks that are unpleasant, too time consuming, for their human co-workers.
Decentralized decisions: Only in the case of exceptions, interferences, or conflicting goals, are tasks delegated to a higher level.

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BIOGEN understands cost drivers and COGS

- Deviations are very expensive
  - Costly to investigate and approve
  - Lost or delayed batches (inventory)
  - Few if any data integrity issues
  - Regulatory sanctions
- Luterbach system greatly reduces number of deviations
  - Human error
  - Monitoring and trending
  - System automatically generates event in QS
    - QA ‘on the floor’ immediately
- Quality system is highly efficient
  - Release by exception greatly reduces human effort
  - No paper chase/mix-up and lost records
- PAT reduces QC effort significantly

Importance of data integrity

- Summarized by the acronym ALCOA Plus
  - **A**ttributable
  - **L**egible
  - **C**ontemporaneous
  - **O**riginal
  - **A**ccurate

  Plus
    - Complete
    - Consistent
    - Enduring
    - Available
- Needed to ensure compliance, quality, and patient safety

"For the purposes of this guidance, data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)." **FDA Data Integrity Guidance 2016**

"Systems and processes should be designed in a way that facilitates compliance with the principles of data integrity." **MHRA Data Integrity Guidance 2018**

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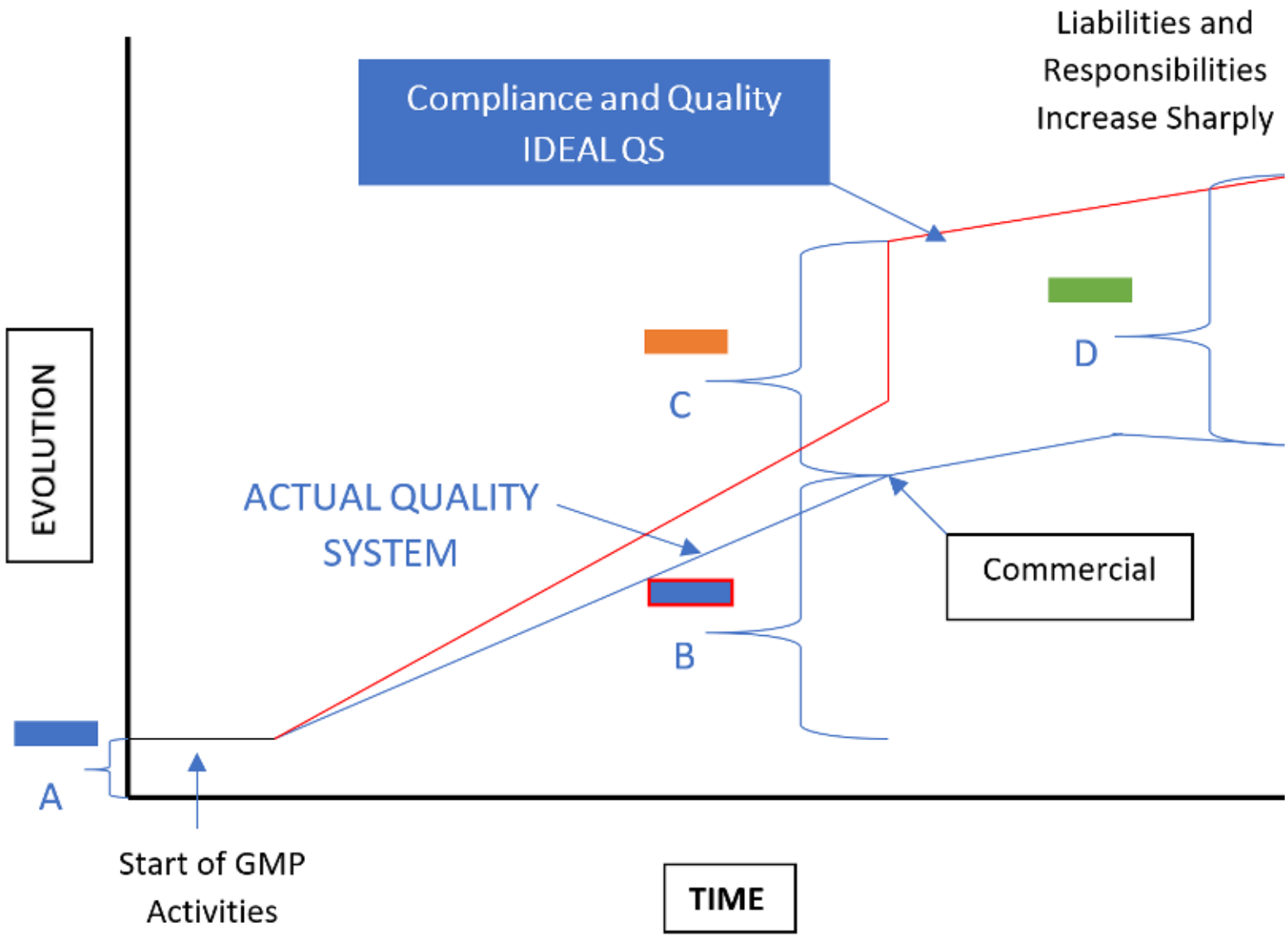
Lifecycle Gaps and Evolution of Quality System



