GLP, GCP & GMP Harmonization

New expectations for a new world

Jay Smith
Sparta Systems
Jay.smith@spartasystems.com

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GLP, GCP, and GMP regulations are often managed independently. There are commonalities across these guidelines and organizations are evaluating how to harmonize approaches to compliance. We compare the regulations, explore how leading companies have created transparency between these phases, and share insights on mitigating risk in an outsourced environment.

GLP, GCP, and GMP

Good Laboratory Practices

"A quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported."

GLPs are regulations published in:

- Code of Federal Regulations (21 CFR part 58)
- The OECD Principles of Good Laboratory Practice

GLP is Non-clinical, animal studies, drug discovery

- 3.5 years
- GLP studies building the protocol

Regulations are very old and strict

- 21 CFR 58.1

GLP Quality Assurance Unit

- QAU is any person or org. element other than the study director
- Study director owns the study but QAU is responsible for quality

Activities include:

- Master Schedule
- Audits
- System
- Process
- Project/Program
- QA Statement

"GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical data are credible."

GCPs are regulations published in:

- E6 Guideline for Good Clinical Practice, Code of Federal Regulations
- ICH Harmonization Tripartite Guideline

GCP Highlights

GCP is the practice of medicine

- Monitor study
- Keep the patient safe

Drug Development, clinical trials

- Drug development phases 1 to 3 (~8.5 years)
- Drug Marketing / Expansion phases

Program (multiple studies)

- Focused on a single compound
- Responsibility by Sponsor and Principal Investigator

Key terms:

- ICH Guideline (International Conference on Harmonization)
- CRF – Case Report Form
- PI – Principal Investigator
- CRA – Clinical Monitor
- AE/SAE – Adverse Event/Serious Adverse Event

"Good manufacturing practice is the part of quality assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use and as required by the Marketing Authorization or product specification. GMP is concerned with both production and quality control."

GMPs are regulations published in:

- Code of Federal Regulations (21 CFR part 210, 211, 820, etc.)
- EU Guidelines to GMP Medicinal products for human and veterinary use

GMP is the manufacture of the drug or device

- Have a Quality System in place and follow procedures. Maintain control of manufacturing processes.

- Capture and review complaints, deviations, CAPA, root cause, audits, change control and effectiveness check for anyone who has a hand in the manufacture of the final product or any component
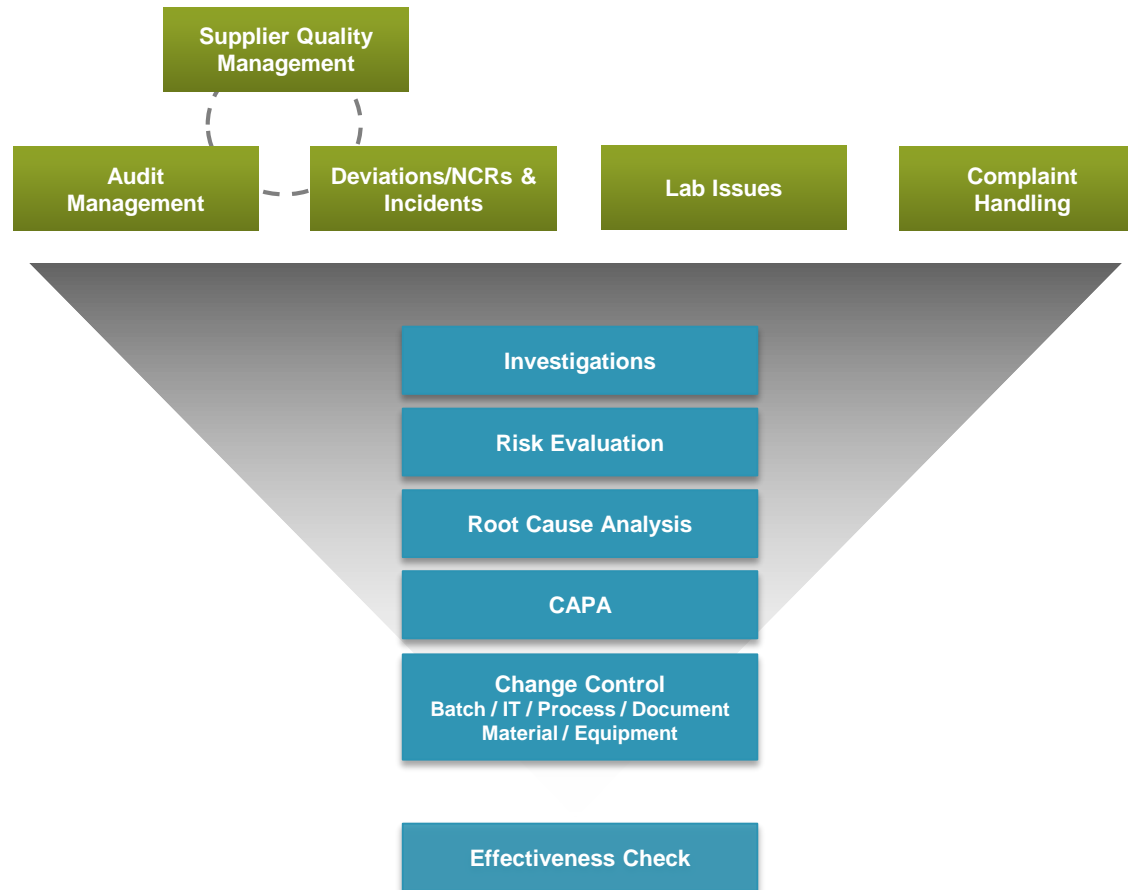
- Roles and Training

