On Time and Within Budget
Make Friends and Even Have Fun While Outsourcing

New England PDA
November 15, 2017

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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

## Outsourcing Strategy
- Corporate Requirements
- Program Requirements

## Integrated Dev Plans
- Clinical
- Drug Substance
- Drug Product
- Drug Safety

## Program & Project Needs
- Development considerations
- Clinical Regulatory & filing strategy
- Partner or Commercial considerations
- Project requirements & vendor selection criteria

## CMO ID & Initial Screen
- Long List & Initial "paper" screen
- Reduce to short list of 4-10
- Focused RFI
- Detailed Phone screen

## RFP
- CDAs
- Finalize RFP & Tech Package
- Issue RFP

## Screening & Selection
- Analyze responses
- Summarize Ratings against criteria
- Q&A and Rebids
- Narrow to top 2-3
- Site Visits
- Paper Audit
- Share MSA

## Final Negotiations & Contracting
- Contingency Plans
- Finalize Scope & Cost
- Confirm Team
- QA Audit & Sign-off
- Site Visits
- Quality Agreement
- MSA, PO/Final OK

## Kick-off & Tech Transfer
- Drive the kick-off
- Fill in technical gaps
- Scientists with scientists
- Proactive management

## Program & Project Needs Considerations
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Sources of Problems We Often See

Outsourcing Strategy
- Corporate Requirements
- Program Requirements

Integrated Dev Plans
- Clinical
- Drug Substance
- Drug Product
- Drug Safety
- Expected Timing & Budget for All Key Items

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## Root Causes We Typically See

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

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

#### Development Strategy
- To Approval
- To POC
- To IND
- Other

#### Approval Strategy
- Fast Track / Accelerated
- Standard
- Orphan
- 505 (b)(2)
- Staged

#### Investment Strategy
- Invest at-risk / move faster later
- Postpone Investment to ALAP

#### Tactical Needs
- Small or large consumption
- Non-GMP & GMP
- Lead Times
- COGS Targets
- Technical Difficulty

#### Technology Issues
- Difficulty
- Handling Issues
- More development required?
- Freedom to operate issues?
- Need to access or remove IP?

#### CMO Approach
- Multiple projects or one-off
- Common Technologies
- Unique technologies
- Location issues
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

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

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<thead>
<tr>
<th>Item</th>
<th>Issues &amp; Responsibilities, Drafting, Review &amp; Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>❑ Org and Personnel</td>
<td>Be aligned on role of Quality Group and training</td>
</tr>
<tr>
<td>❑ Facilities</td>
<td>Commitment to compliance, access control, prevention of cross contamination</td>
</tr>
<tr>
<td>❑ Equipment</td>
<td>Qualification, cleaning logs &amp; control</td>
</tr>
<tr>
<td>❑ Materials &amp; packaging</td>
<td>Spec setting, testing, retention, approval of suppliers</td>
</tr>
<tr>
<td>❑ Production</td>
<td>Development, review and approval of MBR, BR, specs, deviations, reprocessing / rework, EM, retention, definition and handling of deviations</td>
</tr>
<tr>
<td>❑ Analytical</td>
<td>Specs, methods, sampling, OOS / Investigations, Turnaround time, validation, Right to participate in investigations</td>
</tr>
<tr>
<td>❑ QC</td>
<td>CofA, Product Disposition at various stages</td>
</tr>
<tr>
<td>❑ Label, Pkg, Ship &amp; Storage</td>
<td>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./</td>
</tr>
<tr>
<td>❑ Stability</td>
<td>Plan, reporting and approval</td>
</tr>
<tr>
<td>❑ Change Control</td>
<td>Clarity on how it will work</td>
</tr>
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<td>❑ QA</td>
<td>Complaints, recalls, MSDS, Auditing, Release, Timing of notifications</td>
</tr>
<tr>
<td>❑ Audits and Inspections</td>
<td>Access to facility for Audits, manufacturing oversite</td>
</tr>
<tr>
<td>❑ Regulatory Inspections</td>
<td>Notifications, Communications, timing</td>
</tr>
<tr>
<td>❑ Regulatory Filings</td>
<td>Initial, annual and ad hoc</td>
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<tr>
<td>❑ Expiry</td>
<td>R&amp;R</td>
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