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All Things Considered: CMC and QMS Intersection in Process Development

PDA Southern California Chapter Quarterly Event – Biologics
June 15, 2017

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Agenda

- Drug Development: Product Performance
- Todays development challenges- QMS and PR&D
- High Performing Processes
- Case Study: QMS/CMC Transformation Project
- Conclusions
- Q&A

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Phase Appropriate QMS

- PDA TR56: Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (API or Biological Active Substance)
- The guidance provided clarity for the industry, allowing organizations to focus on implementing phase-appropriate recommendations and requirements, depending on their current development state and the evolution of their quality system
- Also serves as a longer term "road-map," providing vision for planning and implementation of increasing regulatory compliance complexity as progress is made through the commercialization process

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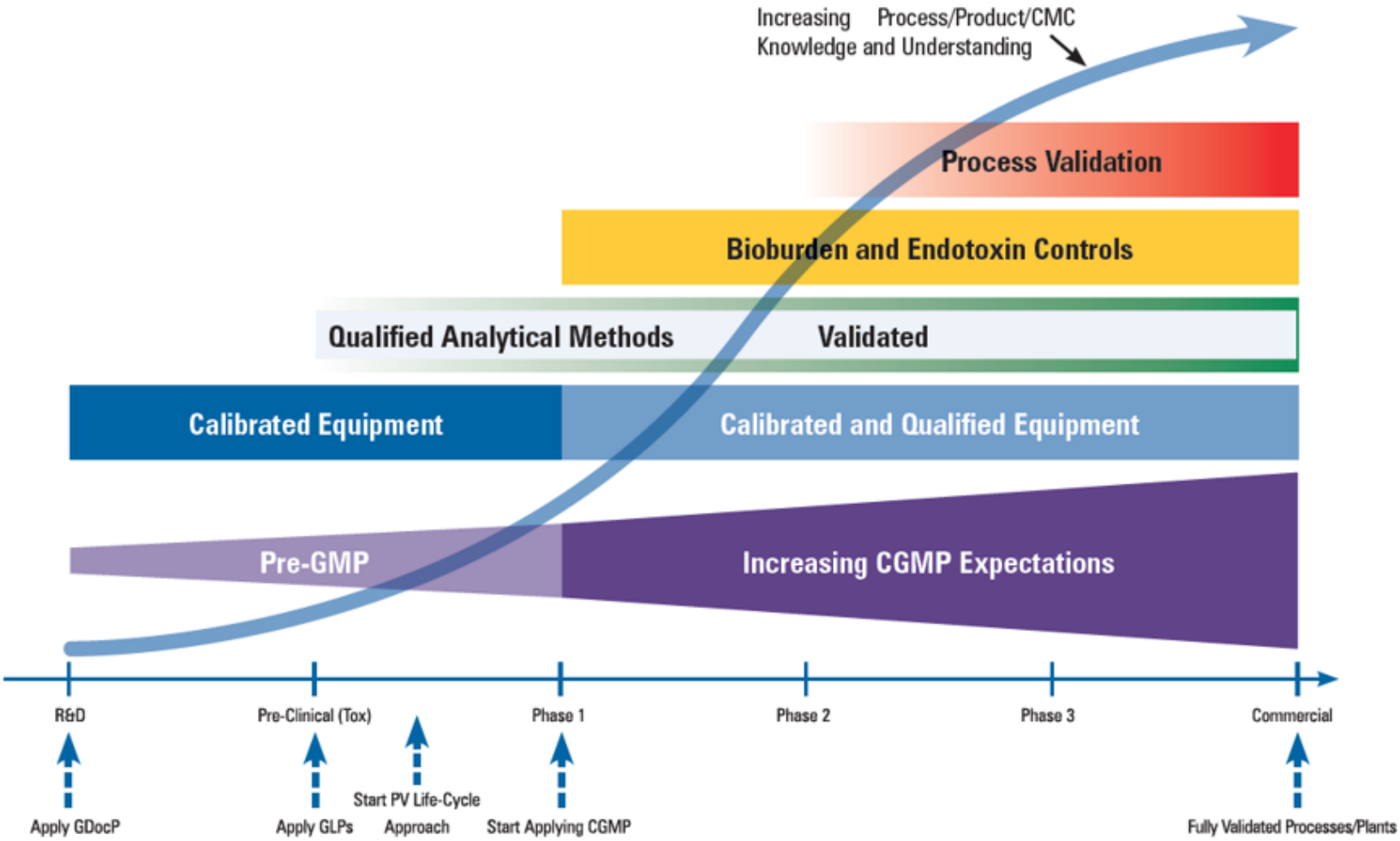
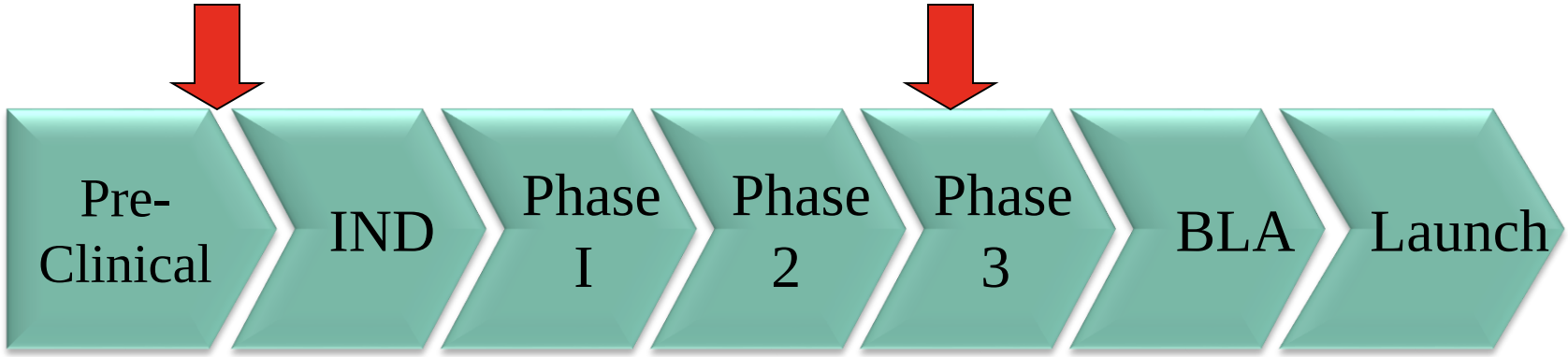
Phase Appropriate QMS



Phase Appropriate QMS

Quality System In Place
QA releases lot
SOP's in place
Deviation system in place
Change control system in place

Full GMP's in place



Good Documentation Practices, Process Understanding as a Basis for Quality

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Applying a Phase Appropriate QMS

- For example, toxicology studies require Good Documentation Practices (GDP) and Good Laboratory Practices (GLP) prior to initiating the studies. GMPs are not required other than managing data integrity
- R&D data has taken on a much bigger role in the development lifecycle and as the quality and safety consequence escalates so must the QMS content
- For those organizations on the left side of the process, the message is also clear that their development work is critical since it serves as the basis for the more stringent and complex manufacturing control strategies, CMC, process validation, method validation, and other requirements necessary to compliantly drive a product to market. The regulatory expectation is that the knowledge gained during development phases continues to grow in terms of manufacturing process understanding and control.

