How to Select a CRO for Support in Chemical Characterization (E&L) Studies

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The Practical Realities of Engaging a CRO for Chemical Characterization Studies

- **The collection, interpretation and utilization of extractables or leachables (E&L) data are not trivial processes** and the scientific and practical requirements for performing these activities may be beyond the technical and/or resource capacities of many organizations …
- As **extractables and/or leachables assessments can be extensive and expensive**, a high level of diligence must be exercised in identifying, qualifying and utilizing a CRO to perform E&L studies.
- **Understanding the nature of the service** that the user seeks from the CRO **and performing a rigorous and in-depth qualification** of the CRO **are key success factors** in establishing an effective and efficient user-supplier relationship.

Source:

D. Jenke. Insights gained into the identification, qualification and utilization of CRO laboratories in extractables and leachables studies. *Pharmaceutical Outsourcing*. **14(2)**: 20, 22, 24-26 (2013).

The sad truth is that
the truth is sad

lemony snicket

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The Practical Realities of Engaging a CRO for Chemical Characterization Studies

On the Positive Side:

There are many “battle-tested” CROs out there who combine the proper analytical capabilities with a passion for excellence and a broad-scope, in-depth understanding of the special issues associated with E&L assessment gained from years of practical experience.

On the Negative Side:

1. There are CROs out there whose expertise is “under development”.
2. Even the best CROs can be earnest but naïve.
3. All companies seeking CRO support have their own unique circumstances and their own tolerance for risk which the CRO must be able to accommodate.

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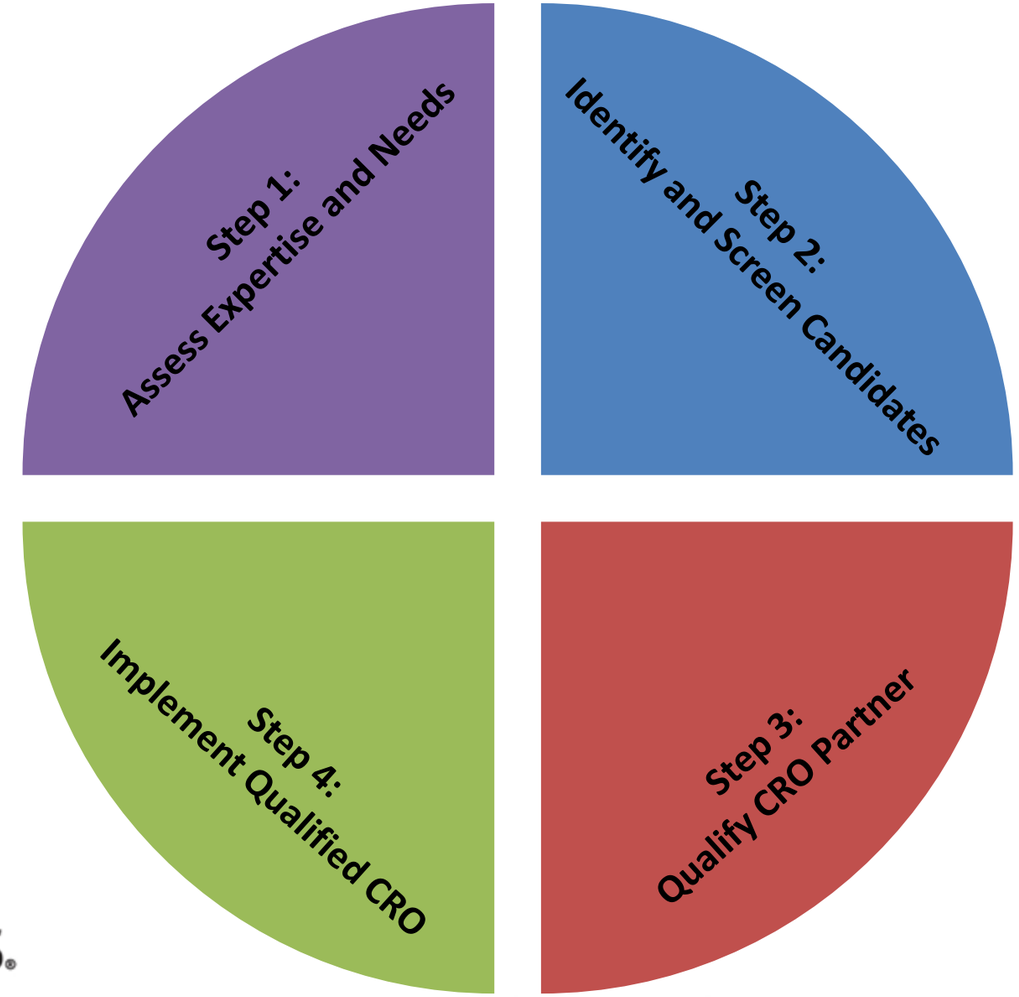
Four Steps to Identify, Qualify and Implement a CRO to Preform E&L Studies

