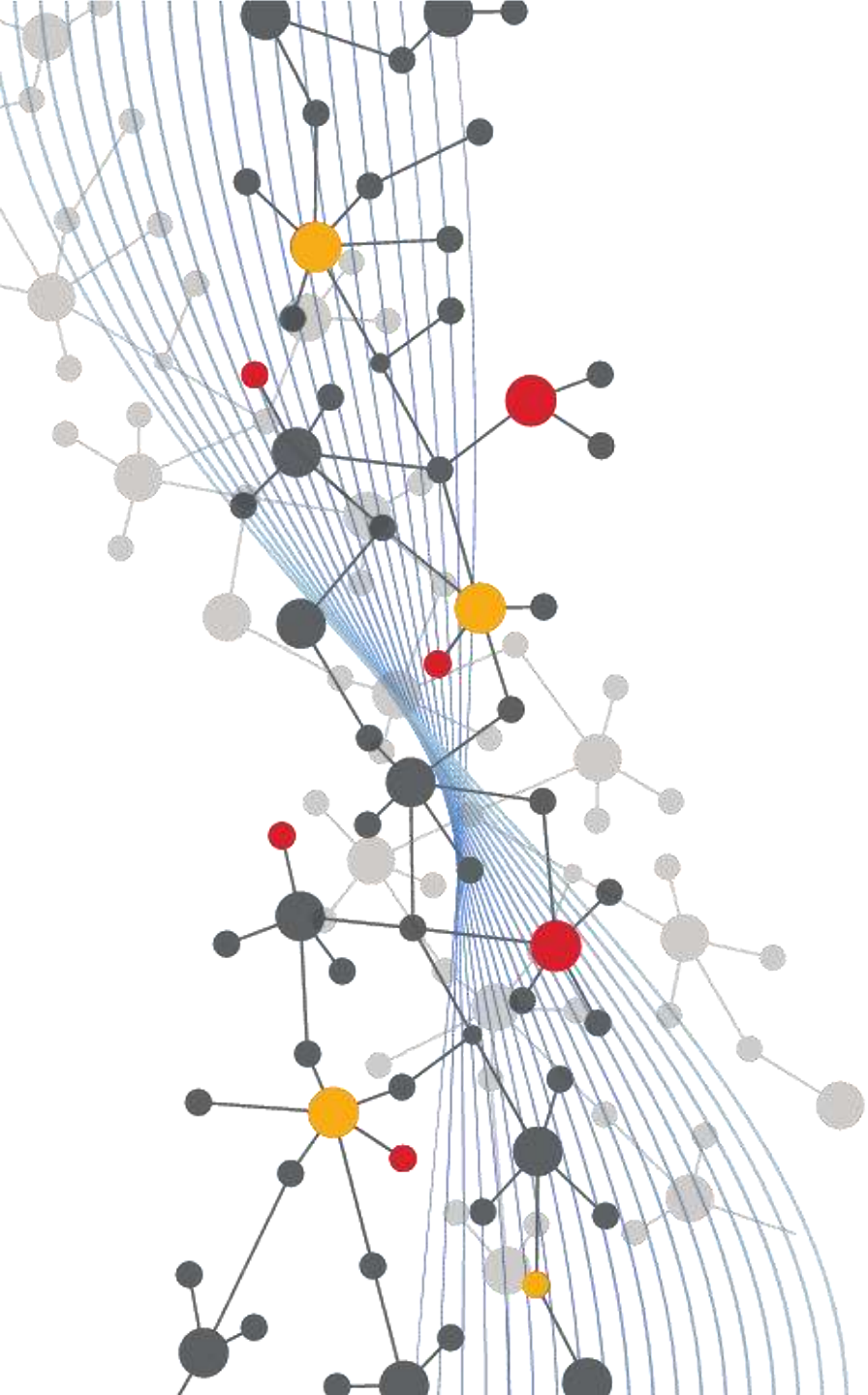

Considerations for building your broader network and value to obtaining external input prior to interacting with FDA