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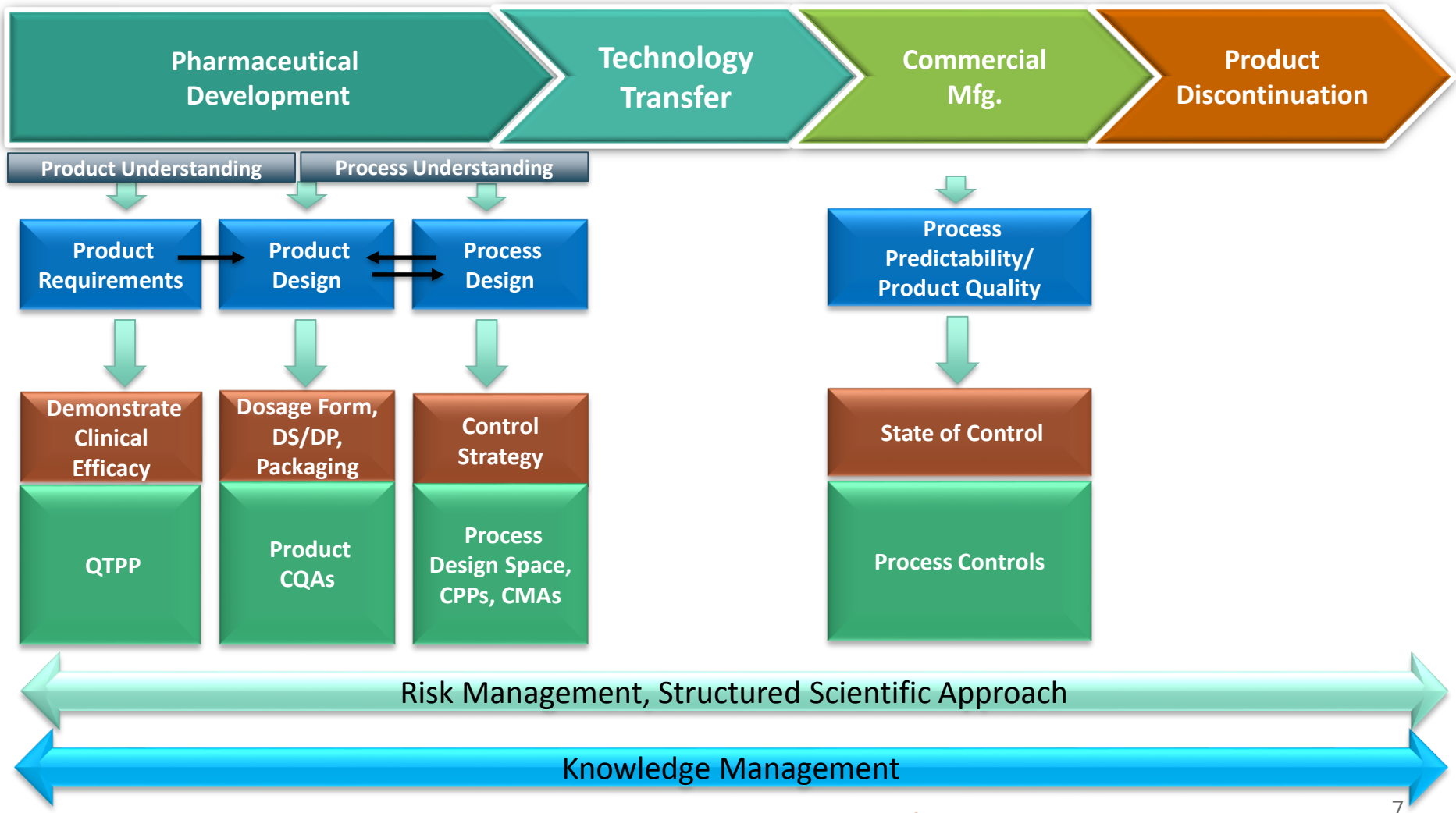
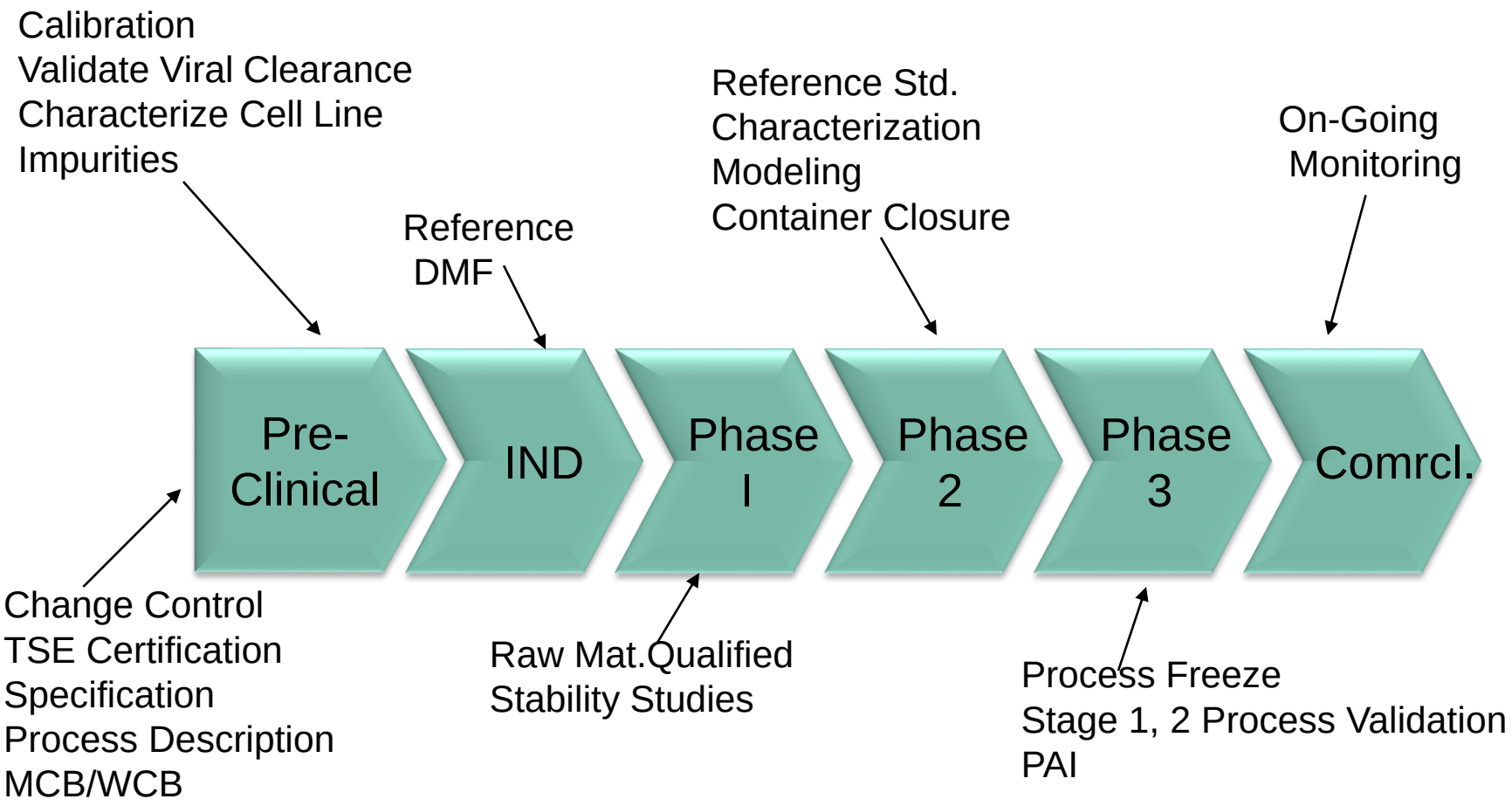
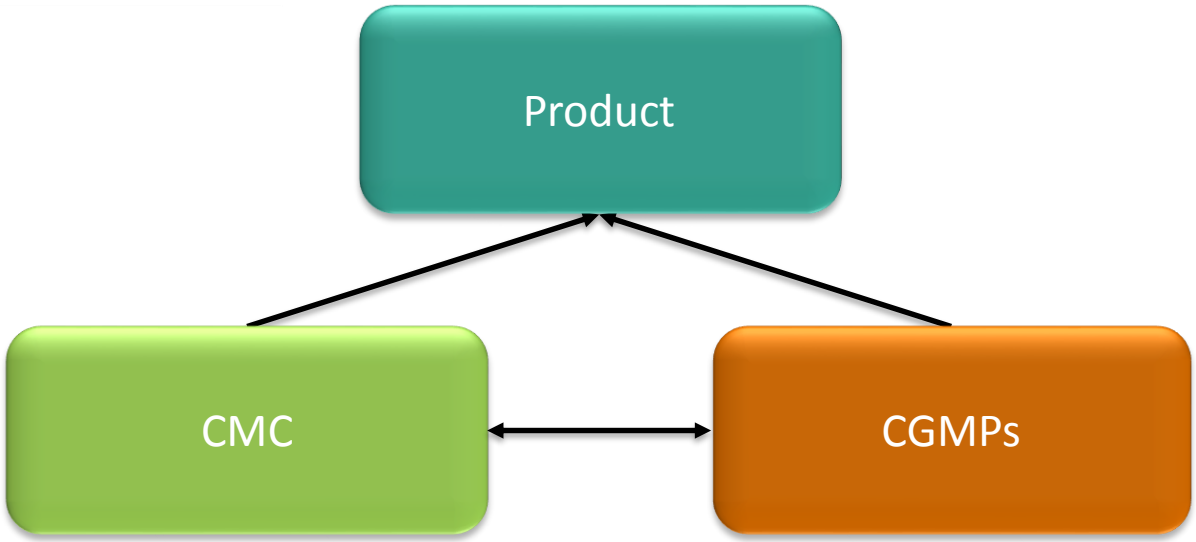
Drug Development: Product Performance



