CMC Outsourcing
Process, Tips and Checklists

September 2018

Don’t Underestimate Lead Times

- Lead times can be
  - 2-6 months to ID and secure CROs or more
- Many factors can add up / compound the issue
  - Time to ID and Screen true capabilities and fit takes time and iterations
  - CDAs can take time
  - Vendors need 2-5 weeks to prepare a good response to RFP
  - Scheduling site visits and audits depends on existing client schedules
  - No two CROs are exactly alike
  - Some technologies / unit opps are not common or all in the same location
  - The CRO you want may not be interested or feel comfortable with your project
  - Negotiations & Contracting iterations
  - Seasonal factors can stretch lead times further

If This Is New to You…

- Manage your Board – timelines and lead-times for selection and start-up
- Get Ts & Cs & Quality Agreement templates with proposal or earlier
- Use the CMO / CRO Quality Agreement templates
- Get some SOPs in place – just a handful needed, most one-pagers
- Go to Outsourcing conferences – build your knowledge and network
- Use good consultants – often DIY = OMG
  - Smart as you are, is the first one the place to learn?
  - Consultants can save you hundreds of thousands and time
- Don't formet to understand need for Analytical methods
- DON'T FILL OUT CMO QUESTIONAIRES
  - With a good RFP you do it once rather than many times
  - Don't contact CMOs until you have initial technical, scale and timing assumptions

Checklist

Descriptions and Tips

Outsourcing Checklist for Success

Item	Comments
✓ Integrated Development Plan	Core Enabler - Always changes but think it through before you start to write RFP
✓ The Right SOPs	Core Enabler - some before RFP, others in time for GMP
✓ Data Plan	Core Enabler - think it through before you write RFP
✓ Resources in-House to Manage	Core Enabler - before you start to write RFP
✓ Process for Selection	Core Enabler
✓ Know Your Requirements	Varies by project but aim to not change after the RFP
✓ Finding CRO Candidates	Varies by Project
✓ Selection Criteria	Varies by Project
✓ RFP Template	Varies by Project
✓ Contracting / Ts & Cs	Be prepared to integrate your needs with CRO's
✓ Quality Agreement	Be prepared to integrate your needs with CRO's