Julie Bullock, PharmD

VP, Integrated Drug Development

Certara

Introduction and Objectives

- Understand purpose and limitations of FDA review during IND development
- Awareness of development pitfalls and items that hold up progress
- Determine how to identify your teams needs
- Understand key considerations for evaluating external partner/consultants

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FDA review team organization

- IND and NDA/BLA review is Multidisciplinary
  - Entire team is aware of programs lacking in components.
- FDA reviewers are balancing
  - Original IND reviews
  - Meeting Package reviews
  - Reviews of Protocols/Protocol amendments
  - Breakthrough Therapy Designation Requests
  - NDA/BLA and sNDA/sBLA

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FDA remit is to review (agree/disagree) your program

- Review is focused on ensuring patient safety and efficacy.
- FDA will not design your program and often does not provide alternative suggestions.
- Client Sponsors are required to put forth sound justifications to support development approach
  - FDA may provide suggestions, but these are left to the sponsor to justify if incorporated (or not incorporated).
- FDA can not stop development of drug with poorly established proof-of-hope unless there is an overt safety risk to humans.

PreIND & Original IND - Focus and Pitfalls

- FDA is focused on **safety**
  - Do the **pharmacology** evaluations support proof of hope in disease?
  - Is **toxicology** data is appropriate to support FIH dose and duration?
  - Is drug **formulation** acceptable for humans and is there enough supply for study?
  - Is the FIH **clinical** study appropriately designed to ensure safety and stated objectives?
  - Are **DDIs or organ impairment** a cause for concern?

Common Reasons for Clinical Holds

Unstable from a chemistry perspective

Animal studies show severe irreversible toxicities or all animals died after the first dose

Eligibility criteria include patients who are at high risk for toxicity or qualify for available efficacious therapy.

Starting dose is too high or dose escalation is inappropriate

Safety monitoring is inadequate

Stopping rules are inadequate

IB is misleading, erroneous or incomplete

The protocol is clearly deficient in design to meet its stated objectives

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IND development – Focus and Pitfalls

- FDA is not responsible for stopping development of drugs with poorly established proof of concept.

- FDA is focused on
  - Safety
  - Obtaining proper data to provide **benefit/risk for an approvable indication**
  - **Multidisciplinary** program acceptability for future NDA/BLA submission

- Efficacy is a large component of drug success, but it is not the only component.
  - All disciplines must cross the finish line at the same time.

Common Pitfalls during IND development

Moving forward when **Proof-of-Concept is not established**

Asking questions not relevant to your stage of development

Asking **hypothetical questions**.

Formulation and Manufacturing changes

Not providing FDA data or justifications to support development decisions

Poorly written and disorganized health authority submissions

Not accepting when **Risk >>> Benefit**

Subset analyses

Ignoring or delaying multidisciplinary development needs

Not identifying **contribution of combination therapies**

Failing to collect data or objectively analyzing data collected.

Not seeking or **ignoring FDA advice**

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Value to obtaining external advice and support

Avoid mistakes, Confirm Certainty

External advisors typically provide…

- More up to date experience
- New perspectives and broader experiences
- Unbiased opinions and assessments of risk.

Increase speed and efficiency

External advisors can help with…

- Time management
- Utilize team strengths, outsource weaknesses
- Backfill Day-to-Day support needs
- Backfill gaps in experience

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Start-up's - Early development team needs

- Core beginning
  - Regulatory, Clinical, CMC, nonclinical (pharmacology/Tox), DMPK
- Core expansion
  - Clinical Trial Operations, Statistical, Clinical Pharmacology
- Bandwidth support
  - n = 1 employees of a specific discipline may need bandwidth or expertise support through subcontractors or consultants
- KOL's and SME's

Individual consultants

- Discipline specific focus
- Focused on smaller number of clients (usually)
- No Peer review
- No backfill or bandwidth support
- Cheaper
- Balancing business and science tasks

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Consulting Groups

- Multidisciplinary
- Varied diversity, depth and breadth of experience
- Backfill support available
- Peer Review/learn from colleagues
- Costly
- Contracting can be slower

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How to evaluate consultants/groups

