



## **Outsourcing**

Perspectives from within a CRO  
and at the consultant/CRO interface

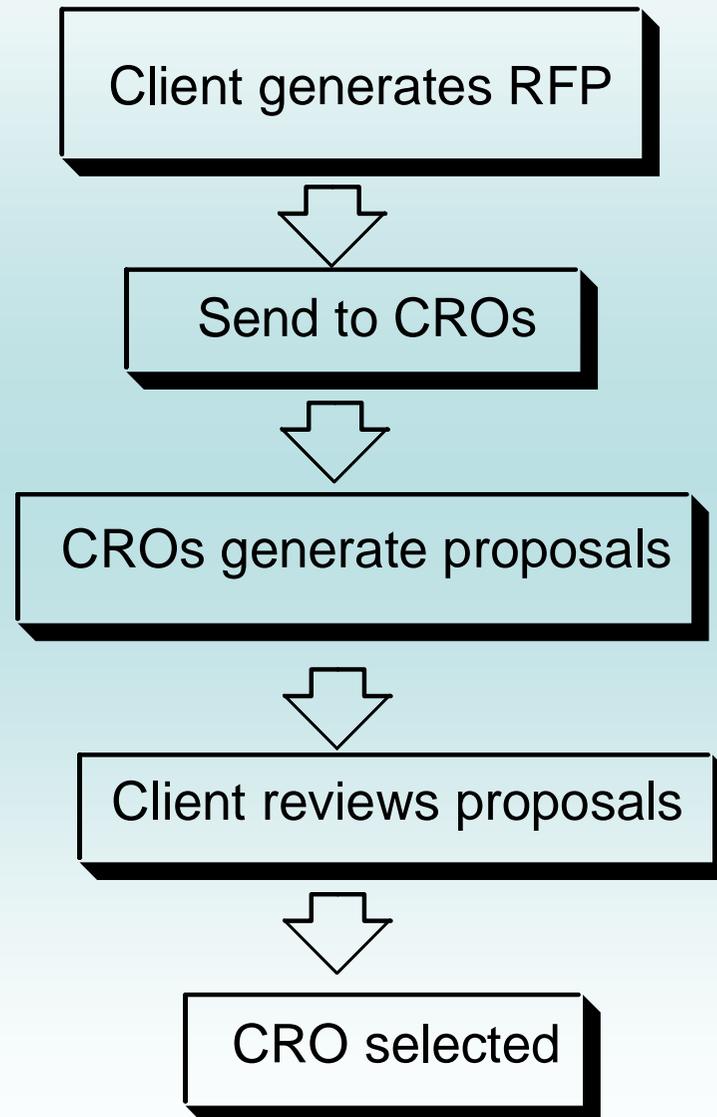
# Outline

- ❖ Common challenges faced by a CRO in early phase development projects
  - receipt of the request for proposal
  - proposal generation
  - developing the working relationships and establishing trust
  - Managing change
- ❖ Discuss a different view from the perspective of a consultant advising clients, covering again a range of challenges from
  - preparing the request for proposal
  - reviewing and comparing proposals – apples with pears?
  - CRO selection
  - project oversight and communication