Manufacturing Facility

- Owned by the head of production, executed by plant quality manager

Key terms:

- Quality Management System

- Batch Release

- Manufacturing Authorization

Quality Management System

Supplier Quality Management

Audit Management

Deviations/NCRs & Incidents

Lab Issues

Complaint Handling

Investigations

Risk Evaluation

Root Cause Analysis

CAPA

Change Control
Batch / IT / Process / Document
Material / Equipment

Effectiveness Check

GxP and the Development Process

Drug Discovery	Preclinical Development	Clinical Trials I, II, III	Manufacturing, APIs, QC Labs

← **GLP** → ← **GCP** → ← **GMP** →

→

Study Based

Process Based

↔

ICH Q10
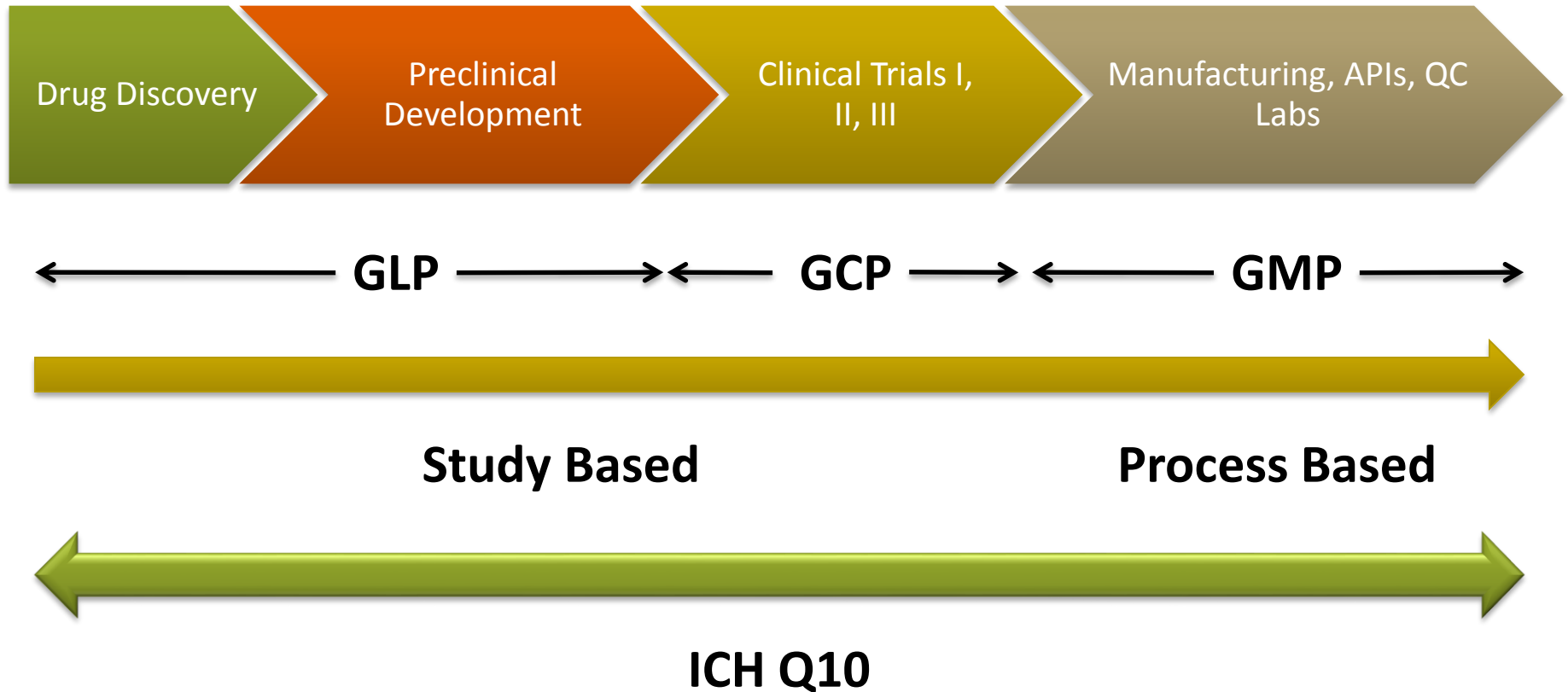
Critical Processes

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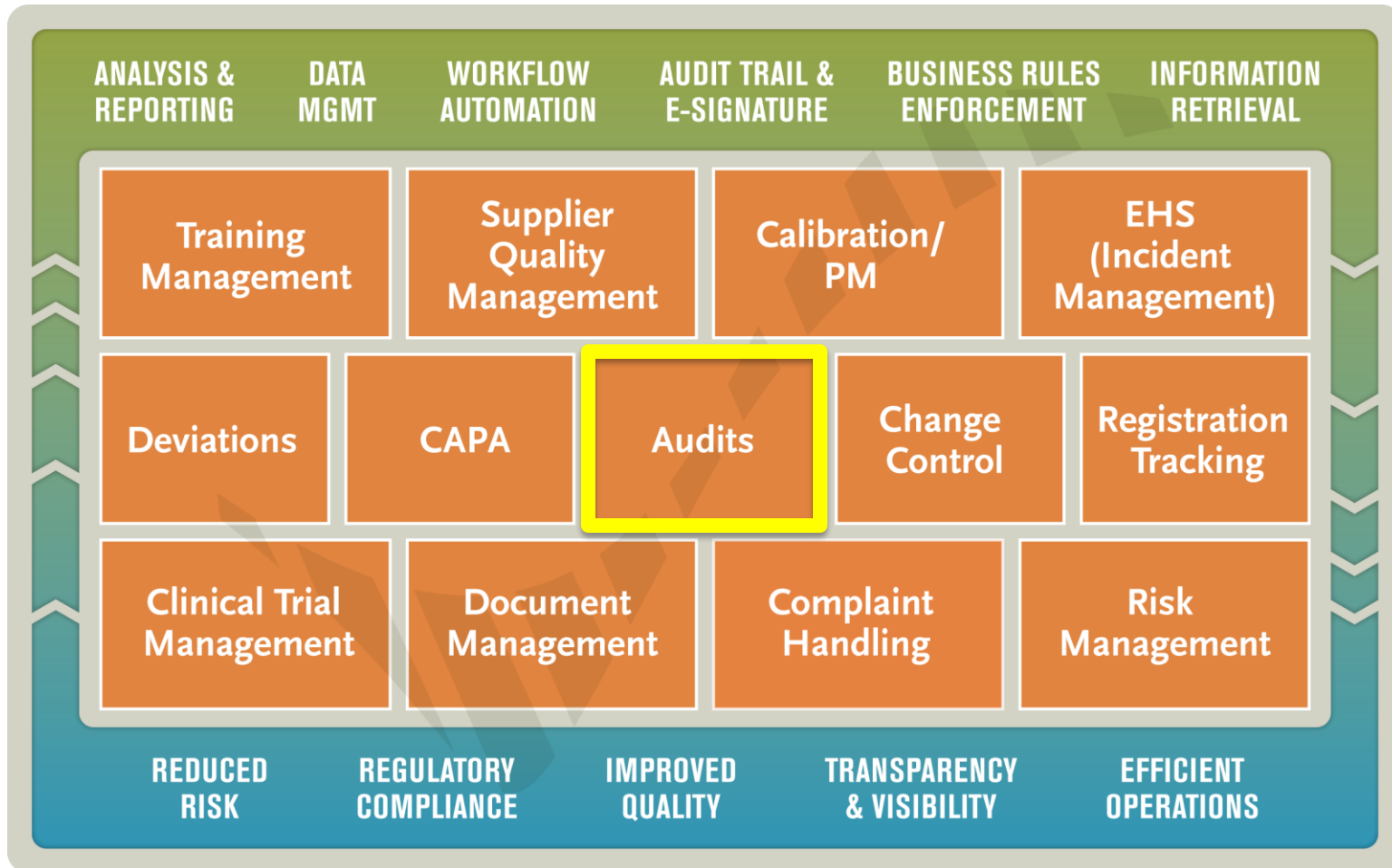
GLP, GCP, GMP Audits

Auting Overview

Audits evaluate processes, systems, product and materials, people, or other corporate operations. Audits can be run internally, by partners, customers, regulatory agencies, or third parties.

Purpose

- Ensure operations and procedures are within stated SOPs
- Serve as evaluations for decisions
- Ensure regulatory compliance

Description

- Audits are run periodically
- Auditors examine the area of focus
- Auditors provide observations, findings, and recommendations
- Action plans are generated using recommendations

Audit Cycle

Audit Cycle

Planning	→	Execution	→	Follow-up

Planning

- Audit lifecycle:
  - Scheduling
  - Preparation
  - Design Audit Templates
  - Report approval
  - Report issuance
  - Response
 - Corrective action (CAPA) tracking

Execution

- Auditors document results
- Provide actionable data for tracking and trending
- Prioritize resources across audit types based on role and department