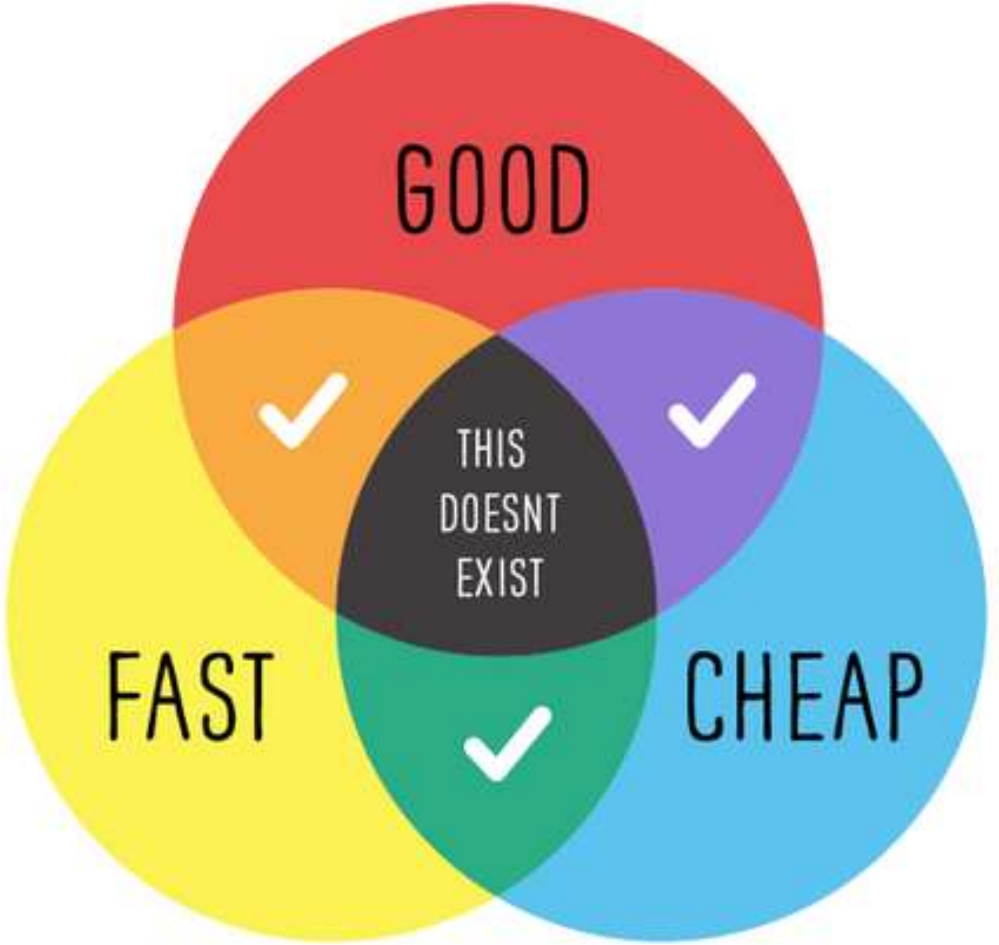
- Decide what you need
  - Is depth and breath important?
  - Will your needs shift as you move through development?
    - Do you want to keep switching consultants or would you prefer to find more of a ‘team’ you can grow with?
- Decide how you need your consultant support you
  - Hands on or supportive activities?
  - SME review only?
- Decide how experienced you need them to be
  - Own the discipline?
  - Support an internal discipline expert?

Working with your extended team – Best Practices

- Do not withhold information
- View consultants as part of the team
  - Meet as a multidisciplinary team
  - Take them with you to FDA
- Listen to them, seek to understand negative or alternative advice
  - What experience or exposure do they have that lead to the advice? Is it valid?
- Follow-up after decisions are made or confirmed.
  - Support learn/confirm cycles

Paying for advice

- Make sure support is scoped appropriately
  - Are you getting what you asked for/need?
  - Are there terms to avoid project budget over run?
- Milestone based contracts still need ad-hoc flexible aims incase scope change or extra support is needed.
- Understand value of the deliverable/advice can often cost more than time spent.
- Retainers are best for part or full-time support
  - Provides committed resource usually at discounted prices
- Consider time or success based pricing models
  - Gives external advisors ‘skin in the game’.