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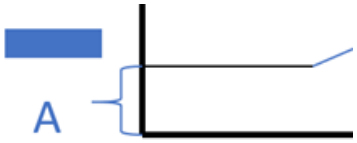
Quality System (QS) at Start of GMP



- Activities:
  - Just starting to work with CMOs; first audits; analytical development; stability
  - Phase 1, 2a
- Needed before GMP production,
  - but needs to support critical activities, e.g., sterility validation
- Very simple quality system
- Small number of people touching system
- Simple procedures
- Almost always paper based
- Needs to be flexible:
  - process changes, in-process control tweaks, specification changes, stability studies needed, analytical methods changes
- Company culture and too much “big pharma” mentality can overburden system and pull resources from critical areas
- KISS

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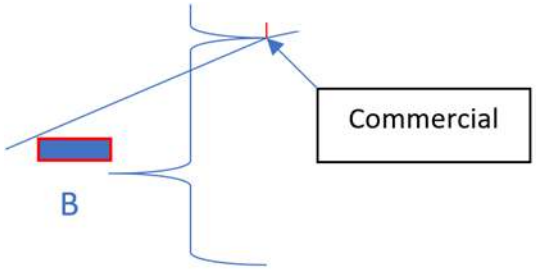
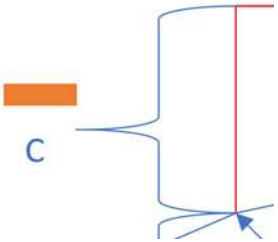
QS Evolution to Start of Commercial



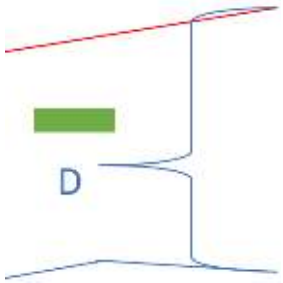
- Activities
  - Process knowledge greatly expanded
  - Process and methods were validated
  - Phase 2b, 3
- System has become significantly more complex
- Change controls tighter; less flexible
- Tens or hundreds of people touching system
- More complex procedures
- Electronic systems often added
- Little attention to optimizing and making efficient
- Time before commercial is critical transition period for QS to mature