Follow-up
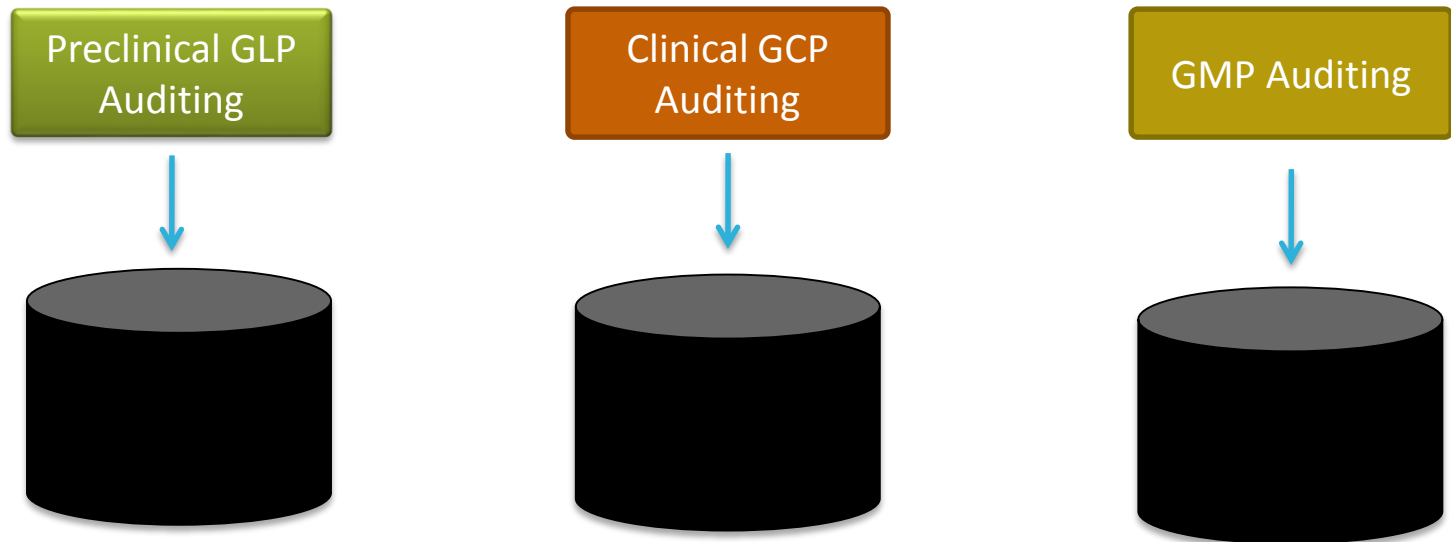
- Ensure appropriate action is taken (CAPAs) and audits are completed and closed out
- Audit reports that can be delivered as needed

Preclinical GLP and Clinical GCP Auditing
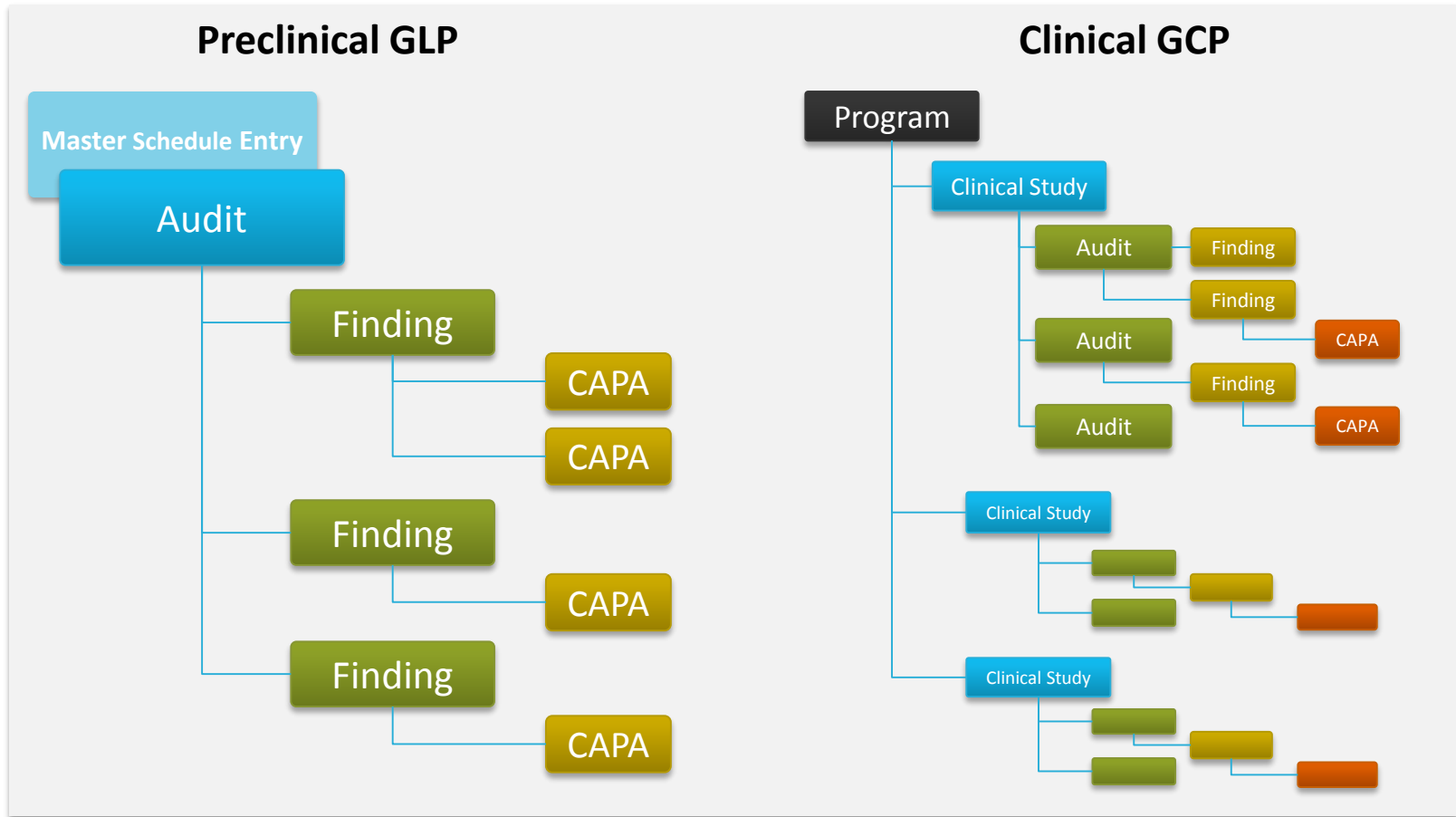
A Point Solution or Holistic Audit Management Solution?