This four-step process represents a systematic approach for identifying, qualifying and implementing a CRO that effectively augments the expertise and meets the needs of the contracting organization.



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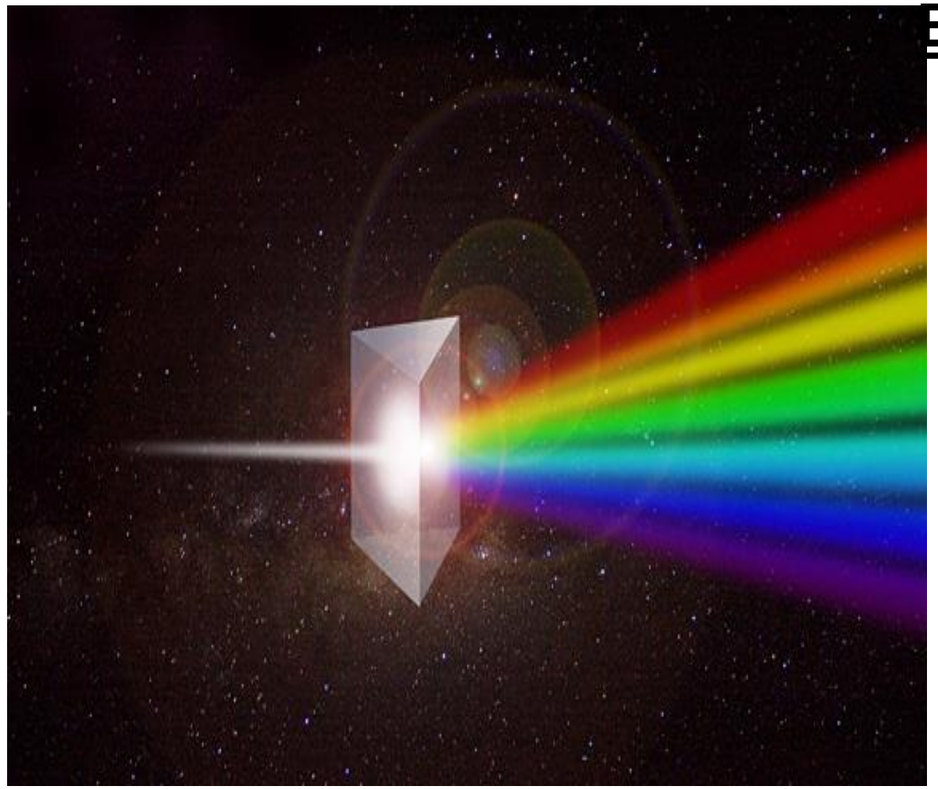
Step #1: Your Level of E&L Expertise Establishes the Type of Support You Need

Where are You on the E&L Experience Spectrum?



E&L Experience	Service Required
Novice	Expertise
↕	↕
Expert	Capacity

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Step #1: The Relative Challenges Faced in Choosing an E&L Partner

The Novice is left out in the cold.

The Expert Holds all the right cards.

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Step #1: Advice for the Novice:

STEP 1:

Hire an E&L Expert to direct (conduct) your E&L Program.

STEP 2:

Have the Conductor identify, qualify and orchestrate the contracted testing laboratory.

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Step #1: More Advice for the Novice:

Possible Fate Awaiting an Unprepared E&L Novice Looking for an E&L CRO Partner

Good Intentions …

… can produce a Not-So-Good Outcome!

Somebody has to provide the strategic vision and the technical oversight.

