On Time and Within Budget

Make Friends and Even Have Fun While Outsourcing

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Discussion Objectives

Keep audience awake after dinner and help audience keep outsourced CMC off the critical path.

- Insights for managing expectations across your organization,
- tools for shrinking lead-times and gaining speed where possible
- often overlooked technical and business considerations
- Some useful checklists
- Shameless self promotion ***(Just Kidding!)***

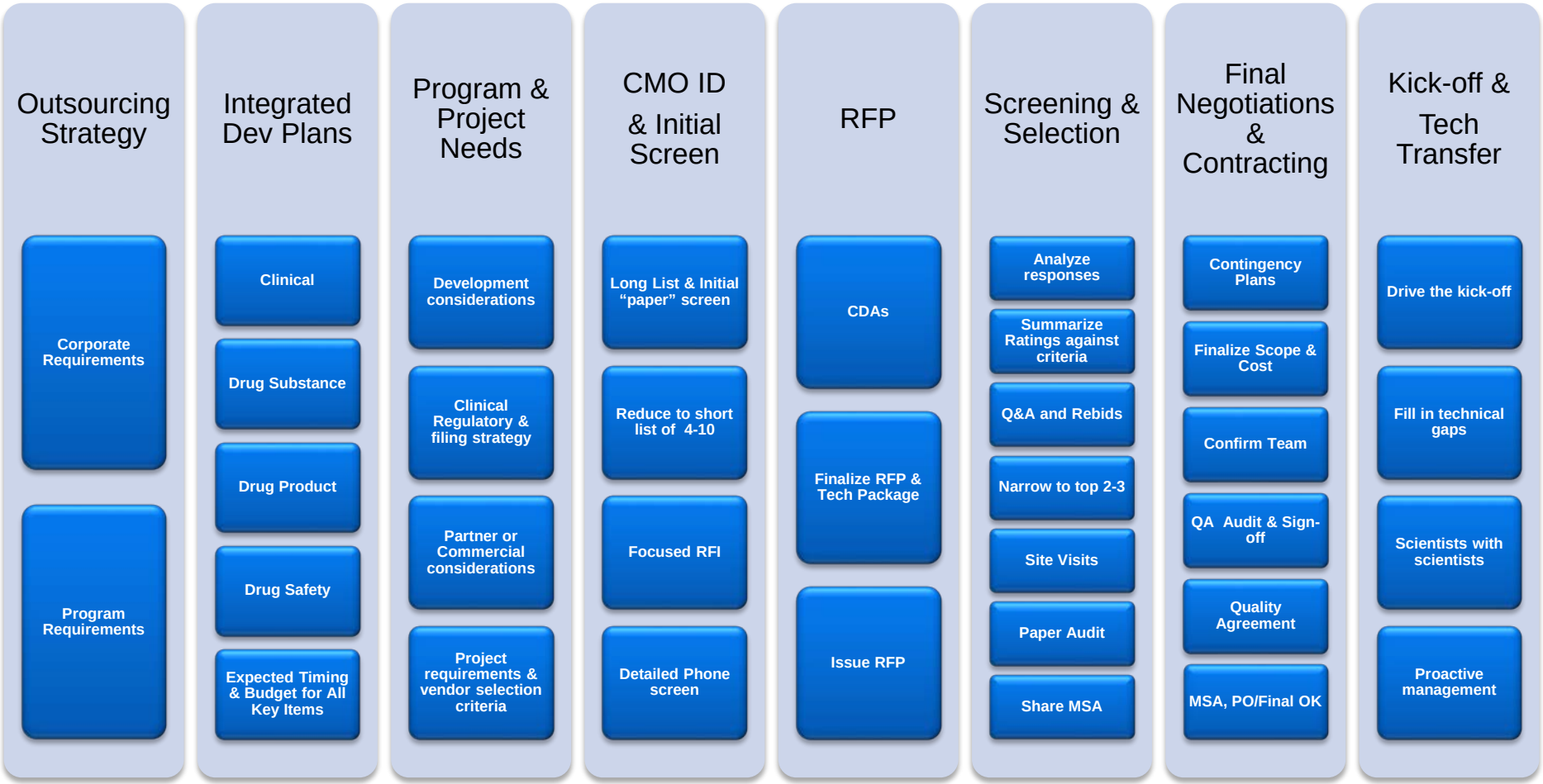
Format

- Survey-level discussion tonight
- The details, checklists and tools as back-up take-aways