Biologic CMC Activities



Supporting Product Quality



Focus	CMC: Submission Dossier	GMP: Facility/Manufacturing/ Testing
Industry Role	Setting Criteria and Controls for manufacturing and quality	Implementing manufacturing and testing practices designed to manufacturing and quality standards
Guidance	ICH: Q1-Q6, Q8, Q9	ICH: Q7, Q9-Q11
Agency Role	Assessment and approval of manufacturing and quality standards and controls	Verification of conformance to GMPs and regulatory standards through inspection and evaluation of QMS

Courtesy of PDA TR 56

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Development Guidance

Q5b Genetic Stability

Q5d Cell Substrates

Q5a Viral Safety Evaluation

Q6b Specifications for Biotechnological Products

Q5c Stability of Biotechnological Products

Q5e Comparability of Biological Products

Q8 Pharmaceutical Development

Q9 Quality Risk Management

Q10 Pharmaceutical Quality Systems

Q11 Dev. and Mfg. of DS

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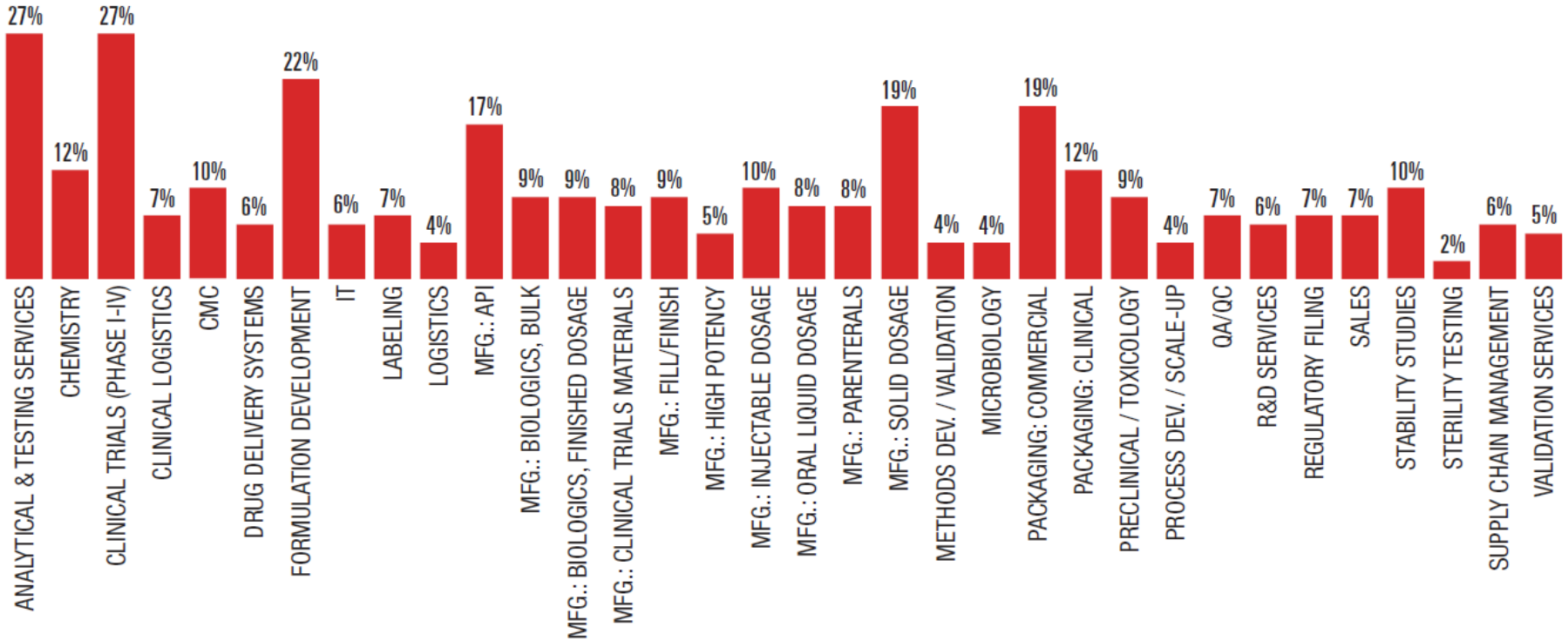
QMS Transformation