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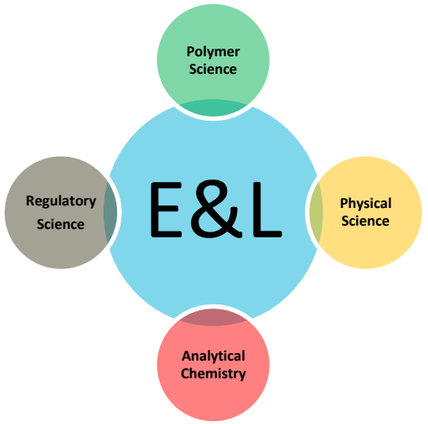
Step #1: Final Advice for the Novice (and a reminder to the expert):

Points to Consider:

1. E&L studies and assessments are not trivial and require a firm understanding of:

   a) Polymer science
   b) Physical science
   c) Analytical chemistry
   d) Regulatory science



2. Regulatory science is not sufficiently evolved that it provides a definitive and explicit road map on how to design, perform, interpret and report E&L studies.

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Step #2: Identifying Potential CRO Partners

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Step #2: Screening Potential CROs as Partners

A larger pool of potential CRO partners should be screened with respect to their essential resources, essential experiences and intangibles so that a smaller number of viable candidates can be identified to move onto the more rigorous vendor qualification process.

Intangibles

Quality Systems
Financial Models
Location
Size
"Vibes"

Essential Experiences

Knowledge in Field
Participation in Field
Experience with Similar Situations
Strategic Thinking

Essential Resources

Essential Instrumentation
Essential Skills
Availability of Resources
Use of Secondary Suppliers

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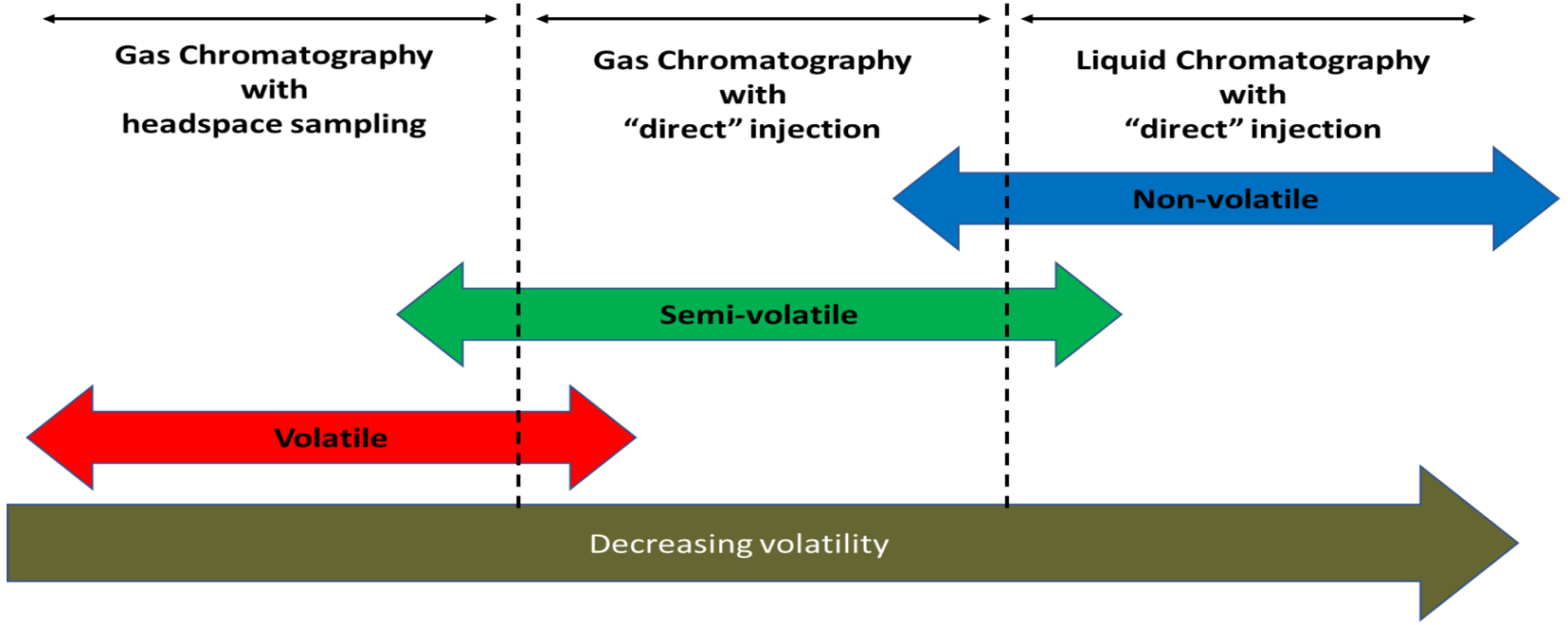
Step #2: Screening Potential CROs as Partners; Essential Instrumentation