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Many companies utilize systems as point solutions for audit management

Preclinical GLP Auditing

Clinical GCP Auditing

GMP Auditing

Auditing Across the Enterprise

- **GLP**
- **GCP**
- **GMP**
- Preclinical Studies
- Pharmacovigilance Audits
- Functional Audits
- Business Conduct Standards
- Compliance
- Validation Audits
- Contractor Compliance Assessment

- Internal Quality Audits
- Risk Assessments
- Internal Controls
- Contractor/Supplier/ Vendor
- Third Party (FDA, ISO & other health)
- Process Audits
- Internal Facility Projects
- Method Validation Audits
- EH&S Audits

Bringing it All Together

SOUTHERN CHIVALRY — ARGUMENT VERSUS CLUB'S.

Example Audit Process

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SOP requires inspection of site at regular intervals

Determine Audit Schedule
- **Triggered**
- **Individually**

Schedule Audit

Audit Preparation
- **Chose Template**
- **Estimate Dates**
- **Identify Site**
- **Identify Team**

Perform Audit

Audit Execution
- **On-line**
- **Off-line**

Create Observation/ Findings

Generate Audit Report To Vendor/Site

Create CAPA Plan
- **Risk Assessment**
- **Check Plan**
- **Approvals**

Issue Report
- **Audit Questionnaire Questions Locked**

Vendor/Site responds

Follow-up
- **Responses received**
- **CAPA's completed**
- **Observations closed**
- **Audit questionnaire locked**

Verify Completion

Close Audit
- **Audit Questionnaire Locked**

Enterprise Quality Management

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Issue Identification

- Supplier Quality Management
- Audit Management
- Deviations/NCRs & Incidents
- Lab Issues
- Complaint Handling
- Adverse Event Reporting
- Product Registration Tracking

Issue Resolution

- Investigations
- Risk Evaluation
- Root Cause Analysis
- CAPA
- Change Control — Batch / IT / Process / Document / Material / Equipment
- Training Management

Analysis and Reporting

- Effectivity Analysis

| Analysis and Reporting | Data Management | Workflow Automation | Audit Trail & e-Signature | Business Rules Enforcement | Information Retrieval |

More Visibility:

- Audit Actions → CAPA → QM
- Audit Action Plans → Change Control
- Visibility Across all Functions

Automation:

- Track all Audit Steps
- Issue Resolution
- Improve Cycle Times

Consistency:

- Common Audit Elements w/ Flexibility
- Audit Analytics
- Audit Prioritization

Quality Systems in Three Dimensions

Quality Process

- GLP/GCP/GMP
- Supplier Qualification
- Corporate Standards
- EHS
- CAPA
- Change Control

Functional Area

- Preclinical
- Clinical
- Internal Manufacturing
- R&D
- Supplier Management

Geography

- Country
- Region
- Business Unit

EQMS and EDMS

EQMS / EDMS Interaction Points

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Enterprise Quality Management System

Enterprise Document Management System

Non-Conformances	Standard Operating Procedures
Audit Management	Design History Files
Change Controls	Lot History Records
Complaints	Design History Record