QS Gap Between Actual and Ideal at Commercial Launch



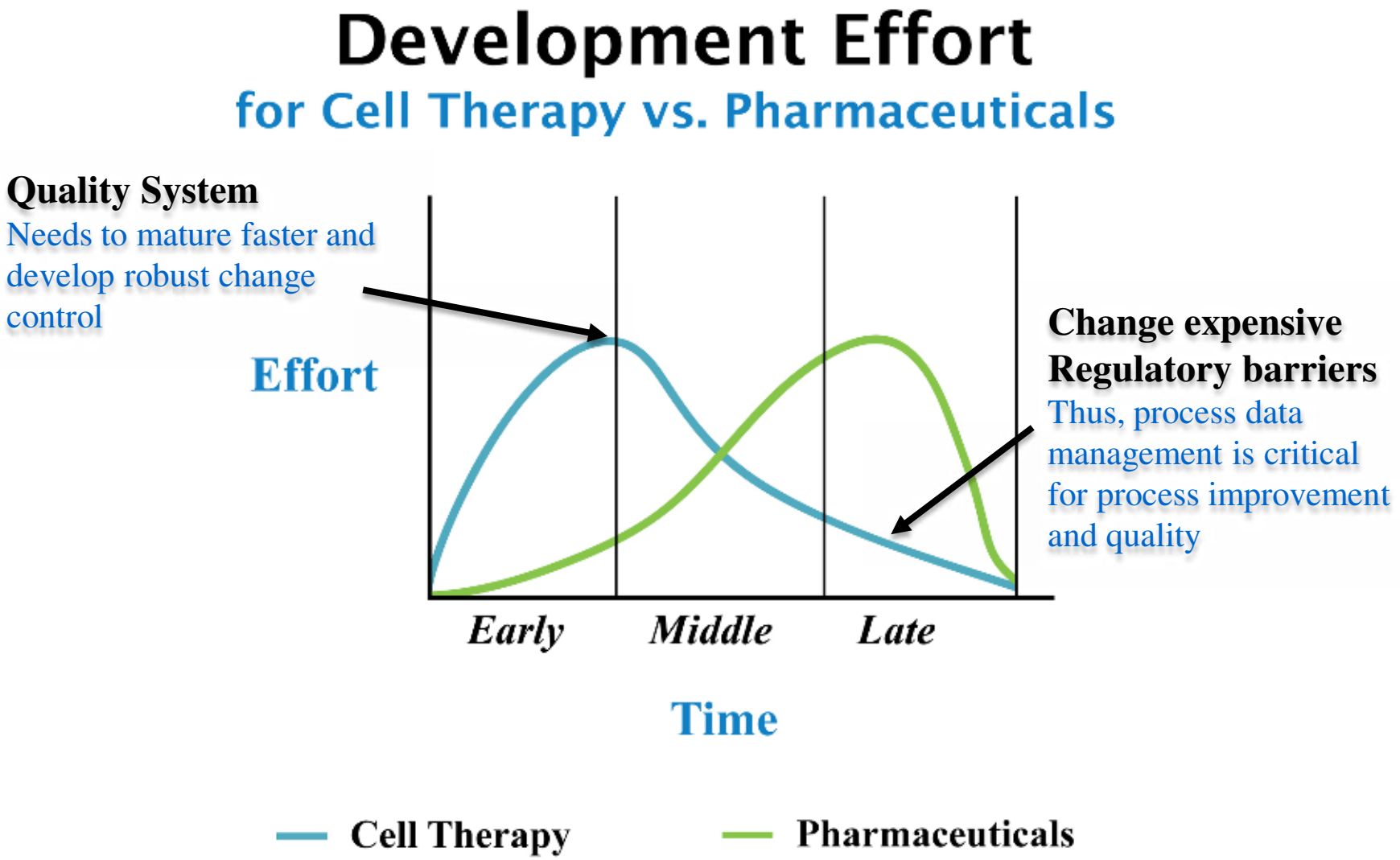
- Commercial responsibilities represent a step change, e.g.,
  - Product Recall System
  - Complaints
  - Reporting requirements to Authorities
- QS has not evolved fast enough
- Elements are not functioning efficiently
- Resources have gone to other priorities
- Data/metrics on performance of system inadequate
- Organization has “other” priorities
- Management doesn’t understand gaps and requirements, doesn’t want to spend money

QS Gap Between Actual and Ideal Later in Lifecycle



- Organizational demands and complexity grows
- QS becomes too complex
- Performance of the system becoming inefficient
- Poor design perpetuates amplifies problems
- Problems and system becomes too large and expensive to fix
- Metrics difficult to develop