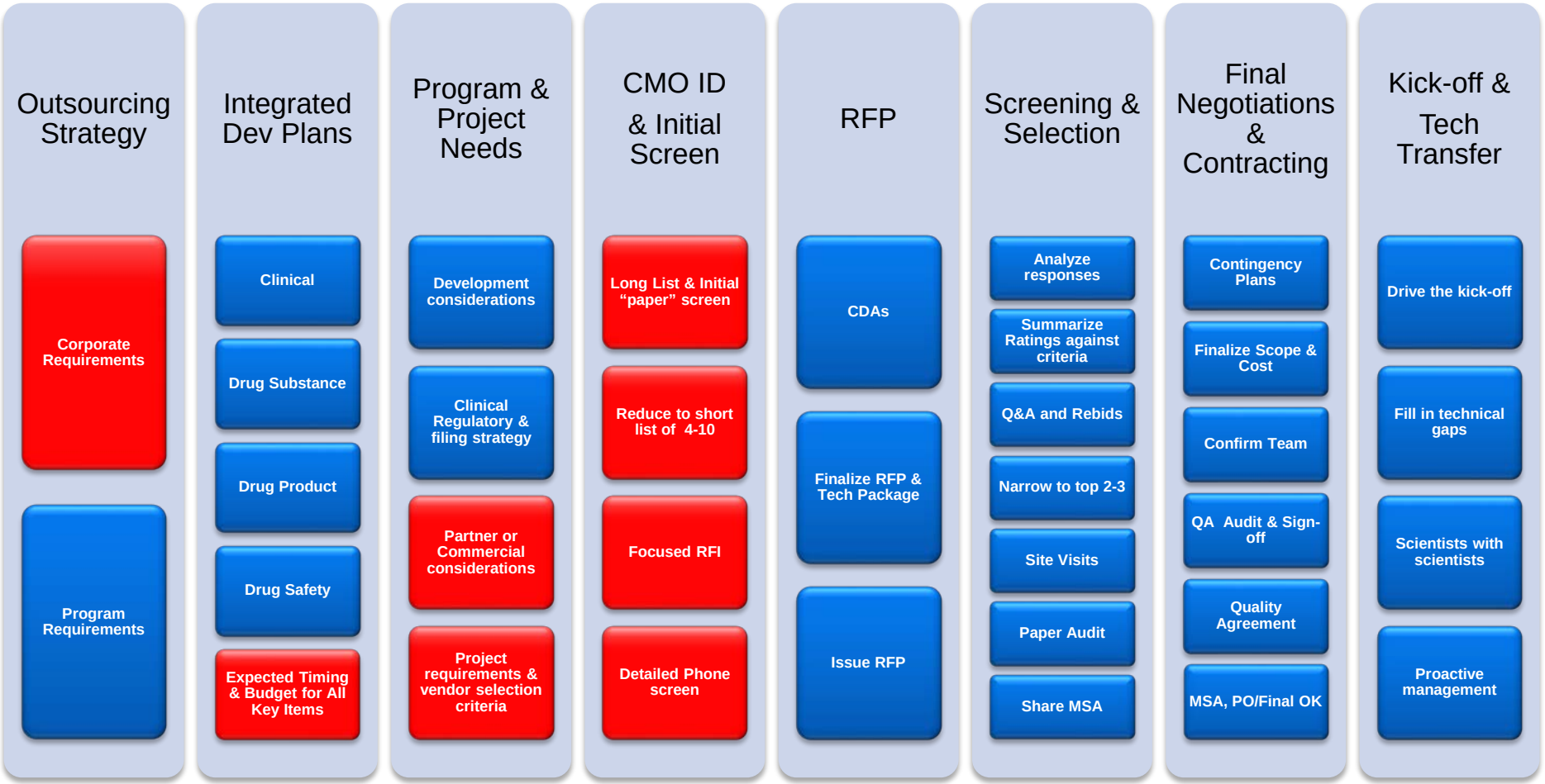
So Your CEO Says Your Part is Easy…

All cars go at the same speed BUT…
The DP caboose is a rougher ride and…
Is moving faster than the API car at the peak

A Structured Process Works! Just Using Parts Can Help



Sources of Problems We Often See



Root Causes We Typically See

Corporate Requirements	• Dictated top down timelines – a fact of life • Management expectations based on Rules of Thumb, big pharma experience or of a retired person on the board
Program Requirements	• Unclear volumes for later stages and commercial • Forget to consider all territories for clinical or commercial • Limited assumptions for transition to future clinical stages • Lifecycle e.g. transition from Lyo to PFS
Development Plan Timing & Budget	• Optimistic lead-times • Lack of actionable integration across functions • PPT development plans
Project Requirements	• Output focused - limited attention to specific equipment needs • Limited attention to analytical needs and ancillary services
CMO ID & Screen	• Reliance on limited recommendation – “hey we had success with…” • Too few candidates
RFI	• Lack of focus on learning HOW the CMO will deliver
RFP	• Missing scope • Incomplete consideration of analytical, packaging, reporting

Planning and Managing Expectations

- Overall
  - Use facts help manage expectations and bring solutions to management
- Planning – Selection Takes Time and Effort
  - 2-6 months to ID and secure CROs or more – CDAs, 3-5 weeks for a proposal
  - No two CMOs are exactly alike
  - Scheduling site visits and audits delays are on both sides
  - Negotiations and contracting
- Planning - Execution
  - Plans for failure and delays – technical, business, operational?
  - Factoring in analytical dev, release of API, validation, components?
- Data Planning
  - Going to need anything for a submission or just making some stuff?

Figuring Out General Requirements

- Volumes
  - Rough volume estimates for later stages and commercial
  - Need for selection and implications for scale-up