Data Plan

A key to Effective Outsourcing

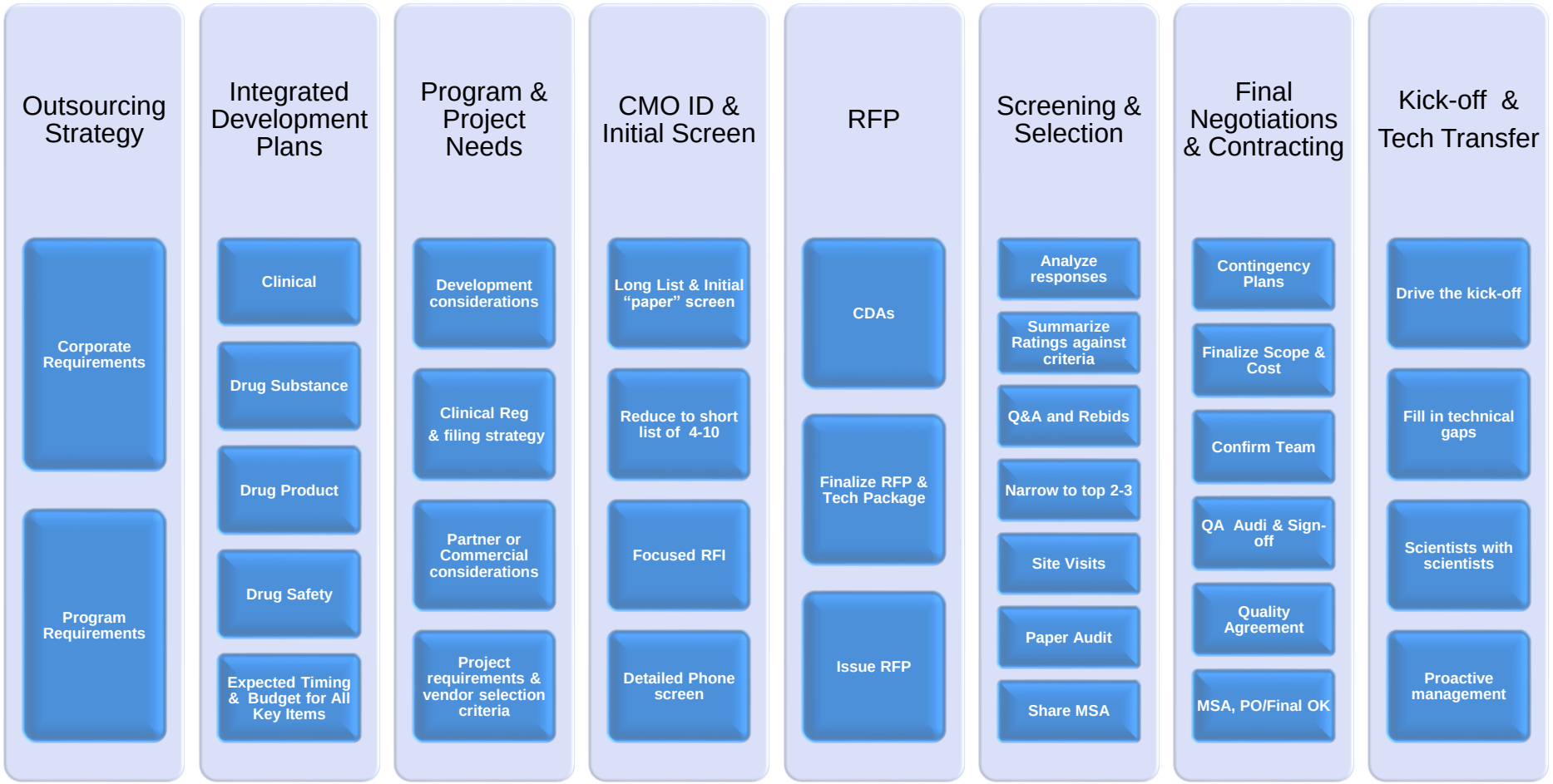
Data Plan and Considerations

- Buying supply, AND technology & registration enabling Information and reports
- Understand data needed for submissions, decisions, partners or for commercial objectives
  - Where will it come from
  - Who will QC, format and write
  - In what form do you need
  - How will you file it / access it when you need it
- What will your Development Reports look like?
  - What was tried, what worked and did not, results, and evolution, linked to notebook records and preliminary reports.
  - How the process and analytical procedures evolved into a manufacturing process and quality control test methods
  - Enable learning / problem solving, process parameters & control strategies for registration
  - Make sure you define / agree the report format up front