Organic Extractables:



Extracted Elements:

Ionic Extractables:

Advanced Instrumentation:

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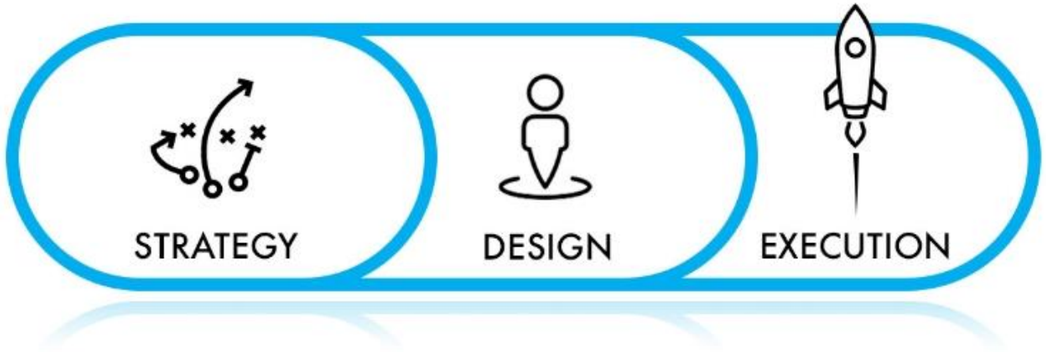
Step #2: Screening Potential CROs as Partners; Essential Skills

- Skills necessary to design and justify E&L studies
- Skills necessary to properly execute the extraction
- Skills necessary to execute the analytical testing
- Skills necessary to process the analytical results
- Skills necessary to distinguish between good data and bad data
- Skills necessary to interpret the analytical data
- Skills necessary to report the analytical data



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Step #2: Screening Potential CROs as Partners; Essential Experiences

"The only source of knowledge is experience."

– *Albert Einstein*

Experience is the best teacher, and the worst experiences teach the best lessons.

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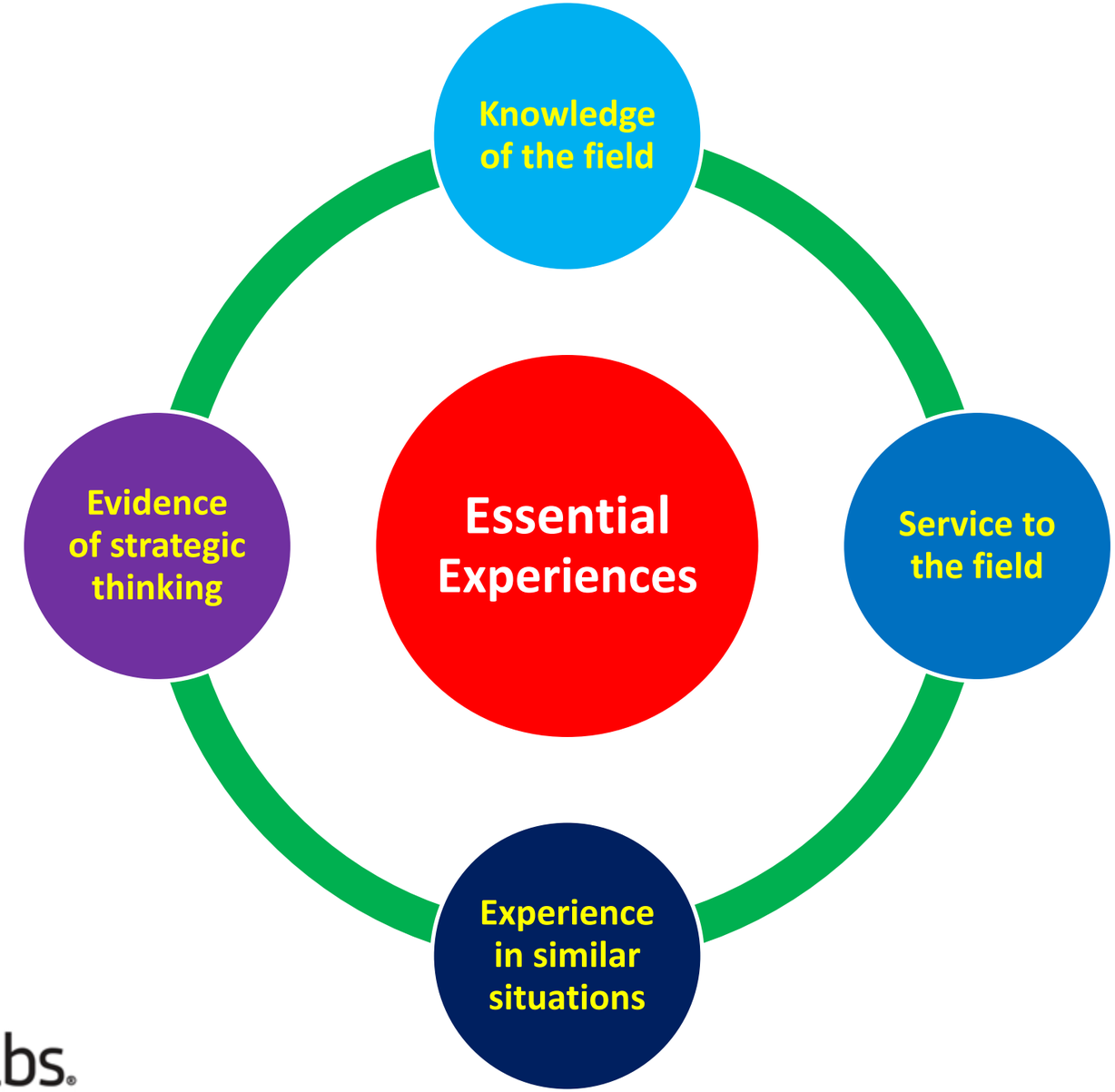
Step #2: Screening Potential CROs as Partners; Essential Experiences