People & Manual Process
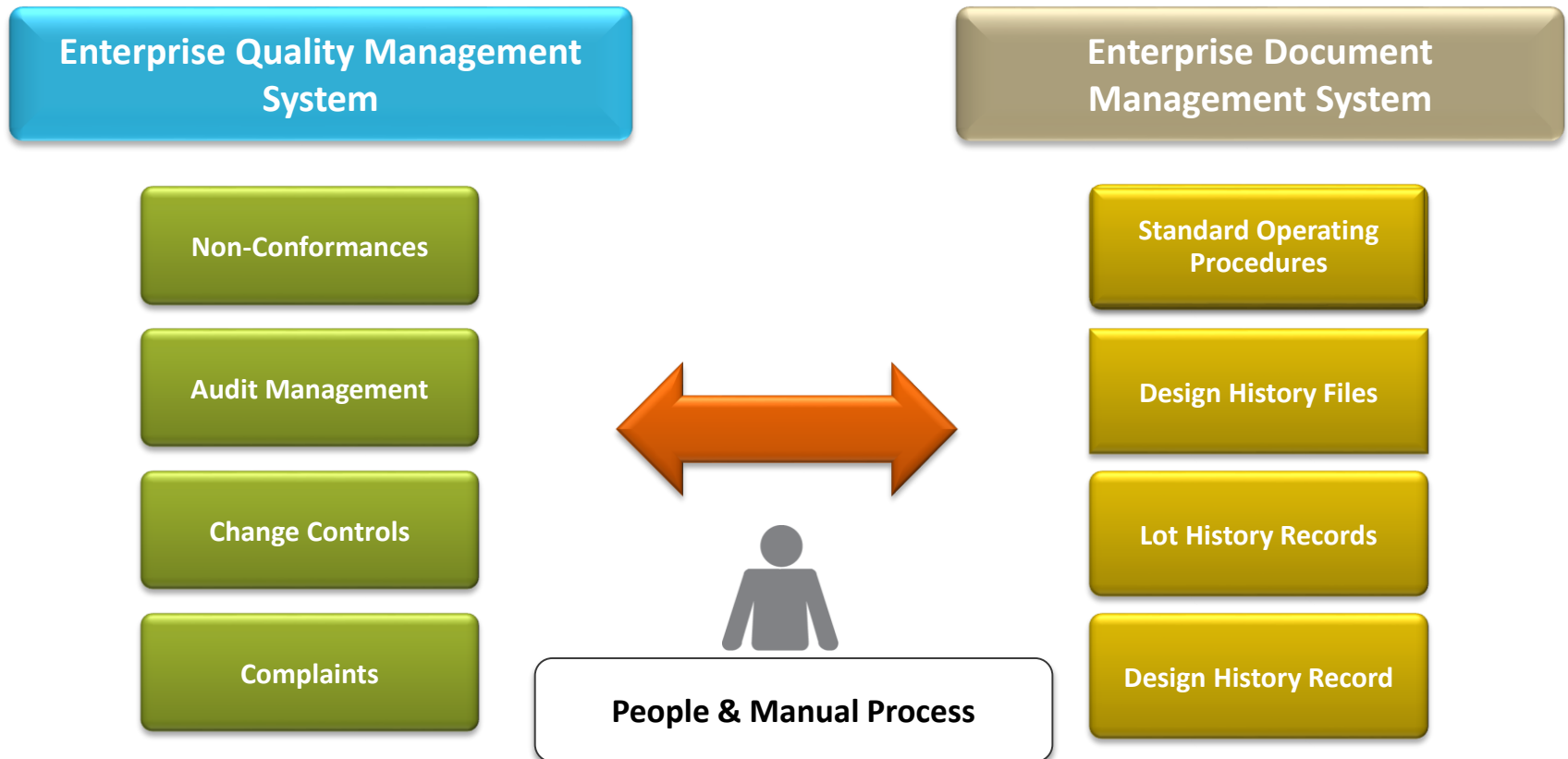
The Document Challenge

Change Control

- Request Change
- Impact Analysis
- Plan
- Execute
- Implement
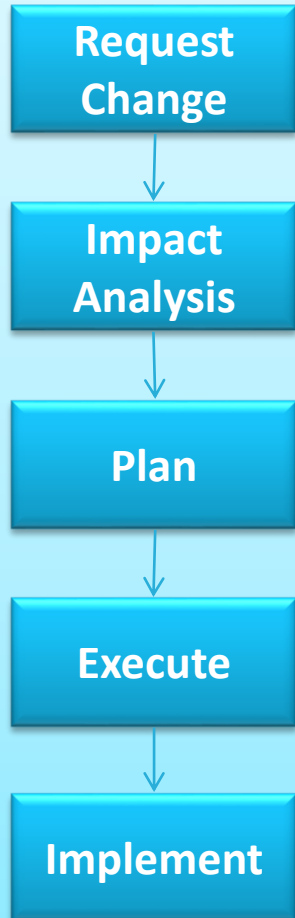
Disconnected Processes Create

Lack of visibility
Data redundancy
Lengthened cycle times
Poor user experience
Degraded audit trail

Document Control

- Author
- Review
- Approve
- Train
- Release

Example Change Control Process

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Quality Management System

| Change Control Opened | → | Impact Analysis | → | Pending Change Plan | → | Pre-Approval | → | Execute Change Plan | | Post-Approval | → | Pending Implement | | Closed - Done |

Search for and link to impacted documents

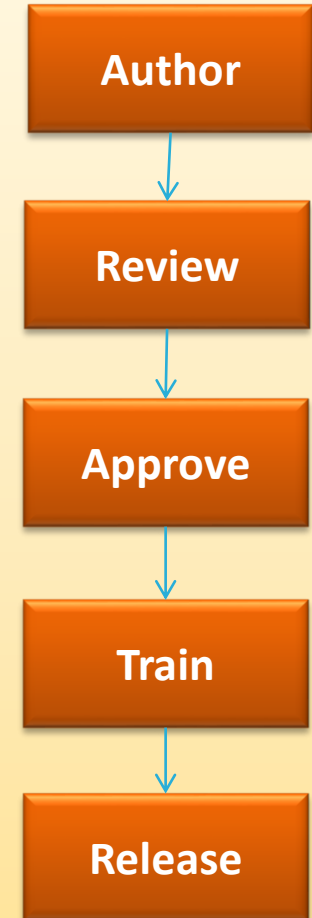| | | | | Action Item Opened | | Pending Approval | | Work in Process | | Complete | | | | Closed - Done |

Create new draft version of impacted document

Action Item is complete when document revision is complete

Action Item is closed when change is implemented

Document Management System

| Effective V1.0 | → | Draft V1.1 | → | In Review | → | Reviewed | → | In Approval | → | Approved V2.0 | → | Issued V2.0 | → | Effective V.2.0 |