- Quality's role is changing, augmenting compliance activities with quality evaluations based upon process and product understanding
- Blurs the traditional lines of development and Quality
- Does not work well with siloed organizations
- QRM, RACI and Governance models are essential to an organization's ability to effectively and efficiently adopt best practices and accommodate business needs

QMS Paradigm Shifting Drivers

Industry

- Outsourcing is replacing vertical development and manufacturing

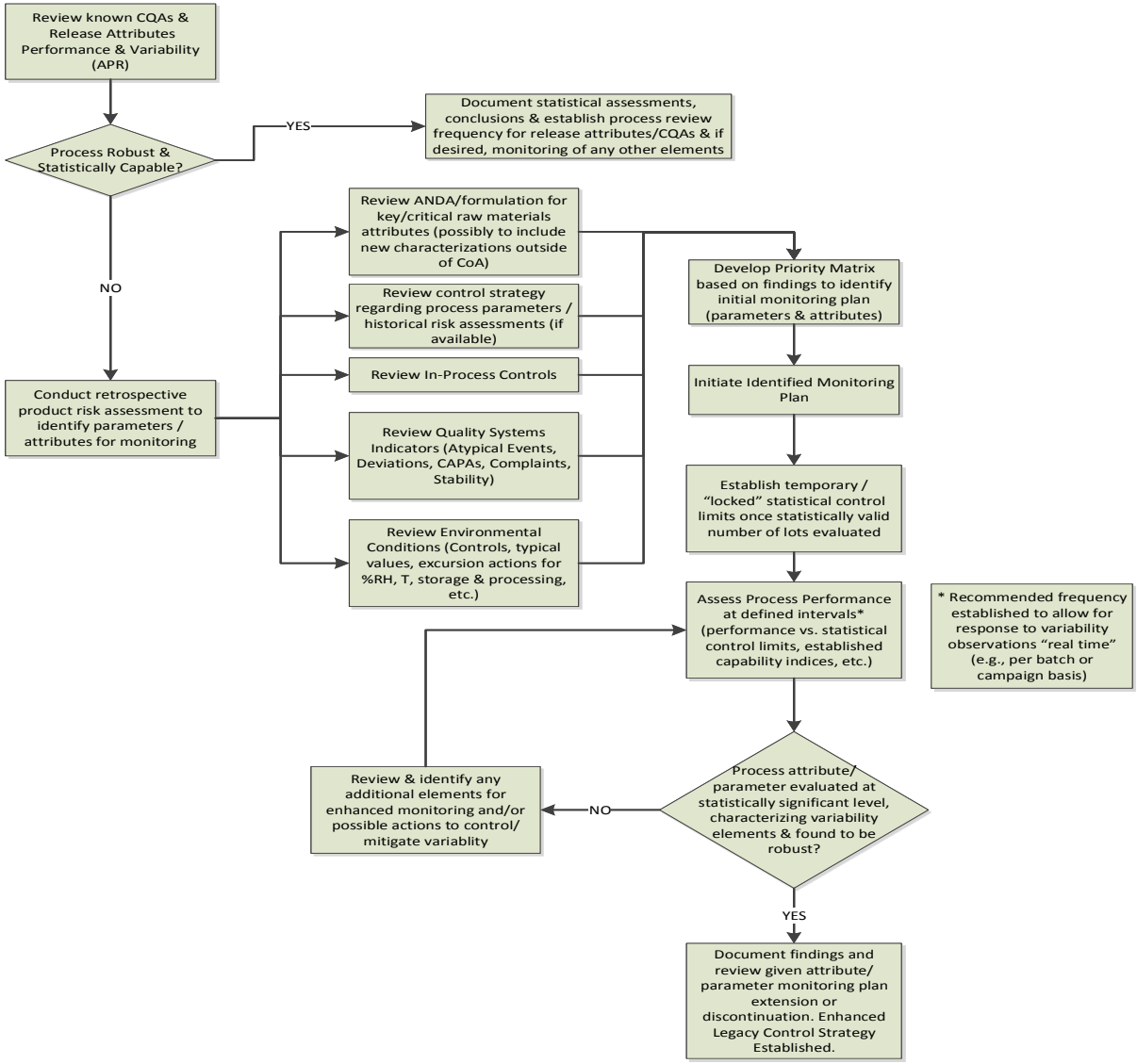


Courtesy of Contract Pharma- 2016 Outsourcing Survey

QMS Paradigm Shifting Drivers

Regulations

- Stage 3 Process Validation: Continued Process Verification (CPV)



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Applying Criticality to CPV

		Monitor		Statistical Review Frequency			
		Yes	No	Month	Quarter	Annual	None
CPP	High Risk	X		X			
	Medium Risk	X			X		
	Low Risk		X				X
Non-CPP	Key	X				X	
	Non-key		X				X
Raw Materials	CMA	X			X		
	Non-CMA		X				X
CQA	High Risk	X		X			
	Medium Risk	X			X		
	Low Risk	X				X	

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CPV Strategies

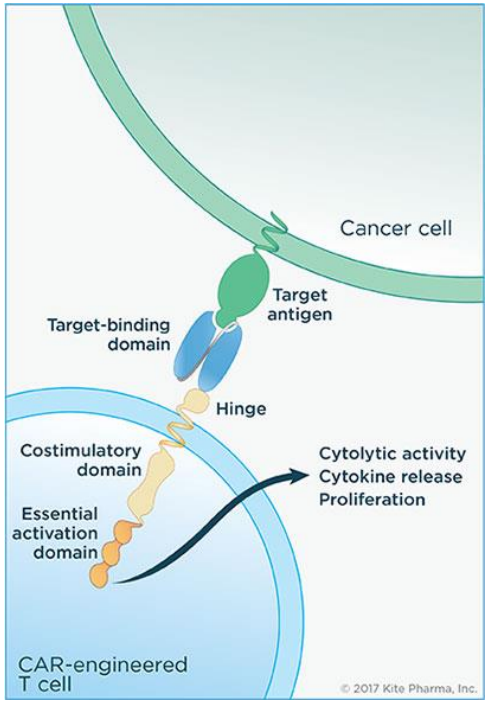
- Statistical evaluation for Out-of-Expectation events
  - Control charts for Outside-of-control limits, Trends, Shifts, Oscillations, etc.
  - Histograms and capability analysis for CQAs
  - Regression analysis where modeled relationships exist between CPPs and/or CMAs and CQAs. CQAs should respond as predicted
- Unlikely statistical events (especially outside-of-control limits) may occur which have no impact to quality
  - Continued monitoring may be preferable to formal investigation if risk to quality is low