Development Cycle for Cell Therapy Products



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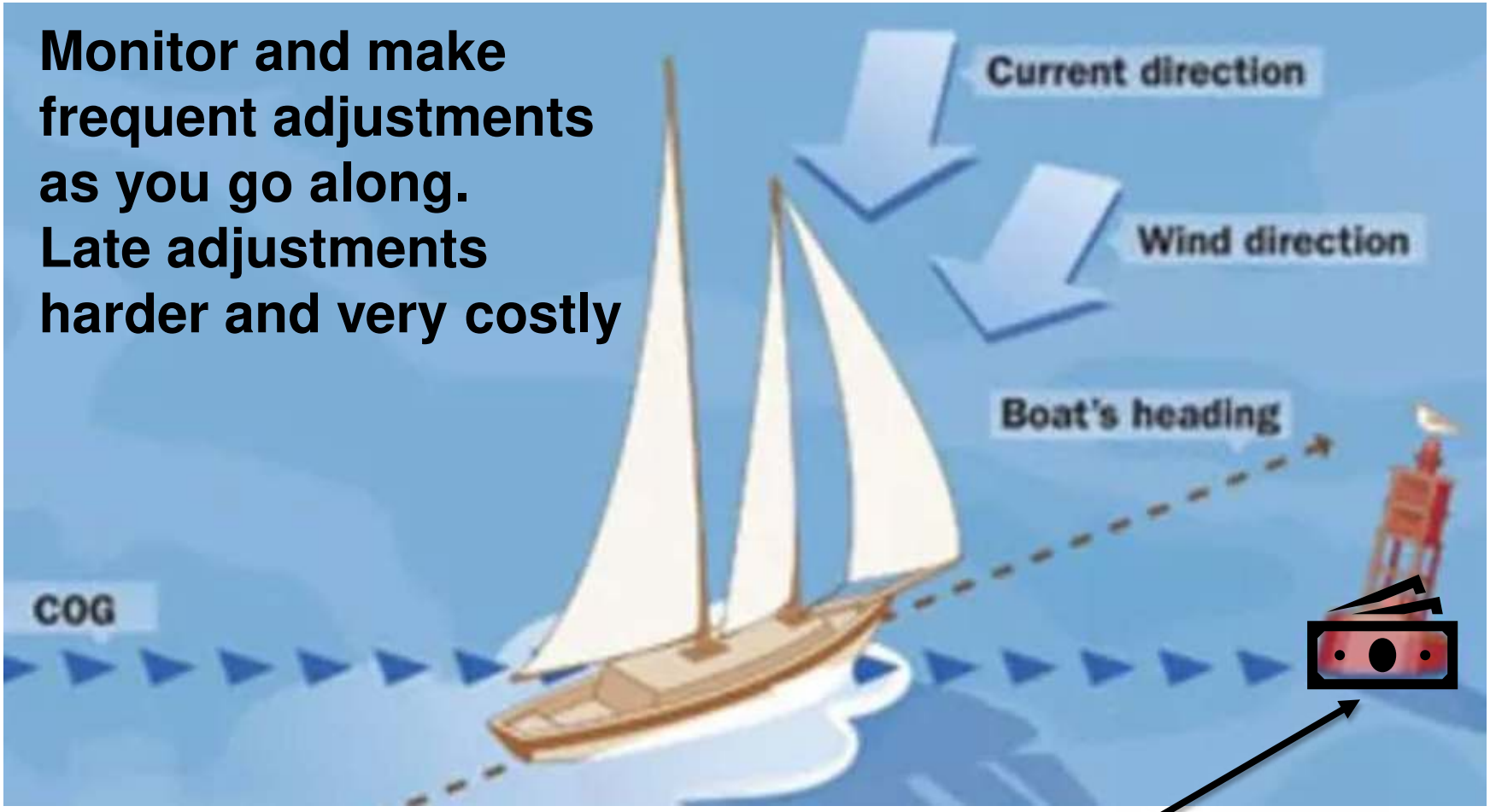
Pay Attention and Make Adjustment to QS As You Go Along or You Could Owe Government for Damages



Government Property/ Consent Decree

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AMGEN Continuous Improvement Journey

2006	• Instituted Risk-Based Classification System and Class 1 Nonconformance Quick Close Process
2007	• Improved Trending of Nonconformances
2008	• Improved Management Review • Developed Network Metric Control Plans
2010	• Standardized Root Cause Analysis
2011	• Developed Technical Writing Course for Investigators • Involved Quality Sciences in Investigations
2012	• Initiated Investigator Mentoring, Qualification & Certification Program

"Conducting Effective Science-Based Investigations", Jill Peirick, ISPE 2014

Investigations Perennially Top Regulatory Compliance Issues

Top 5 Deficiencies

- 211.22 (d) – Responsibility of Quality Control Unit
- **211.192 – Production Record Review (Investigation of Deviations)**
- 211.100 (b) – Written procedures; deviations
- 211.100 (a) – Written procedures; deviations
- 211.110 (a) – Sampling and testing of in-process materials and drug products