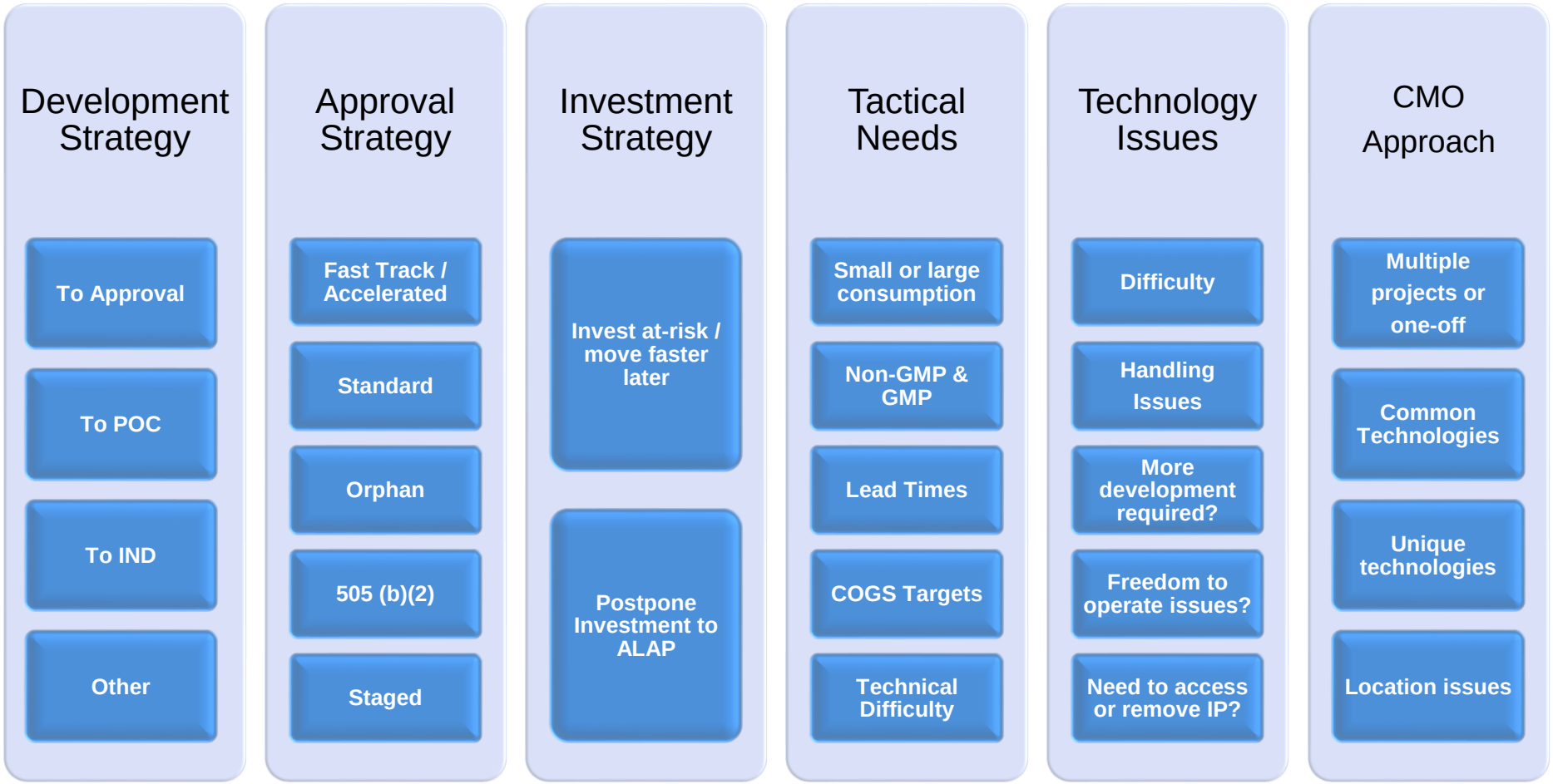
Vendor Selection

Effective Outsourcing

CMC Example
Structured Process Tips for Success



Variables to Consider for CMC Outsourcing



RFPs – They Save Time and Money

A Key to Effective Outsourcing

RFP Package

- Package to assemble
  - Workscope
  - Technical and Timing Requirements
- RFP structured to
  - Enable objective and complete comparison of the candidates
  - Expedite the development of a contract
  - Help CMO understand required scope, potential for expansion / change and their risk
  - Help CMO to understand their risk
    - Avoid taking on a project with more scope that visible
    - Understand potential impediments to meeting timeline
    - Fit with their skills and schedule
- Complete enough to provide the basis for workscope, pricing and terms
- Background described in the RFP once can be leveraged across functions

RFP Contents

- Brief description of your company (optional)
- Brief description of the product (along with Material Safety Data Sheet and handling instructions)
- Overall project objectives and timeline
- Detailed scope for CRO's portion of the project:
  - Process description with flow chart and bill of materials if appropriate
  - In-process and product test methods and target specifications
  - What will be delivered to CRO and by when
  - What the CRO is expected to deliver back and when
  - Desired pricing structure (i.e., fixed price versus time and materials, unit price versus batch price, etc.)
- Requests for information, including:
  - Financial status of the company and description of pharmaceutical development and commercialization programs, if any.
  - Confirmation of absence of conflicts of interest
  - References, inspection history
  - Manufacturing success rate
- RFP response instructions (due date for submission of response, name and address of person to whom the responses should be directed, etc.)

Tech Package for Vendors

A key to Effective Outsourcing

CMC Technical Package and Tech Transfer

Drug Substance

- Technology – Route, process
- Raw Material specs & vendors
- Unit Operations as practiced
- PD History, if any
- Batch Manufacturing History
- Current IPCs at R&D stage, rationale and CPPs
- Storage requirements for raws, in process and final product
- Mass Balance as complete as possible
- EH&S info; Process Risks and Controls – incl waste streams, MSDS
- Analytical Requirements
- Dev Reports, Methods protocols, tech trans plans, & validation reports, if ready
- Proposed specs for API
- Batch size assumptions – CTM, Reg batch, validation batch, commercial and projected forecast