QMS Paradigm Shifting Drivers

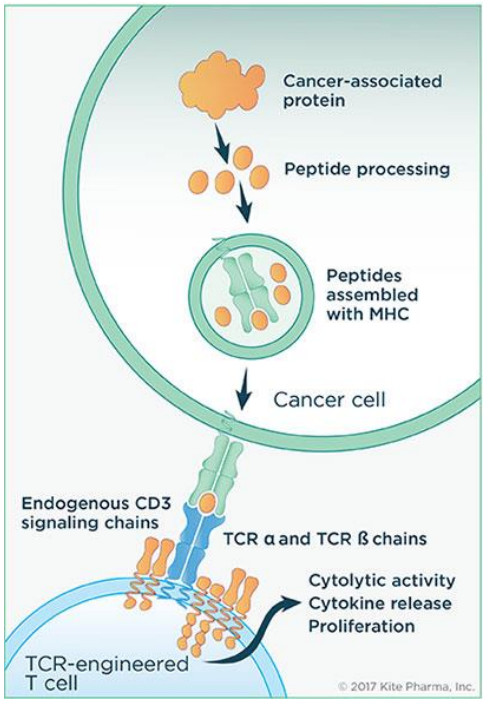
Advanced Therapies

- Personalized Medicine- CAR, TCR

Chimeric Antigen Receptor



T- Cell Receptor

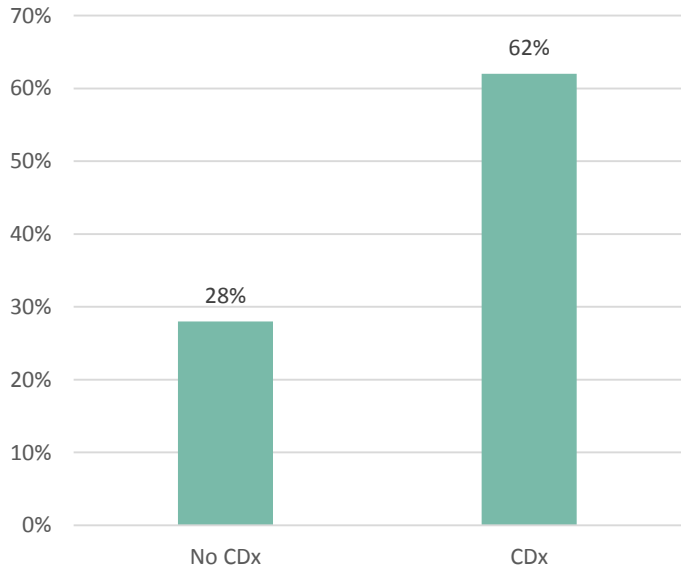


QMS Paradigm Shifting Drivers

Diagnostics

- Next Generation Gene Sequencing (NGS)/Companion Diagnostics

- For pharma manufacturers that use CDx during drug development improves the success rate of drugs being tested in clinical trials
- Analyzed 676 clinical trials and 199 unique compounds between 1998 and 2012. The data showed that Phase III trial failure proved the biggest obstacle to drug approval, with an overall success rate of only 28%. But in biomarker-guided trials, the success rate reached 62%



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Institutionalizing Risk Management

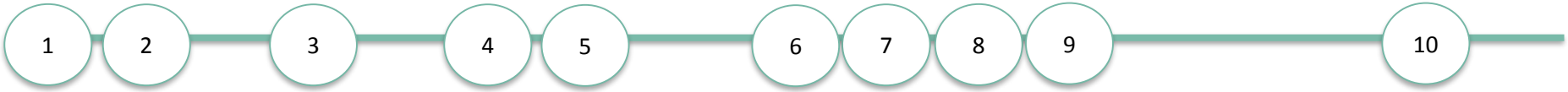
- The QMS must provide a framework for asking the relevant questions for addressing quality and compliance
- Quality and CMC must evaluate the impact of data or QMS excursions within the context on product safety, quality, identity, potency and purity (SQIPP)
- Utilizing a structured risk framework is essential to being able to evaluate and adjudicate quality and CMC data as it moves from discovery to commercial manufacturing