Data Source: Turbo EIR: January 2010 to February 17, 2011

Top 5 Deficiencies

- **Investigations**
- Change Control
- **CAPA**
- Complaints & Recalls
- Quality Management

Data Source: MHRA Presentation title: April 2011 to March 2012 Deficiency Data Review

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AMGEN's Multifaceted Approach to Investigation Improvement

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Amgen Business Case- Quality is Free

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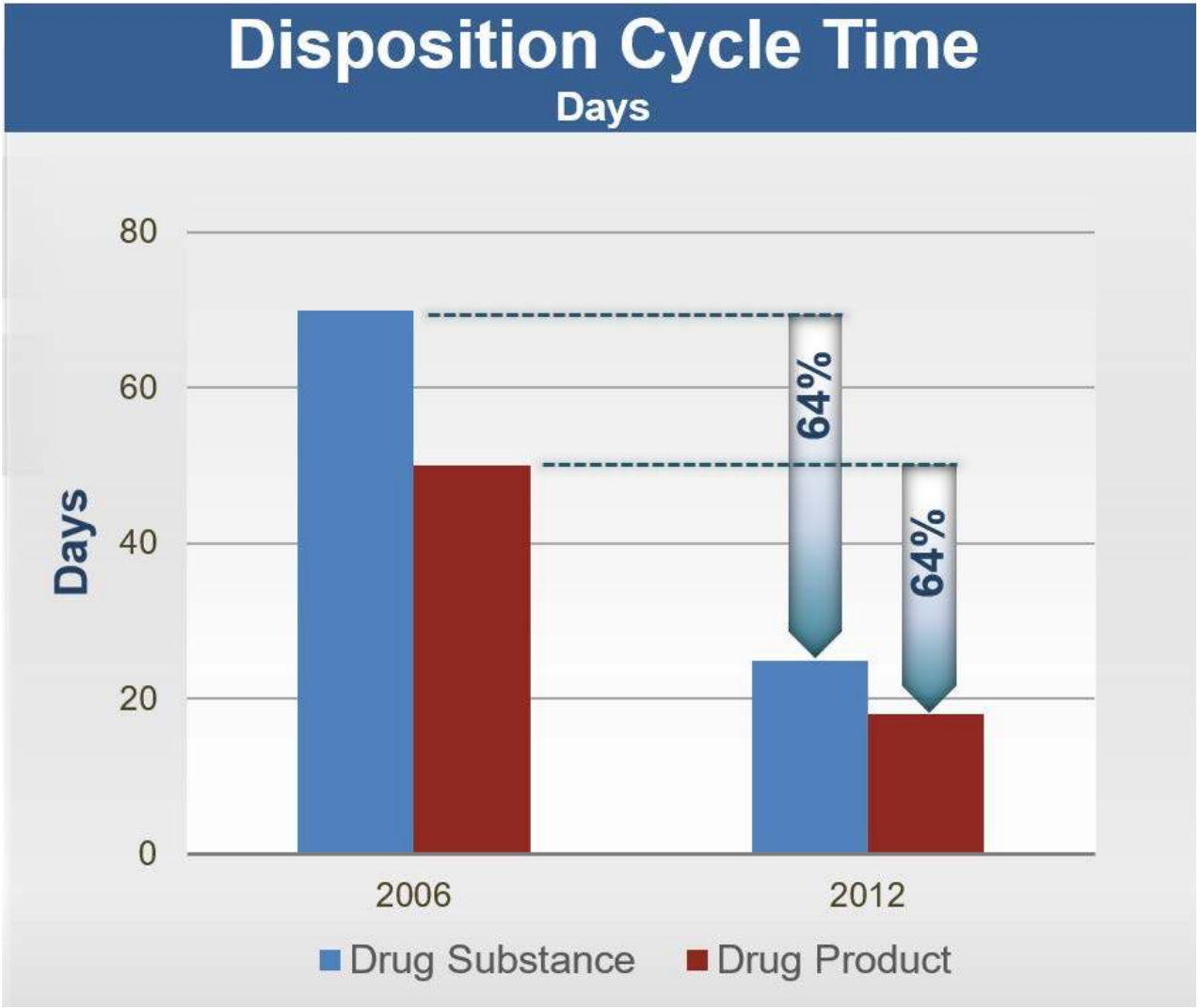
AMGEN Cycle Time- Almost 2/3 Reduction