Drug Product

- API and Excipient grades & suppliers
- Batch Mfg. History
- Specs for API and excipients incl micro
- Excipient functionality
- EH&S info, risks, incl waste streams,
- Detailed characterization
- PD History Report
- Current IPCs and rationale and CPPs
- MBR & , ancillary batch docs
- Storage for raws, wip & final product
- Dev. Reports, Methods protocols, tech trans plans, & validation reports, if ready
- Stability information (API, intermediates and final product)
- Cleaning procedures and tests: operator exposure, disposal etc.
- Packaging
- Batch size assumptions – CTM, Reg batch, validation batch, commercial and projected forecast

Vendor Selection Criteria

A key to Effective Outsourcing

Often Overlooked Considerations

Criteria	Consideration / Capability
Capacity / Scale	• Current Stage vs. later needs and implications
Overall Capability	• Tech Transfer (ability in and out to someone else) • Experience supporting submissions • Ability to source of all raw materials
Project Specific Technical Capability	• Unique technical deliverables and their “transportability” • Response to RFP and scientific approach
Quality	• FDA inspection or approval history • Capabilities & Phases the Quality System can support • Import / export processes for incoming and outgoing • Strength of their Vendor Qualification Program
Location	• Your capacity to manage distance and cultural issues • Internal tech transfer capability across locations
Proprietary technology /tech transfer	• Does CRO propose to use proprietary technology / royalty burden • Ability to transfer process or qualify back-up CRO / CMO
Other	• Adequately capitalized • Recent performance vs. dated perceptions • How busy are they • Size / fit – how important are you to them • Personal chemistry of the actual team that will do your work

Contracting & Negotiations

A Key to Effective Outsourcing

Other Business Agreement Elements

Future issues can be avoided by anticipating needs and building them into contract terms

- Provision for future supply and/or additional projects
- Rights to all IP and know how required to produce the product
- The right to transfer the production technology and qualify other sites to produce the product
- Pricing to manage risk
  - Payment obligations triggered by acceptance of deliverables
  - Bonus payments for development and demonstration of specific yields, which in turn tie to lower unit pricing for product supply
- Dealing with risk of loss
  - Typically DP CMOs do not add enough value to take on risk of loss of API value
  - Coverage of Negligence and Misconduct
  - Ability to negotiate assumption of risk of batch failure increases with process maturity, validation
- Alignment with Quality Agreement

Commercial Agreements

- When is the right time in development to begin the discussion and frame the elements business arrangement
  - Pricing
  - Mechanism for price changes
  - Handling of yield
  - Ability to go elsewhere
  - Risk Mitigation

Quality Agreement Checklist

A Key to Effective CMC Outsourcing

Quality Agreement

- Clearly articulate technical and regulatory roles and responsibilities
- Phase-appropriate differences
- Integrated with Terms and Conditions, MSA or Supply Agreement
- Roles and Responsibilities matrix is more easily read and used by operating personnel than a legalese document but both are important
- Needed for GMP
- Not typical in US for GLP

Quality Agreement R&R

Item	Issues & Responsibilities, Drafting, Review & Approval
❑ Org and Personnel	Be aligned on role of Quality Group and training
❑ Facilities	Commitment to compliance, access control, prevention of cross contamination
❑ Equipment	Qualification, cleaning logs & control
❑ Materials & packaging	Spec setting, testing, retention, approval of suppliers
❑ Production	Development, review and approval of MBR, BR, specs, deviations, reprocessing / rework, EM, retention, definition and handling of deviations
❑ Analytical	Specs, methods, sampling, OOS / Investigations, Turnaround time, validation, Right to participate in investigations
❑ QC	CofA, Product Disposition at various stages
❑ Label, Pkg, Ship & Storage	Label text, layout, retention, retest dates, storage conditions, shipping, inspection. Consider if need is more than 5 years and receiving at end of the period.
❑ Stability	Plan, reporting and approval
❑ Change Control	Clarity on how it will work
❑ QA	Complaints, recalls, MSDS, Auditing, Release, Timing of notifications
❑ Audits and Inspections	Access to facility for Audits, manufacturing oversite
❑ Regulatory Inspections	Notifications, Communications, timing
❑ Regulatory Filings	Initial, annual and ad hoc
❑ Expiry	R&R

We hope this was helpful!

For more information please contact:

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