Train

Release and Supersede V1.0

EQMS and EDMS

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Issue Identification
- Supplier Quality Management
- Audit Management
- Deviations/NCRs & Incidents
- Lab Issues
- Complaint Handling

Issue Resolution
- Policy, Regulation, and SOP References
- SOP Updates for Read and Understand
- Quality Training Courses
- Training Management
- Investigations
- Risk Evaluation
- Root Cause Analysis
- CAPA
- Change Control — Batch / IT / Process / Document Material / Equipment
- Adverse Event Reporting
- Product Registration Tracking
- Design and Lot History Files
- Risk Assessment Evidence
- Preventative Maintenance Plan
- Design or Spec Changes

Analysis and Reporting
- Effectivity Analysis
- Objective Evidence

Analysis and Reporting | Data Management | Workflow Automation | Audit Trail & e-Signature | Business Rules Enforcement | Information Retrieval

New Regulations, New Expectations

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Update of regulation to address counterfeiting of drugs

- Manufacturers of active substances and excipients are subject to inspection

- Whether inside or outside of the EU, any manufacturer of ingredients intended for use in a drug product to be sold in the EU should follow GMP's

- Pharmaceutical manufacturers must have written confirmation that they have verified GMP compliance by suppliers

  - Should be done through an audit of the supplier

  - If a supplier is found to be non-compliant with GMP's, pharma company is required to report this to local regulatory authority

  - Suppliers are not allowed to self audit, or order third party audit as proof of compliance

Update of regulation to address counterfeiting of drugs (cont.)

- Manufacturers, importers & distributors must be registered with the competent authority in the country where they market products or provide active substances or excipients for products sold within the Union

- Local findings of non-compliance are to be supplied by the exporting 3rd party country to the union

- Importers, manufacturers & distributors of active substances who are established in the Union, must register with their authority

  - Must register at least 60 days prior to commencing activity

  - Authority may require inspection prior to commencement

  - Companies must report changes annually

  - Any change that impacts quality or safety must be reported immediately

EU 2011/62/EU Falsified Medicinal Products Directive

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Update of regulation to address counterfeiting of drugs (cont.)

- Manufacturers, suppliers, importers & distributors **"must maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities"**

- The competent authority of a Member State may carry out inspections of material manufacturers and suppliers at the specific request of the manufacturer

Food & Drug Administration Safety & Innovation Act

Key highlights:

- Signed into law July 9, 2012

- Directs FDA to create a Unique Facility Identifier (UFI) system to electronically store registration & listing information

  - Excipient manufacturers & importers required to have a UFI

  - If a drug or device is from an unregistered facility it is misbranded

- Increase in funding for inspections

- Drug establishments will be inspected on a "risk-based" schedule

- Foreign government inspections of foreign registered companies will be recognized

  - FDA has taken enforcement action based on a non-FDA inspection

Food & Drug Administration Safety & Innovation Act

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Key highlights (cont.):

- Allows FDA to request records & information prior to or in lieu of an inspection

- Drugs will be misbranded if manufactured at any establishment that "delays, denies or limits an inspection or refuses to permit entry or inspection"

- cGMP's are to include "managing the risk and establishing the safety of raw materials, materials used in the manufacturing of drugs and finished drug products"

- A new risk based standard of admission and screening for imported drug products to be implemented