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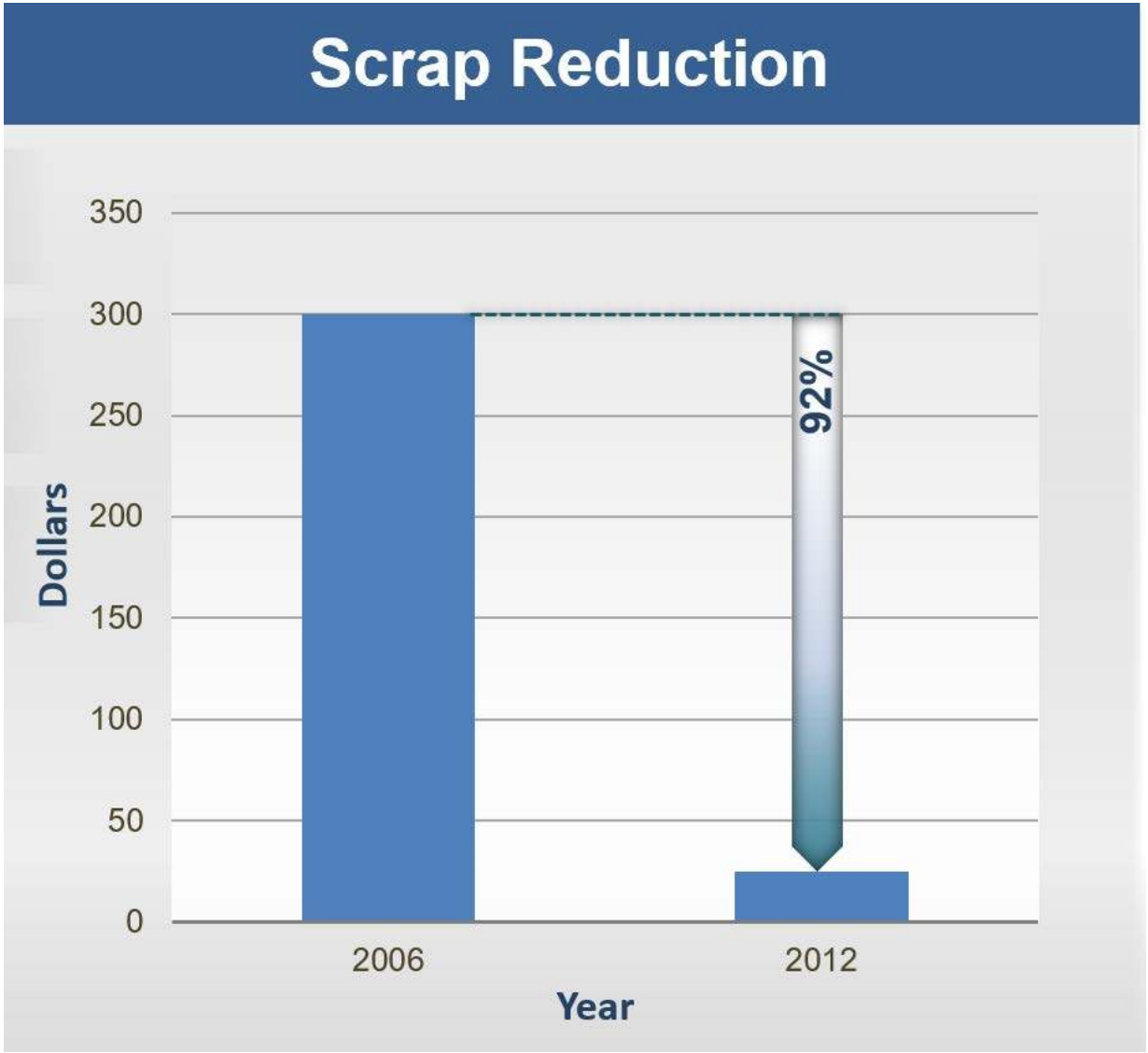
AMGEN Scrap Reduction- 92%