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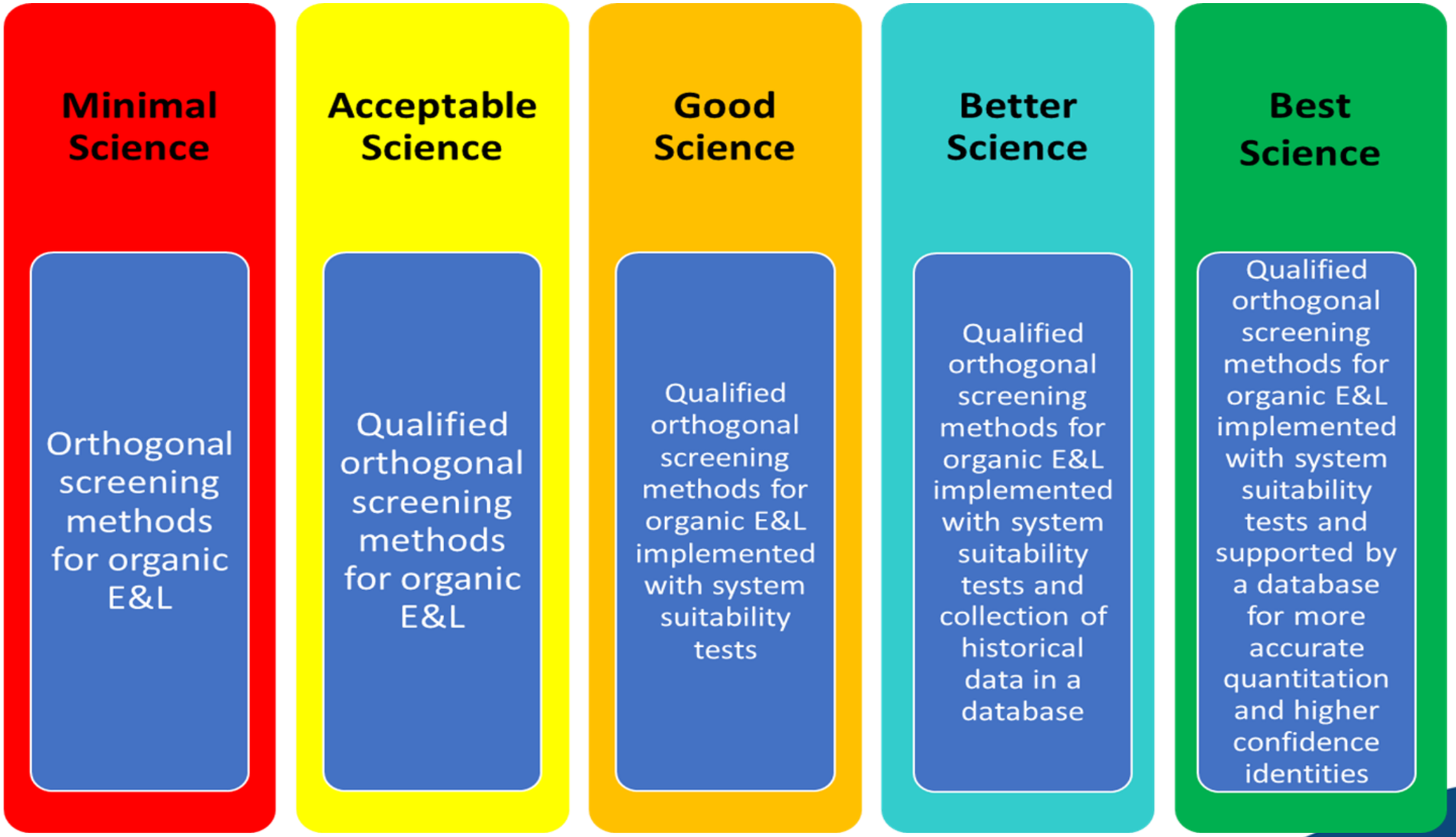
Step #2: What is “State of the ART” in E&L Practices?