  - Us a “planning” estimate for internal input, not commitment
  - If there are no estimates of potential, why are you in the clinic?
- QA
  - Plan for your Quality Unit – rarely see it done early.
  - Only need a handful of SOPs can enable speed
  - Less for FDA than for Partners at early stage
  - How will you handle batch disposition, deviations and change control

Figuring Out Scope-Specific Needs

- Analytical
  - Testing and technology for apples and apples comparisons and completeness
  - Lab equipment that partners use if partnering out – easy to transfer?
- Packaging
  - Container closure can be one of the longest sterile fill lead times
  - Kitting and other clinical considerations / links with clin-ops
  - Combo product / vendor / human factors considerations
  - Serialization and anti counterfeiting if later stage – many CMOs inexperienced
- Future plans
  - Can this CMO really do what you need next? Long term?
  - Are you and Management aligned on transfer timing and cost if not?
  - Timing and type of development expertise needed

Data – Not Just Buying CTM…

- Buying supply, AND technology & info for submissions
- What's data need for submissions, decisions, partners or commercial
  - 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, evolution
  - Linked to notebook records and preliminary reports.
  - Enable learning, problem solving, control strategies, info for Due Diligence
  - Define / agree the report format early

How to Look

- Document your requirements
  - Not just what but how
  - Vessels, scale of TS or Lyo, process technologies needed
- Don’t rely on recommendations alone
  - Just because someone knows someone that was good does not mean…
  - Things change for better and worse
  - Remember the rule about golf courses
- Don’t contact too early
  - Have your requirements done – don’t let CMO define
  - Waste CMOs time, may set wrong expectations down wrong path
  - You may end up paying more
  - Do you want to fill out many questionnaires?