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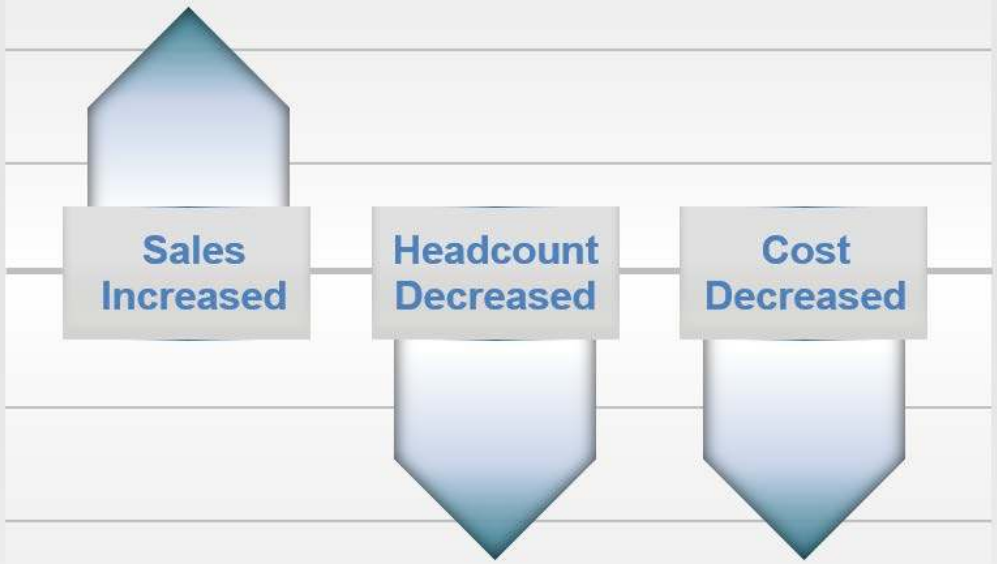
AMGEN Business Performance

This All Happened While:



And we supplied every patient, every time

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CGMPs and Lean Can Work Synergistically

KISS!

Use Lean to Keep Operations and Quality System Simple and Effective

Guiding Principles:

- ❑Standard work
- ❑Clear relationships and communications
- ❑Simple flow
- ❑Scientific method
  - ❑Risk Based
  - ❑PAT

Lean manufacturing practice in a cGMP environment, D. O'Rourke, A. Greene; Oct 01, 2006

Table 2 A comparison of lean and GMP manufacturing.

Area	cGMP	Lean manufacturing
Objectives	· Ensure product effectiveness · Prevent harm	· Reduce waste · Create value
Focus	· Product development, manufacturing and quality assurance	· Value stream
Approach to manufacturing	· Quality first	· Quality balanced with productivity
Improvement	· Regulated and prudent	· Continuous and simultaneous
Typical goals	· Follow validated process · Prevent deviation	· Reduce cost · Improve quality · Decrease cycle time · Reduce inventory · Improve delivery
Typical tools	· Documentation · Personnel qualifications and training · Cleanliness · Validation and qualification · Complaint review · Audits	· Value stream mapping · Kaizen improvement · Error proofing · Moving to pull · Simple flow · Training · Quality function deployment

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Quality Drives Compliance

COMPLIANCE ≠ QUALITY

QUALITY = COMPLIANCE

Quality System- Guidance for Development Companies

- Begin with end in mind
- Monitor system performance
  - Develop metrics
- Grow system to meet needs, but keep phase appropriate
  - …but do so thoughtfully and by keeping it as simple as you can
- Develop a roadmap during early pivotal trials for advancing system for commercial responsibilities- THIS IS A CRITICAL PERIOD
- Use roadmap to run as hard as you can to develop a QS of excellence
- Integrate with partner with CMOs for quality and communications
  - Don't accept substandard investigations and change controls
- Staff adequately and don't give them broken systems

Two examples:

1. Deviation Investigations- AMGEN learnings can guide approach for smaller companies
2. Change Control- Clear communications and work flows that are science and risk based

- Be a learning organization- "Get it right the second time in order to get it right the first time"
- Develop good documentation/archiving practices, starting early stage