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Paying for advice

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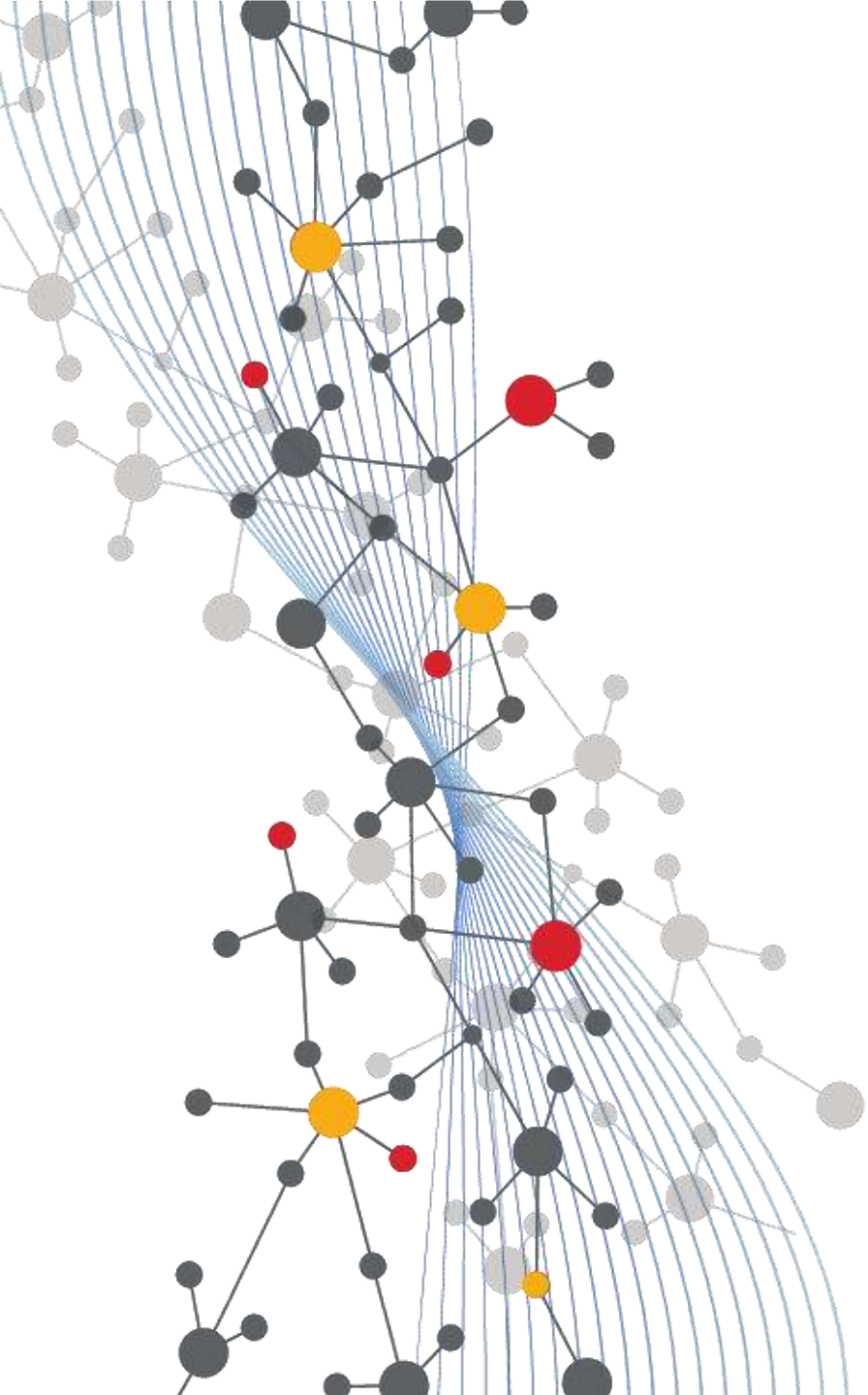

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Accelerating Medicines, Together

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