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Step 3: Aspects of Qualifying CRO Partners

1. Get the Paperwork in Place (Confidentiality Agreements, etc.)
2. Supplier Audit, Focus on Quality Systems
3. Financial Audit
    a. Available financial models
        i. Project-based
        ii. FTE Model
        iii. Hybrid
    b. Compatibility of financial systems
4. Technical Audit
    a. More detailed review of resource inventory
    b. Detailed review of methods and procedures
    c. Competency evaluation

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Step #3: Qualifying CRO Partners; Technical Audit

1. Detailed review of technical inventory

a. Detailed instrumentation and facilities reviews; focus on both extract generation and extract testing.
b. Detailed personnel review (“quality” and quantity).
c. General review of relevant technical documents (e.g., method SOPs).

2. Detailed review of methods and procedures

a. Detailed, “line by line” review of SOPs, looking for technical gaps and “high level” thinking (e.g., use of system suitability).
b. “How do you handle this?” session.
c. Generation and review of a mock Proposal (protocol).

3. Competency Evaluation

a. Intra-laboratory testing.
b. Characterization of test mixture.
c. Review of other studies.

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Step 3: Qualifying CRO Partners; “Soft” Aspects of Technical Qualification

- ***How much time has the CRO spent with you understanding your product, your process, you ultimate objectives and your circumstances?***

- **Are you getting their “standard, one size fits all” package or are you getting a customized approach tailored to fit your circumstances and needs?**

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Step 3: Qualifying CRO Partners; Competency Evaluation (Mock Protocol)

A. About Extracts:

1. **How well do the proposed extraction conditions mimic the conditions of contact?**
2. **How well do the proposed extraction conditions mimic the chemical nature of the drug product?**
3. **How well do the proposed extraction conditions address the purpose of the study?**
4. **Is there a technical justification for the extractions conditions and if yes, how strong is the technical justification of the extraction conditions?**

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Step 3: Qualifying CRO Partners; Competency Evaluation (Mock Protocol)

B. About Extract Analysis:

1. **How low will you go (and what is your justification)?**
   a) **What is the AET (and how was it calculated)?**
   b) **Was an uncertainty factor applied (and if so, what was its value and justification?)**
   c) **What was your LoD/LoQ and will they be lower than the AET?**
   d) **What are you going to do if the LoD or LoQ is higher then the AET?**
2. **What is your identification and quantitation strategy (and what is their justification)?**
3. **How do you know that you are not missing anything?**
4. **If you are missing something, how will you capture what you are missing?**

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Step 3: Qualifying CRO Partners; Competency Evaluation; The Trial Run

Strategies for Performing a Trial Run

1. Review of a redacted study report.
2. The CRO is provided with a well-characterized reference material (that is, a reference material with a well-known extractables profile) and asked to establish its extractables profile following well-defined extraction instructions.
3. The CRO is provided with an actual “real world” extract that has been previously profiled and asked to generate its own extractables profile.
4. The CRO is provided with an “artificial” extract (a sample of an extraction medium that has been fortified to contain known extractables at known levels) and asked to establish the “extract’s” extractables profile.

