Effective Oversight of Analytical Method Development, Qualification, and Testing for a Bioproduct Portfolio in a FIPNET World

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Agenda

• Models for Outsourcing
  – Sourcing Considerations
  – Technical Considerations
  – Building Collaborative Relationships

• Examples of Technical Challenges
  – Non-compendial methods
  – Characterization methods
Models for Outsourcing

• Considerations for CRO selection
• Analytical and formulation deliverables for early-phase projects
• Logistical considerations
• Building collaborative relationships
Sourcing considerations and CRO selection criteria

What ‘work’ will be outsourced?

- Phase and scope of work
  - Candidate selection to initiation of commercialization
  - Commercial development (prior to Ph3)
  - Routine testing for Phase 3 / Commercial
- Timing criticality
  - Urgency
- Technical complexity
- Lilly’s technical capability
- Knowledge-rich or rules-based work
  - Control strategy/ DP design
  - Lab work
- Capacity (internal/ external)
  - Is internal capacity availability?

Where should we outsource?

- Technical capability of CRO
  - MAb, analytical, characterization, biophysical, formulation/DP process dev
  - Instrumentation/ equipment
  - # of experienced scientists
- Quality systems
- Cost
- Logistics (impact on cost and efficiency)
  - Potential to bundle with CT manufacture or API development manufacturing
  - Sample / material shipping
Candidate Selection to First Human Dose: What’s done internally versus externally

Lilly formulation/ analytical team member
• Provide input for CMC plan (strategy, timeline, budget etc)
• Functional strategy, plan and execution (RFP, work order, protocol/ data/ report reviews, method transfer )
• Data interpretation & key decisions (e.g. formulation selection, analytical control strategy)
• Technical agenda (data interpretation/ technical problem-solving)
• Key documents (spec document, PFD, stability protocol, clinical dosing instructions, pharmacy brochure)
• Interfacing with program teams (understanding tox and clinical needs,)
• CT interface (RFP, tech transfer, dating extensions, temp excursion justification)
• Regulatory documents (INDs, responses to questions, annual reports, amendments)

CRO Deliverables per typical RFP for early phase:
Analytical
• Method development/ optimization (DS and DP)
• Method qualification
• Test development samples (DS process, formulation)
• Reference standard filling and characterization)  
• Development lot (prototype, tox, etc) characterization & stability
• Elucidation of structure
• GMP release testing (DS and DP)
• GMP stability storage and testing (DS and DP)
• In process testing for API GMP lots (support of pilot plant)
Formulation
• Preformulation studies
• Lyophilized formulation development
• Demo lot manufacture and robustness studies
• Tech transfer for CT manufacturing
• One solution formulation stability
• Clinical in-use and compatibility study

For all of the above, draft/ complete protocol, execute study, complete data integrity and write reports

*Lab supporting underlined testing needs to be geographically close to customer group to streamline logistics
Capability and Logistics

- Bundle work as much as possible
- Creates efficiency, simplified workstreams, and flexibility

API Process Development
- GMP API Manufacturing

Bioassay
- Analytical Development and GMP Testing

Formulation Development
- GMP DP Manufacturing
Potential Implications of Different Models

- Insourcing – provides flexibility and access to internal systems, but least technical oversight by CRO
- Stand-alone analytical testing – CRO has limited access to process information, sometimes has limited investment, particularly if methods were transferred to, rather than developed at, CRO
- Bundled analytical development (± formulation development) and GMP testing – potential for high capability / investment
- Bundled analytical testing and GMP manufacture – potential for high capability / investment; also potential for delayed communication to sponsor

Risks to productive relationships:
- Staff at sponsor institution are concerned about own job security
- Direct contact between scientists limited by cumbersome business processes
Building Collaborative Relationships

CRO Responsibilities
• Meeting commitments with respect to technical, quality, and timing agreements
• Communication of difficulties
• Support of regulatory requests

Sponsor Responsibilities
• Clear expectations, defined upfront
• Timely response
• Technical expertise
• Prioritization, when needed
• Respect and appreciation

Analytical outsourcing is a joint project
• Goal: *Our* data, *our* methods
Control and Characterization Methods

• Compendial Methods
  – Sample preparation
  – Demonstration of suitability

• Non-compendial methods
  – Challenges with GMP testing (CEX, RP)

• Characterization tests
  – Control of methods not covered by quality system
  – Scope of methodology (lack of clear acceptance criteria)
CEX Method Example

- Method transferred successfully to new lab.
- Method had been routinely used for ~5 years (testing across 6 other labs)
- Observation in new lab was that columns were not performing well when new, or function well for one run then lose resolution.