QRM Deployment

Clinical Development Phases

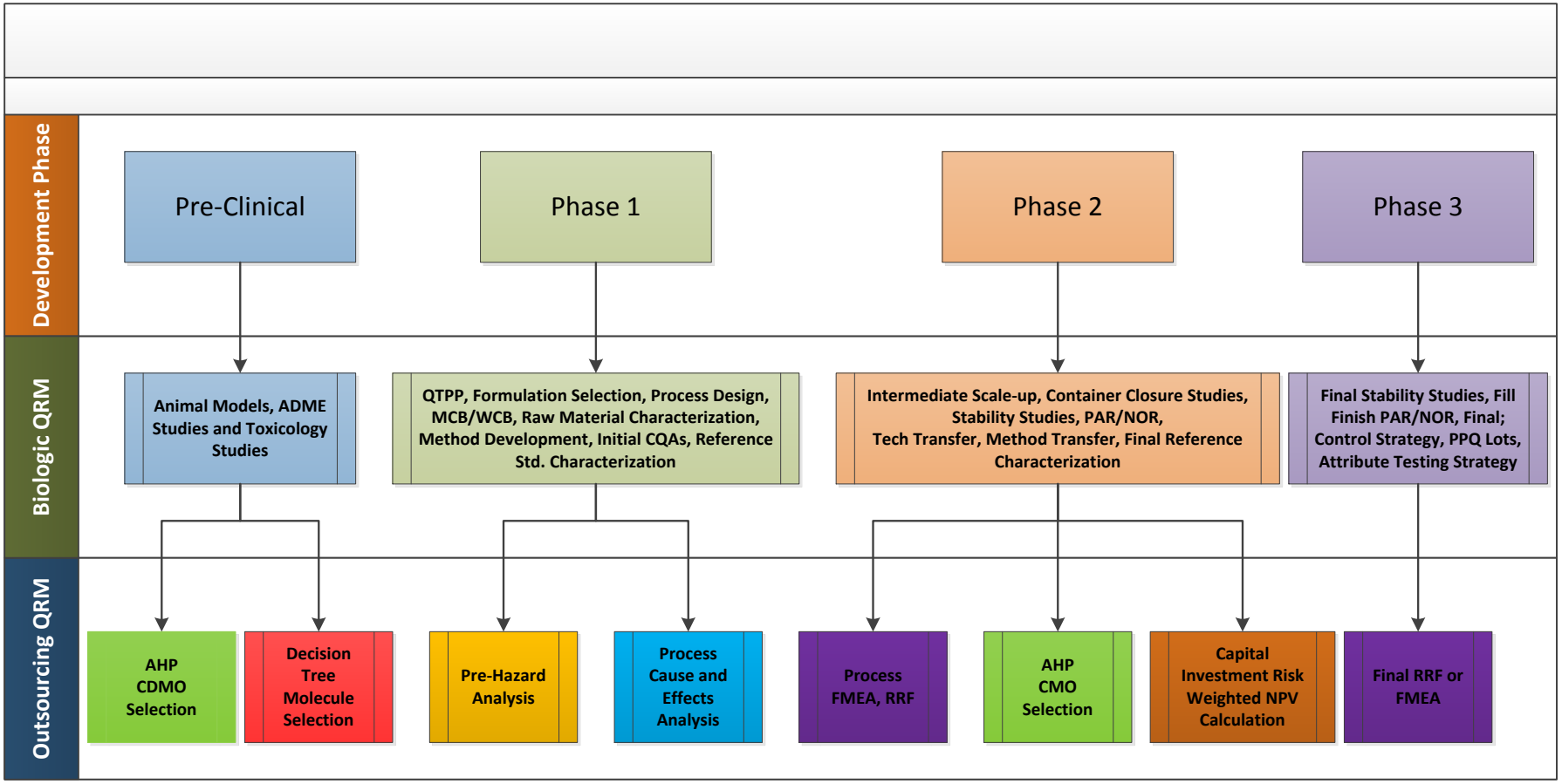
Product and Process Development Phases

Formalized Risk Assessments and Milestones



1. TPP establishment
2. QTPP Establishment
3. CQA RA
4. Product PHA
5. Initial Process RA
6. Updated Process RA
7. Design Space Establishment
8. Control Strategy RA
9. Control Strategy
10. CPV Prioritization Matrix/Continuous Improvement

Product Development and QRM Tools



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Theory of High Performing Processes

- The works of Dr. W. Edwards Deming, Dr. Joseph Juran and Armand Feigenbaum all referenced process awareness as keys to high performing organizational effectiveness. Deming wrote a number of papers on the 'Theory of Profound Knowledge.'
- Despite an abundance of material on this subject, organizations still tend to over-manage functional department performance (silos) and under-manage cross-functional departmental performance.

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Characteristics of High Performing Business Processes

RTFT

- RTFT Metrics are established at the strategic level for Development and cascade down to each individual- balanced scorecard

Involvement

- RACI framework across functional areas, departments, and divisions are clearly articulated

Accountability

- RACI understanding is clearly enforced and practiced in program development with clearly agreed-upon decision making authority

Prevention of Defects

- Procedures define standard practice tools and when to apply them. Includes technical/quality prerequisites for each major step

Conformance to Requirements

- Procedures capture primary outputs across processes

C/S Partnerships

- Outputs and purpose are clearly understood and agreed upon by both parties of the C/S relationship based upon risk, activity and contribution to overall success metrics

Measurement

- Meaningful (cause and effect) metrics are in place and utilized by the organization to continuously strengthen performance

Cross-Functional Process Mgt.

- Cross-functional value-stream management processes are embedded in the management structure to optimize overall performance.

Continuous Improvement

- Development organizations who actively embrace QbD, QRM and ICHQ10 principles as a foundation of their QMS.

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Case Study- QMS Transformation to ICH Q10

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Project Background

- Established Small and Large Molecule Development organization
- Up and down history of regulatory actions
- Current QMS is a belt and suspenders approach derived from their commercial QA program
- Regularly audited by their corporate QA group
- Business model has shifted from solely internal discovery to include in-licensing and co-development programs
- Internal GMP pilot scale facility for large molecule DS (mammalian and microbial) through Phase 3
- All other clinical manufacturing and packaging is outsourced

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Problem Statement

Extracted from Project Charter:

- The current QMS is too prescriptive and emphasizes ***how*** to execute each phase of the QMS rather than emphasizing the objective of the QMS step. Current practice includes non-value added practices as it relates to truly ensuring the quality of the product.
- Decision making is often by consensus due to lack of clarity in terms of roles and responsibilities. The major cornerstones of the QMS, e.g. Deviation, CC, CAPA, Doc Control, ECO do not leverage QRM as a platform for QMS and hence it is very disruptive and difficult to adapt to new business processes that do not exactly follow the prescribed systems.
- The consequence is a rigid system which is not capable of accommodating anything but pre-defined processes.

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QMS Process Improvement Goals

1. How can we become more flexible?
2. How can we become more agile?
3. How can we make risk more easily and meaningfully visible?
4. How can we reduce complexity to the right level?
5. How can the QMS become a competitive advantage?

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Diagnostic Approach

- Very short evaluation period- 3 months
- 2100+ SOPs spanning drug discovery through clinical manufacturing
- Problems rooted in procedural, cultural, organizational and technical issues
- Required a customized framework to identify drivers that were inhibiting QMS from synchronizing with CMC
- Utilized a VSM framework to identify problem areas in the QMS process
- Mapped the entire drug development process including clinical supplies for a large molecule product, using an external CMO with a comparator included in the clinical supplies

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Output

- Identified 6 major sub processes which were representative of systems and behaviors which were problem areas for both CMC and QMS
- Detailed each sub process by creating a VMS identifying problem areas and opportunities for improvement
- Identified 120+ opportunities which were distilled into findings that drove conclusions and recommendations for improving the QMS