Where to Look

- Build a good list
  - Many will drop out – sometimes all!
  - Often drop out late in the game!
  - It is a new effort every time
- Don't assume one stop shop
  - Been “ on the horizon” for 20 years
  - DS and DP in same suite or building?
  - CMO Sharing FTEs across DS & DP?
  - Are current roll-ups benefitting us or more a play for Wall Street?
- Company Size matters
  - What is their mix of customers like you?

Contracting - Preparation

- MSA or no MSA?
  - If managed right, won't slow things down
  - Time and cost to revise CMO Ts & Cs anyway
  - Know what you MUST have in there in advance
- Understand the value of what you are buying before you start
  - Time-in-plant need, cost of consumables, development needed
- Understand the value of the API that will actually be in CMO's hands
  - Avoid misalignment on level of potential risk of loss
- Consider staged workscope or LOI to start fast

Contracting – Speeding up the Process

- Get CMOs MSA and Quality Agreement when you send RFP
  - Start with CMOs Quality Agreement
  - Don't want an exception process for the CMO Operators
- Align MSA / Ts & Cs with Quality Agreement early in the process
  - Ensure completeness and no conflicts– can agree on QTA first?
- Work out the business and technical issues before bringing in the lawyers
  - Great as they are, only a few areas where Lawyers can speed things up

The Contract

- Some things we see people overlook:
  - Rights to transfer the technology and qualify other CMOs
  - CMO commitment to support of transfer
  - Payment triggered by acceptance of deliverables if practical
    - Consider bonus payments for certain situations
  - Clarity on content of batch documentation, time to review BRs, ability to reject and process for determining responsibility
  - Risk of Loss
    - Typically scope value to CMO to low to take on risk of loss
    - BUT coverage of Negligence and Misconduct is not unfair
    - Yield incentives and penalties for validated process
  - Lead-time for site closure or change
  - Alignment with the MSA
  - Of course, future supply and/or additional projects, Rights to all IP etc.

Commercial Considerations

- When is the right time to Negotiate a Commercial Supply Agreement?
  - Why not start earlier
  - Understand and agree or define the negotiation for the business elements and some of the mechanisms that will govern the commercial relationship
  - Can be done with limited commitment on both sides
  - Some elements to understand
    - Range of pricing given assumptions
    - Mechanism for price Increases
    - Forecast horizons and commitment expectations
    - Mechanisms for Gain / Risk sharing re yield and improvements
    - Capacity availability / queue

Relationship - Basics

- Careful how you use the word “partner” - Partnership is a legal relation existing between two or more parties contractually associated as joint principals in a business usually involving close cooperation between parties having specified and joint rights and responsibilities”
- Pharmaceutical Outsourcing still in infancy – Best Practices evolving
- CROs are in a very challenging and often up and down business
  - It costs real money to generate a proposal
  - CMOs focus on doing what customers ask – they may not tell you you’re wrong
- CROs are a service business, you are one of many clients with changes impacting CMO ability to adjust
- Clients that keep changing their mind create a ripple effect of cost
  - What if your boss treated you as you treat your CMO – insulate your CMO from your boss…

Relationship – Proactive and Early!

- Success enablers often set before kick-off
  - Be proactive and have realistic expectations of timing as things change
  - Have adequate resources for CMO guidance, oversight and to cover distance & cultural issues
  - Constant planning - only certainty is that things will go wrong so plan accordingly with lead times in mind
  - Understand CMO need to balance multiple client schedules
  - Early on-site involvement often means less time fixing things later
  - Clear PM roles and info flow BUT enable scientist-to-scientist interaction when needed
  - Strive to be easy to do business with while being clear and firm on your requirements
  - Be sensitive to how your changes impact the CRO
- More often than not, the sponsor could have avoided the problem