Trial runs such as those described in items 2 through 4 previous should be challenging but “fair”. Thus, the extracts to be profiled should not contain only difficult to identify compounds at levels near either the AET or LoD. Rather, they should include a mixture of both “gimmes” and challemges.

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Step 3: Qualifying CRO Partners; Competency Evaluation; The Trial Run

Acceptance Criteria for the Trial Run

Trial runs such as those described in items 2 through 4 previous should be challenging but “fair”. Thus, the extracts to be profiled should not contain only difficult to identify compounds at levels near either the AET or LoD. Rather, they should include a mixture of both “gimmes” and “challenges”.

1. All major extractables should be discovered.
2. All major extractables should be properly identified.
3. All major extractables should be quantified to an acceptable level of accuracy (50 – 200 %).
4. A majority of the “gimme” minor extractables should be discovered.
5. Those “gimme” minor extractables that are discovered should be properly identified.
6. Those “gimme” minor extractables that are discovered should be quantified to an acceptable level of accuracy (50 – 200 %).
7. Many of the “challenging” minor extractables should be discovered.
8. The identities of those “challenging” minor extractables that were discovered should be credible.
9. The estimated levels of the “challenging” minor extractables that were discovered should be “in the ball park”.

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Step 4: Implementing a Qualified CRO; The De-Brief

WHAT IS DEBRIEFING?

Making thinking and learning skills 'visible'

'Debriefing' refers to the discussion that takes place following or during a learning episode.

Debrief

1. What did you notice?
2. What did you feel?
   a. *What was difficult?*
   b. *What was easy?*
   c. *What was surprising?*
3. How does this apply to your world?

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Concluding Thoughts

1. Needing external resources to design, implement, interpret and report E&L studies is the new normal.
2. The design, implementation, interpretation and reporting of effective, efficient and compliant E&L studies is a complex, multifaceted exercise involving multiple technical and practical considerations that requires more than just a pretty brochure and good intentions to accomplish.
3. Thus, identifying, screening, qualifying and implementing the right CRO is an intentional, thoughtful and meticulous process that requires an investment on both the part of the client and the prospective supplier.
4. Successfully identifying, screening, qualifying and implementing the right CRO requires that the client have sufficient E&L expertise to be able to distinguish between “good and bad”, “right and wrong”, and “the talk from the walk”.
5. Most clients focus on the analytical aspect of E&L and neglect to remember the concept of “garbage in = garbage out” when it comes to essential processes like extraction, preparing the extract for instrumental analysis, and data analysis/interpretation.
6. “Soft” aspects of the working relationship, such as culture, financial models, etc. are an important part of the assessment.
7. If at all possible, do not be the “guinea pig” project where the CRO gets to “try something new”.
8. The suffering that comes from choosing the wrong CRO is never-ending.

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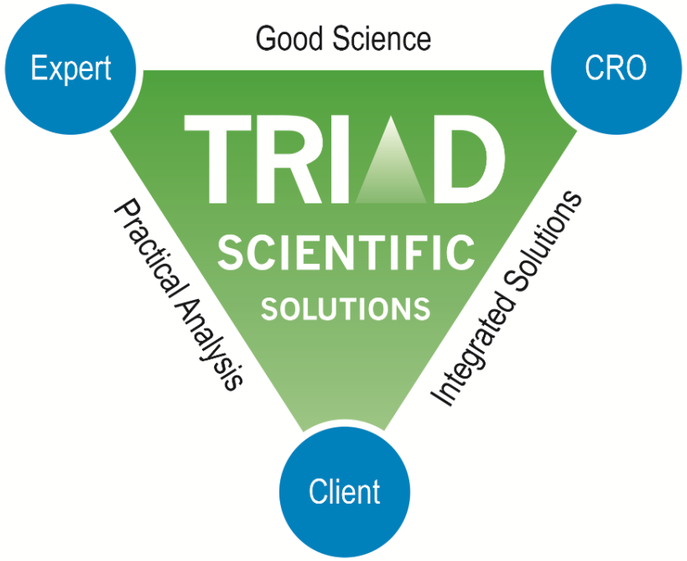
Thank you and Time for Questions



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2. Jenke, D. Insights gained into the identification, qualification and utilization of CRO laboratories in extractables and leachables studies. *Pharm Outsourcing*. **14(2)**: 20, 22, 24-26 (2013).
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