Identified that organic rinse solutions were being used as a standard lab practice, and the exposure to organic solutions was impacting column performance.
Protein Fc-Fusion

- Molecule subject to proteolysis and oxidation
- Reduced RP method developed to monitor closely related species in ~50 kDa polypeptides
- Required close collaboration between Analytical and MS functions (at both sponsor and CRO)
Protein Fc-Fusion

- Process changes resulted in material with different stability and different profiles
- Created challenges for analytical and formulation
  - Different distribution of clipped forms changed tactics for method qualification
  - Some pre-formulation work repeated
- Required modification of contract

RS#1 Main Peak = 61.8%
RS#2 Main Peak = 60.9%
Proto DS Main Peak = 61.8%
Control of Draft Methods

- Development of RP methods for protein-Fc fusion
  - Technically challenging separation, coupled with process changes
  - Drafts incremented with changes
    - Data summaries include unique method identifier
    - Allows tracking of changes across studies or lots
  - Extended to subsequent projects and to characterization methods – building best practices
Characterization Methods

• Exist outside of standard specification paradigm
• Regulatory expectation
• New methodologies, but methods generally less characterized than specification tests

• How to run these so as to generate reliable data?
  – Set criteria, expectations, targets, alert limits,…
• How to turn a complex technique into a routine method? How to run so as to avoid endless rework loops or excessive reliance on off-site experts?
  – Limit scope
  – Build “second-stage” testing into method
DLS Applications by Phase

• Early phase (formulation development)
  – **Purpose:** Quickly discharge risk associated with HMW species that may not be detected by other analytical techniques
  – **Requirements:** Low technical complexity, amenable to high-throughput, output is straightforward to interpret
  – **Solution:** “Binary” result (HMWs = yes or no); tool used to identify need for further investigation

• Late phase (e.g. DP process development)
  – **Purpose:** Correlate failure modes with measurable solution properties; try to generate first-principles understanding
  – **Requirements:** Flexible and highly adaptable method to accommodate unique customer requirements; extract maximum information content from measurement
  – **Solution:** Iterative approach; use in combination with separation processes (e.g. sequential filtration) or other sample manipulations; look at all available outputs, beyond “binary”
DLS Examples

Early phase

Need to distinguish among...

Evidence of HMWs - possible trigger for additional investigation

No HMWs - risk is discharged

False positive - artifacts from sample prep or measurement

...as efficiently as possible

Late phase

Investigate filter clogging

+DLS shows good sensitivity to very low levels of HMWs generated by mixing
+After 0.22um filtration, scattering returns to baseline
+Used in combination with other particle characterization techniques
Dynamic Light Scattering Method, version 1

• Analysis detects presence of HMW species

• Issue: When result is unclear, confidence in data quality must be established
  – Existing suitability criteria control overall signal strength, consistency and correlation function
  – Criteria don’t include technical evaluation by SME
  – Criteria are missing an evaluation of consistency of modeled data (which is the presented output)

• Data mining: Main peak width variability critical parameter

• Solution: Implement more comprehensive, quantitative data review, instructions for alternative sample preparation, and data reporting.
Dynamic Light Scattering Decision Flowchart

Obtain Data: Determine cps, cps %RSD, Z_{avg} %RSD, Peak 1 Width %RSD, y-intercept, correlogram resolved plateaus

Pass System Suit?

1^\text{st} \text{ iteration}

No

SME Analysis: Including aggregate evidence, molecule size, sample concentration

Accept Data?

No

Centrifuge Sample Use new cuvette

Yes

Report all data sets: Peak 1 Size, Peak 1 Width, Z_{avg}, PdI, Modality, Size Distribution by Intensity Overlay, Corellogram Overlay

2^\text{nd} \text{ iteration}

Yes

No

1^\text{st} \text{ iteration}

No

Centrifuge Sample Use new cuvette

Yes

Report all data sets: Peak 1 Size, Peak 1 Width, Z_{avg}, PdI, Modality, Size Distribution by Intensity Overlay, Corellogram Overlay
Conclusions

• Multiple models for analytical outsourcing
• Relationships most successful when well-managed
• Technical challenges similar to in-house
  – Made more difficult by distance and dual QA systems
• Good potential – often realized – for strong collaborations and effective drug development
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