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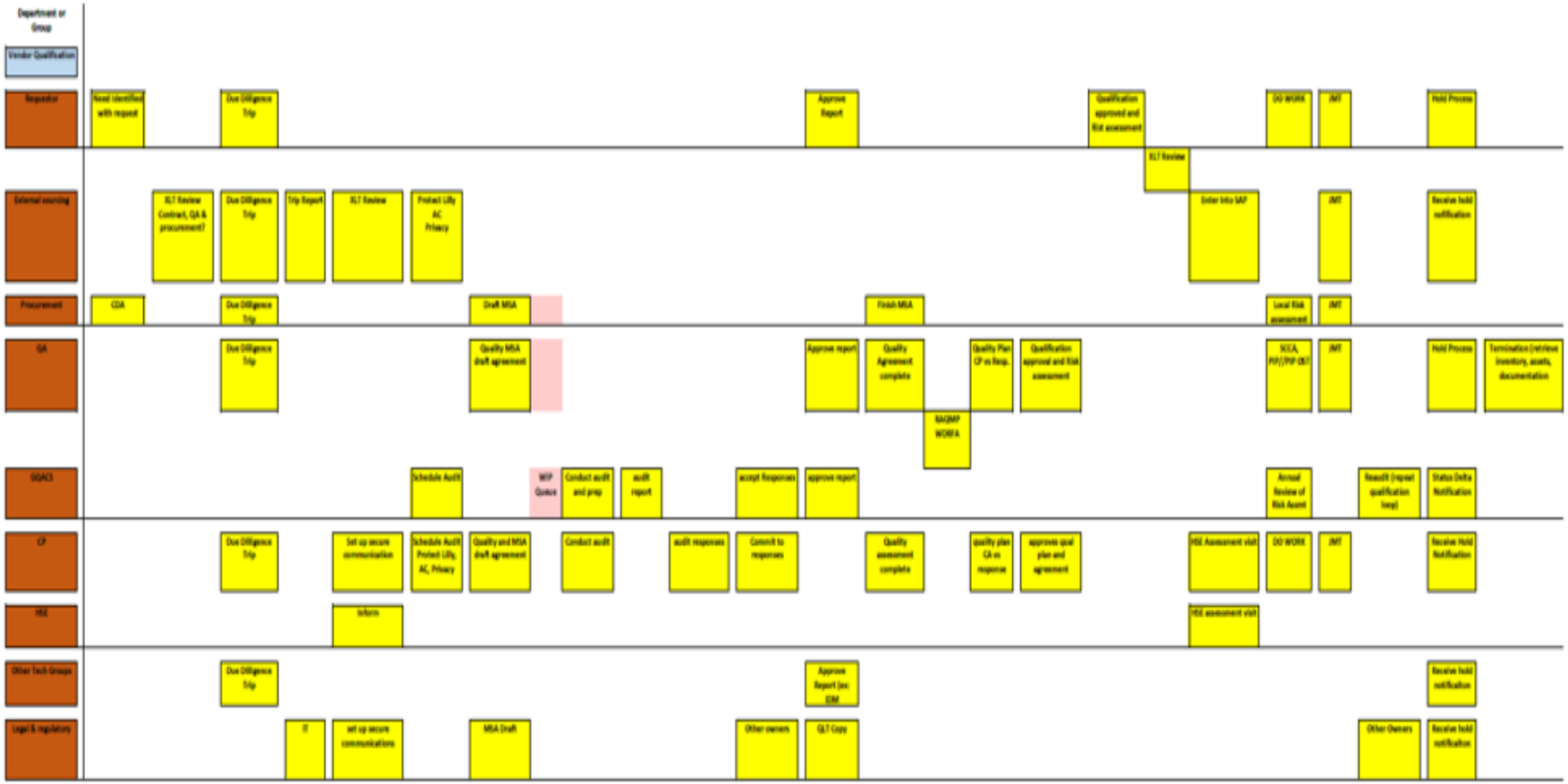
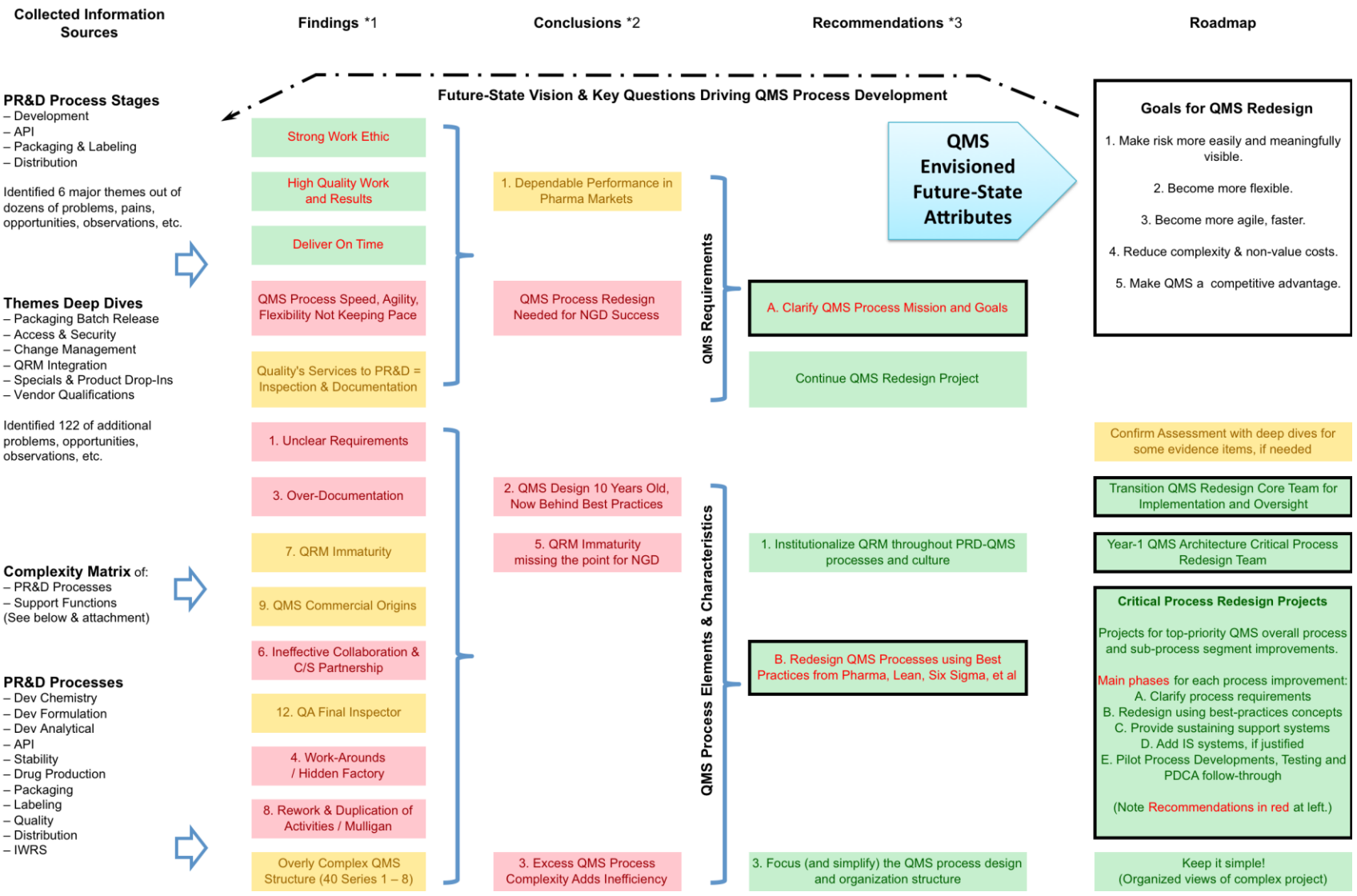
Vendor Qualification Process



Output from System Diagnostics



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QMS Redesign Recommendations

Year 1 QMS Architecture for High-Performing Organization

1. Replace Outdated QMS Framework
2. Establish Modern QRM Practices
3. Establish Consistent Standardized Work and GMP Documentation Hierarchy
4. Establish Enforced RACI Mechanisms for Responsible, Accountable, Consulted, Informed Roles
5. Establish Governance Processes for PRD-QMS
6. QMS Integrated Process Redesign & Management

When applied in an overall QMS Process Redesign, various combinations of these address the QMS Process key goals questions in the following pages…..

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Q#1: How can we become more flexible?

- Current State — Outdated QMS Framework
  - Outdated FDA definition of GMPs and quality
  - Based upon inspection and documentation, as the foundation for defining product quality
  - Ensuring traceability when all under one roof in past

- Future State — Knowledge-Based Culture
  - Conclusion #1: shift QMS focus to science & process understanding as the foundation for ensuring product quality
  - Deemphasize non-value inspection and documentation

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Q#1: How can we become more flexible?