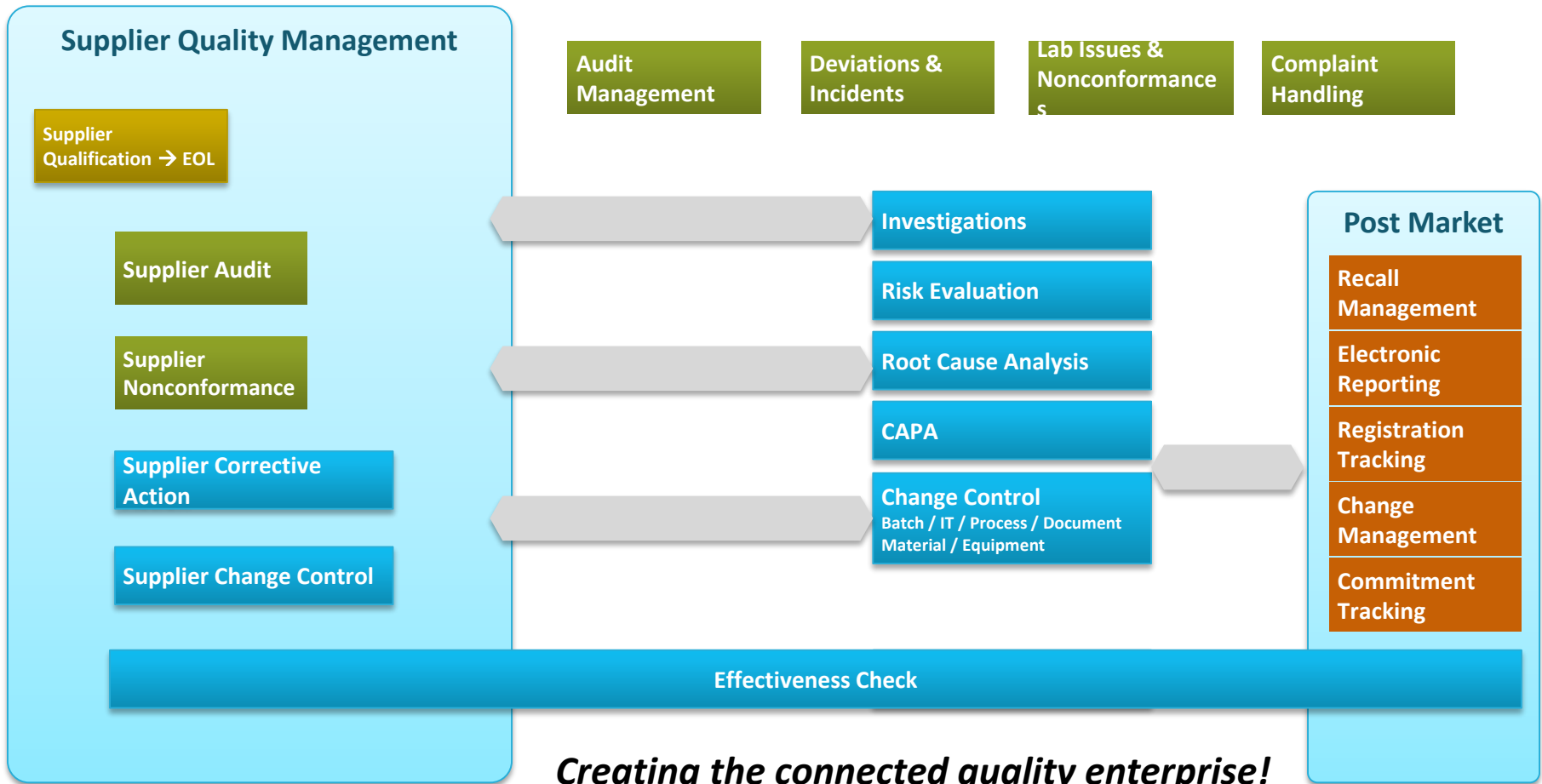- Drug adulteration penalties of up to 20 years in prison and $1 million in fines established

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"However, there was no review and approval conducted by your QA group for this deviation report that was prepared by your third party supplier."

"We reviewed your firm's written responses and conclude that they were not adequate to address these deviations because no evidence was provided to demonstrate that your firm will be able to adequately control the review and disposition process for nonconforming product. The proper review and disposition of nonconforming product is essential for ensuring the safety and effectiveness of devices"

"Complaint trending was not being performed, CAPA's were not opened based on complaints, and complaint trending is not part of the Management Review key performance indicators"

"We reviewed your firm's responses and conclude that they were not adequate because no evidence was provided to demonstrate that your firm will be able to investigate the cause of nonconformities relating to product, processes, and the quality system; verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device"

"Specifically, your firm has failed to implement a vendor management policy by not performing a audit of a vendor who provides your firm with a service for your product."
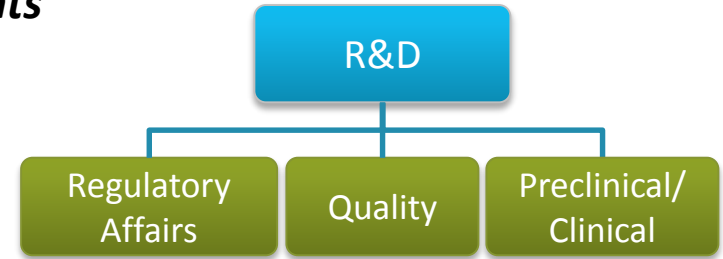
Operating Outside "The Four Walls"

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Supplier Quality Management

Supplier Qualification → EOL

Supplier Audit

Supplier Nonconformance

Supplier Corrective Action

Supplier Change Control

Audit Management

Deviations & Incidents

Lab Issues & Nonconformances

Complaint Handling

Investigations

Risk Evaluation

Root Cause Analysis

CAPA

Change Control
Batch / IT / Process / Document
Material / Equipment

Post Market

Recall Management

Electronic Reporting

Registration Tracking

Change Management

Commitment Tracking

Effectiveness Check

Creating the connected quality enterprise!

The Extended Quality Enterprise

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- Trends
- Approvals
- Reports
- Status
- Audits

Mobile Devices

Emerging Requirements & Capabilities

Mobile Employees

R&D

Regulatory Affairs

Quality

Preclinical/ Clinical

Suppliers, Contractors, CMOs, Distributors

- Incidents
  - Investigations
    - Deviations
      - NCs
        - Audits
      - Corrective Actions
    - Supplier Defects
  - Product Complaints
- Change Control
- Commitments

Commercial Manufacturing
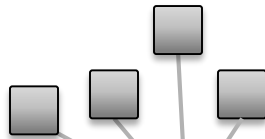
External Quality Views

- Commitments
- Audit Observations
- Corrective Actions
- Deviations / Events
- Product Complaints
- Certifications

External Agencies

Regulatory Affairs

EHS

Q&A

For more information, contact

Jay Smith
Director, Product Management
Sparta Systems Inc.
Jay.Smith@SpartaSystems.com

Thank You

The Technology of Quality