FDA Guidance on Specifications for PDFs

PORTABLE DOCUMENT FORMAT (PDF) SPECIFICATIONS

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

For questions regarding this technical specifications document, contact CDER at esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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BLA/NDA

Guiding Principles and Thoughts

- Begin with the end in mind
  - What is target filing date?
  - Set initial completion of CMC sections well before filing date
    - Drive to this but keep flexibility to fall back
- Form teams around SME experts
- Identify and assemble your eCTD team early (internal and external)
- Ensure you have internal/external experts highly experienced in filings (writing/eCTD)
- Need one or two outstanding project managers
  - Develop project plan around CTD. Show dates and status and risks
  - Weekly team calls
- Assign senior executive to break logjams and make decisions
- Staff adequately for preparation and ability to support ongoing operations

- Perform gap analysis early of information needed to:
  1. Write dossier
  2. Include in dossier (KISS- only include what is necessary)
  3. Are PDFs rendered and meet Agency requirements?
     1. FDA guidance- adopt as policy early in lifecycle
- Two writing models
  - Internal experts supplemented by external resources
  - External experts supplemented by internal resources
  - Use standardized templates
    - CMC experts should focus on writing and not formatting
- Communicate very early with external partners, e.g. CMOs, CROs
  - Responsibilities, expectations, deliverables, timelines
  - Manage them and make part of project plan and communications
- Communicate, Communicate, Communicate!!!!!
- Establishing good documentation practices early as a development company will pay many, many dividends later

PAI

Guiding Principles and Thoughts

- PAI picks up where NDA/BLA leaves off…
  - Information and issues not in CMC filing are inspection targets
  - e.g., investigations/OOSs, CAPAs, Change Control, EM, equipment/facility qualification and validation, process validation, SOPs. Training
  - Although, information in filing will be verified
- Product centric, but CGMP system is also a target
  - That QS is not a target is a common misconception
- "Ready for Inspection" at time of submission
  - Indicate on 356h form, if not ready, then when
- Always pre-announced, based on manufacturing schedule
  - Schedule provided in a communication at time of submission
  - R.O.Thumb, ~halfway through the review cycle,
    - i.e., 4-6 months, could be earlier for breakthrough therapy designation

- Start a “Most Feared Questions” list during submission writing and segregate issues directly linked to submission and those to PAI
  - Assign SMEs to develop answers
  - Develop remediation plans as needed
- Develop “Wrap Around” reports on specific, key issues that are likely to arise during inspection
- Consider a presentation on especially critical issues
  - Sometimes better to “fall on your own sword than have someone else take it to you”
- Develop remediation plan for outstanding issues to show inspectors issues are being addressed
  - Revalidation protocol and report (at least signed protocol)
- Perform Mock Inspections, including key suppliers- help them prepare
  - Participate in your supplier’s inspections
- Train organization so handle inspectors and their questions
  - Answer just the question; clarify; you only owe them your memory; if don’t have answer, commit to get it
- Prepare war room and responsibilities; manage tightly during inspection

Information to be Available for Review and Inspection

CMC, History Section	Production Related Qualifications	Equipment	Quality Related
• Development Reports • SOPs • Change Control • Investigations (i.e., nonconformances, failures, deviations) • Field Alerts	• Process validation protocols & reports where done • System validations (e.g., water, gas, steam computer) •Critical Process Parameters (CPP)	• Batch production records • Raw material usage • Cleaning validation • Environmental Monitoring	• Complaints • Investigations • Failures •Reworks/reprocess laboratory • Raw data • Methods validation • Stability • Bioequivalence

Preparing for the Pre-Approval Inspection What to do Before the FDA Arrives, B. Friedman, PDA

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In Conclusion

- Begin with the end in mind
- Think simplicity and for flexibility
  - Risk and science based, Lean principles
- Monitor and continuously improve, starting early
- “Get it right the second time” during the journey- A Learning Organization
- Benchmark leading organizations and distill lessons to your company
  - Even if small and developmental

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Contact Information

James Blackwell, Ph.D. M.B.A.
President and Principal Consultant
The Windshire Group, LLC
Boston, MA
Email: info@windshire.com
Main: 844-686-5750, ext. 101
windshire.com

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