- Current State — Immature QRM Culture
  - Not consistently using Risk Management tools
  - Risk Management is secondary to documentation accuracy, even for non-significant items
- Future State — Rigorous Use of QRM
  - Conclusion #2: Quality decision-making based on scientific application of risk analysis
  - More holistic framework
  - Move QMS to Fit-for-Purpose

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Q#2: How can we become more Agile?

- Current State — Inconsistent Standard Work
  - Inconsistent GMP documentation hierarchy
  - Architecture OK, but inconsistently used
  - RACI structures exist, but not used or agreed upon

- Future State — Rigorous Process Management
  - Conclusion #3: Standardized tasks done Right The First Time
  - Conclusion #4: Formal use of RACI agreements

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Q#3: How to make risk more easily and meaningfully visible?

- Current State — Very Silo-Oriented
  - Little visibility into cross-functional activities
  - Metrics primarily lagging
  - No apparent governance of cross-functional activities

- Future State — Cross-Functional Process Mgt
  - Conclusion #5 Proactive governance of cross-functional activities
  - More use of leading performance metrics for quick CA
  - More accountability via RACI agreements
  - Visible process-performance metrics

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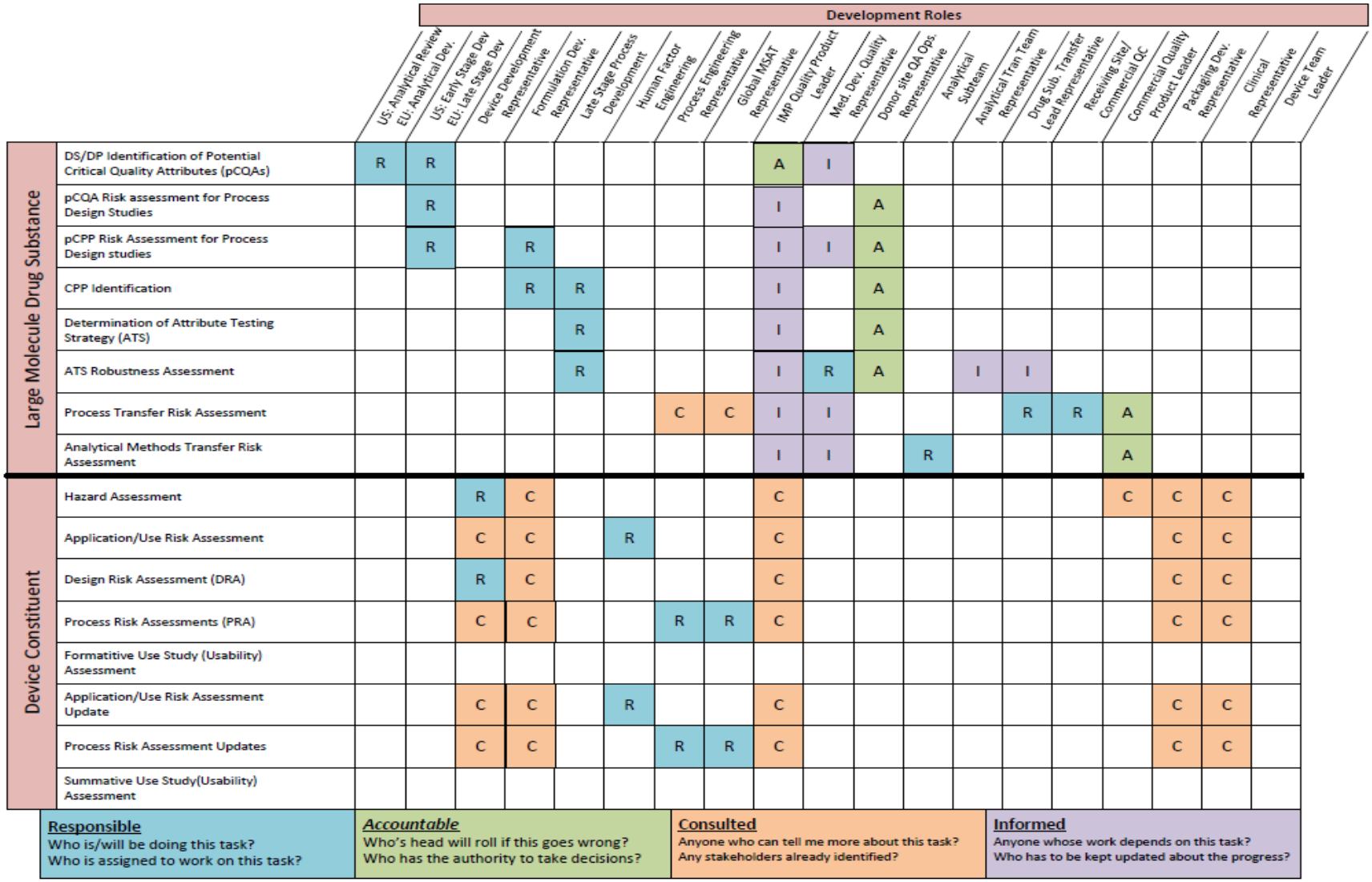
RACI



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Q#4: How to reduce operating complexity?

- Current State — Process Sub-Optimization
  - Five conclusions regarding process design deficiencies
  - Siloed organization; no end-to-end process management
  - Unclear decision-making responsibilities
  - Inconsistently defined process documentation
  - Process problems are solved with added procedures and continuously increasing process complexity (and costs)

- **Future State — Cross-Functional Optimization**
  - Cross-functional process management, collaboration and continuous improvement
  - Team-based practices for rapid continuous improvement

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Q#5: How to make QMS a competitive advantage?

- Current State — Increasing QMS Non-Value Overhead
  - Siloed organization; no end-to-end process management
  - Five conclusions regarding process design deficiencies
  - Process problems are solved with added procedures and continuously increasing process complexity (and costs)

- Future State — QMS Facilitates PR&D Aggressive CI
  - QMS process design and operations with the recommended improvements (1 – 5) focused on:
    - Continuously improving QMS support of PR&D operations
    - Reducing response times and turnaround times of the QMS interactions within the PR&D value-stream flow
  - Noticeably overtaking competitors

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Recommendations

- Localized Quick Fixes — Not Recommended
  - Continues process sub-optimization
  - Continuously increasing process complexity (and costs)
- High-Performing Organization — Recommended
  - All foundational elements in place; no weak links
  - Fully integrated QMS process and management
  - No process sub-optimization or increasing fragmentation
  - Continuously reducing response times and turnaround times
- **Best-In-Class Organization — TBD**
  - Level 5 performance all areas of QMS Processes
  - Potential QPL organization structure

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Conclusion

- Phase appropriate QMS requires a strong foundation in scientific understanding and framework for application as part of the drug development process
- Integrating risk management tools as part of the overall drug development process provides a framework for evaluating both CMC and Quality issues
- The key criteria which define high performing processes can be used to understand the current impediments within the QMS which are impacting product development

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