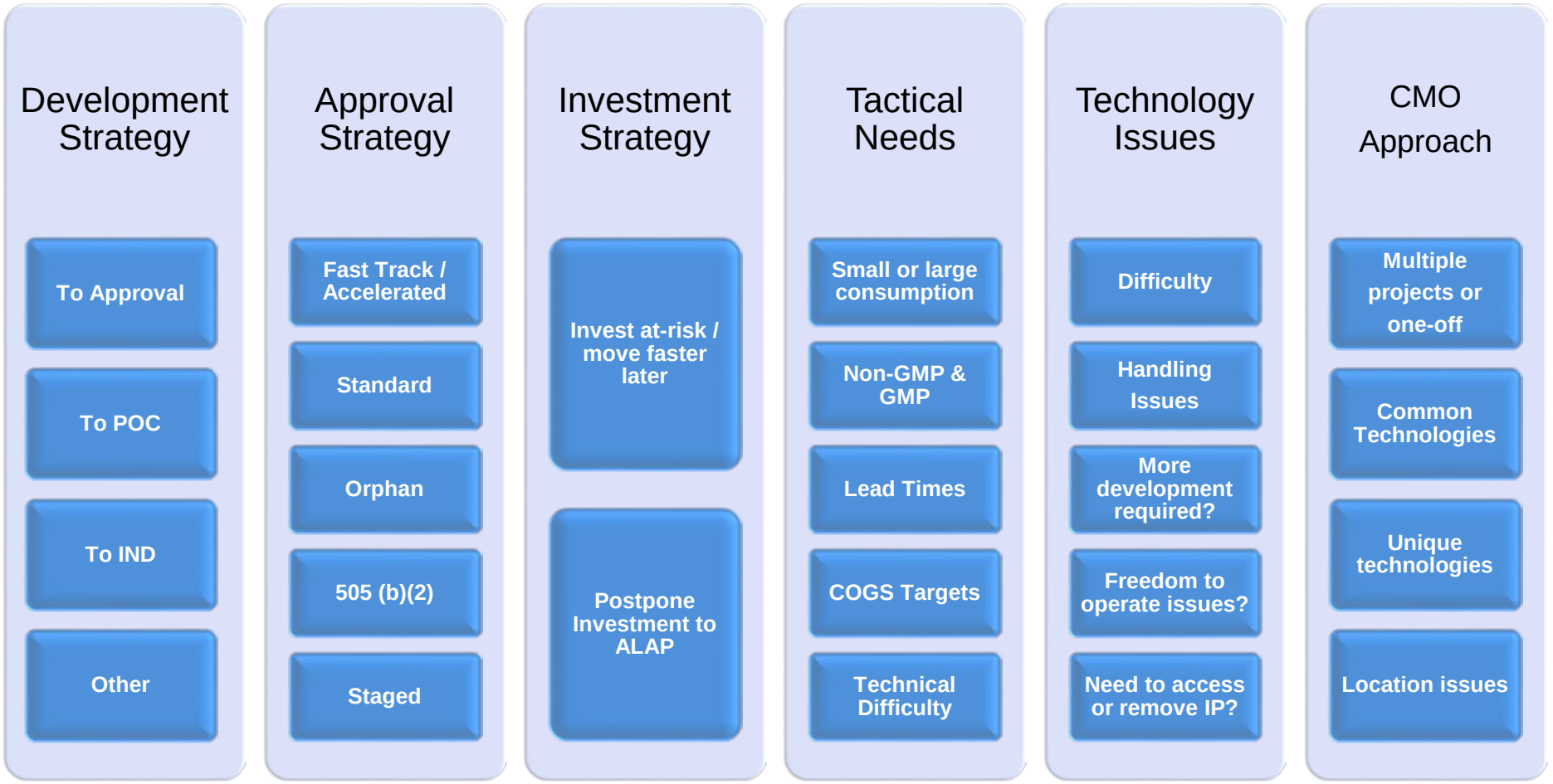
Checklists Etc.

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 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

Variables to Consider



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

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 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

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 than they proposed on
    - 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 that there are no 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.)

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. Decide if need is more than 5 years and having them sent back after that./
❑ 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

Hope it was helpful…
Thanks for your participation!

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