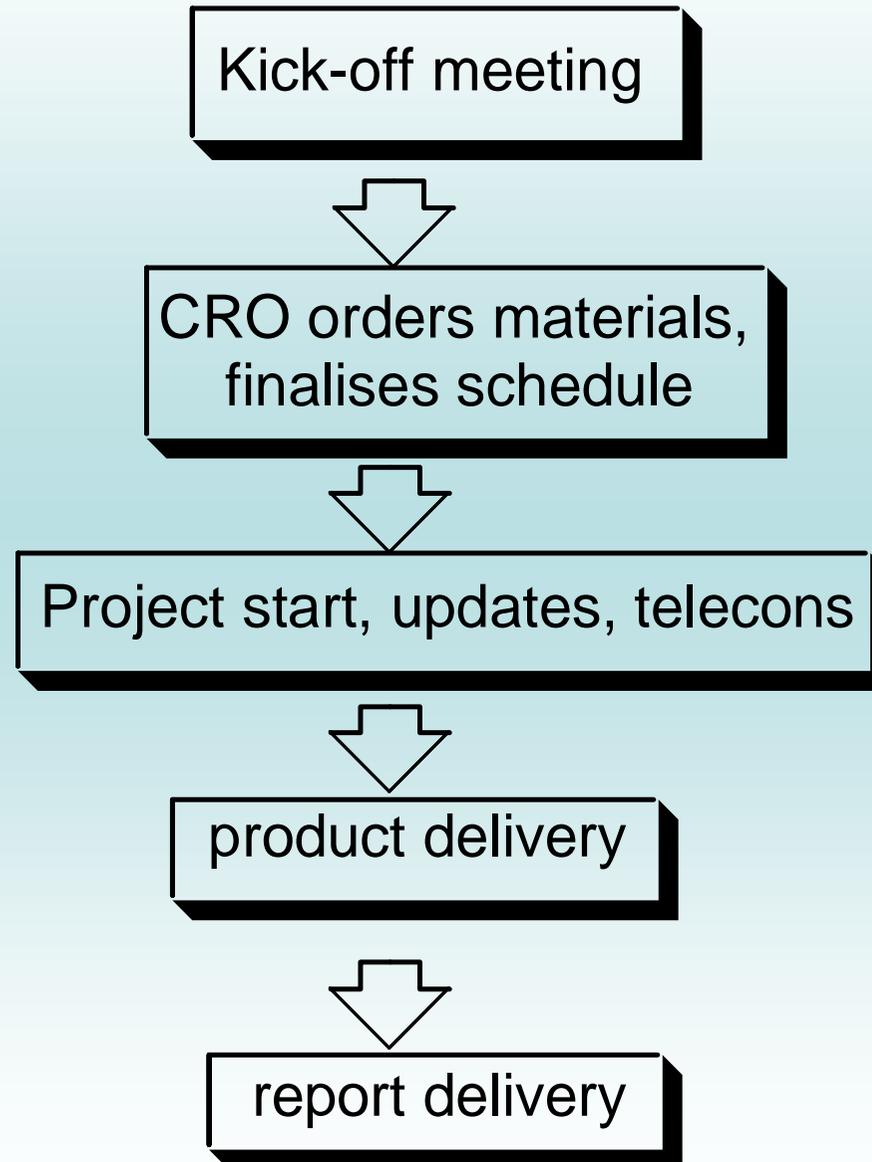
# Broad project types

- ❖ Pre-GMP late stage intermediate
- ❖ Pre-GMP target material for toxicological evaluation
- ❖ GMP manufacture of late stage intermediate
- ❖ GMP manufacture of target material

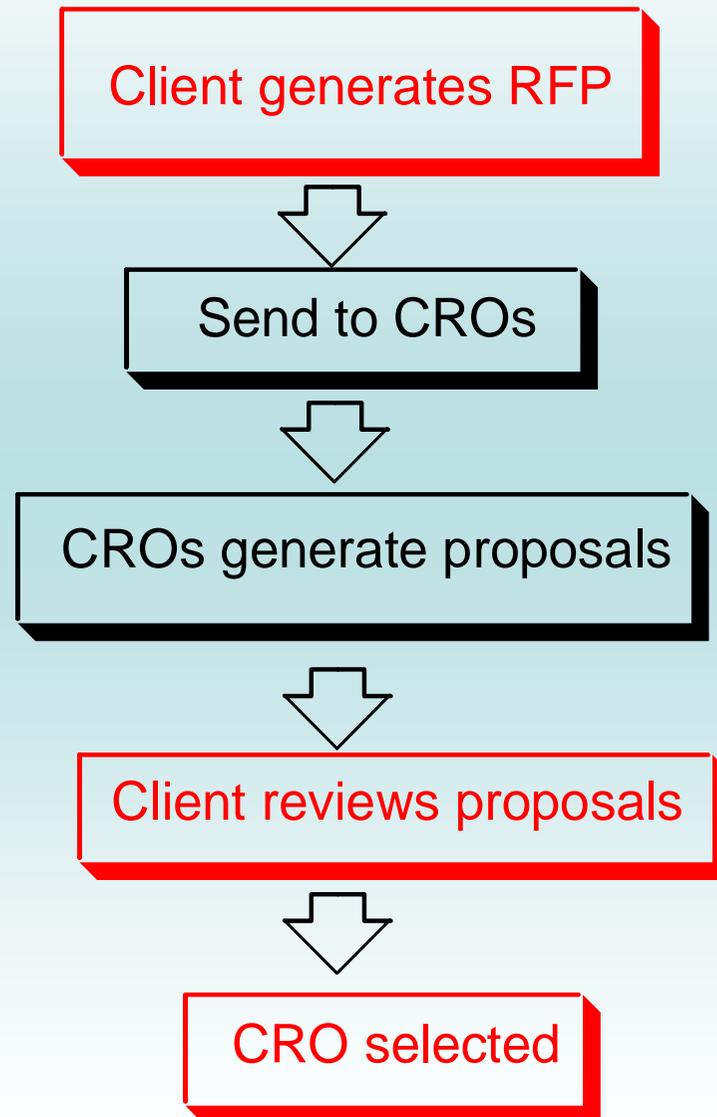
# Sequence of events



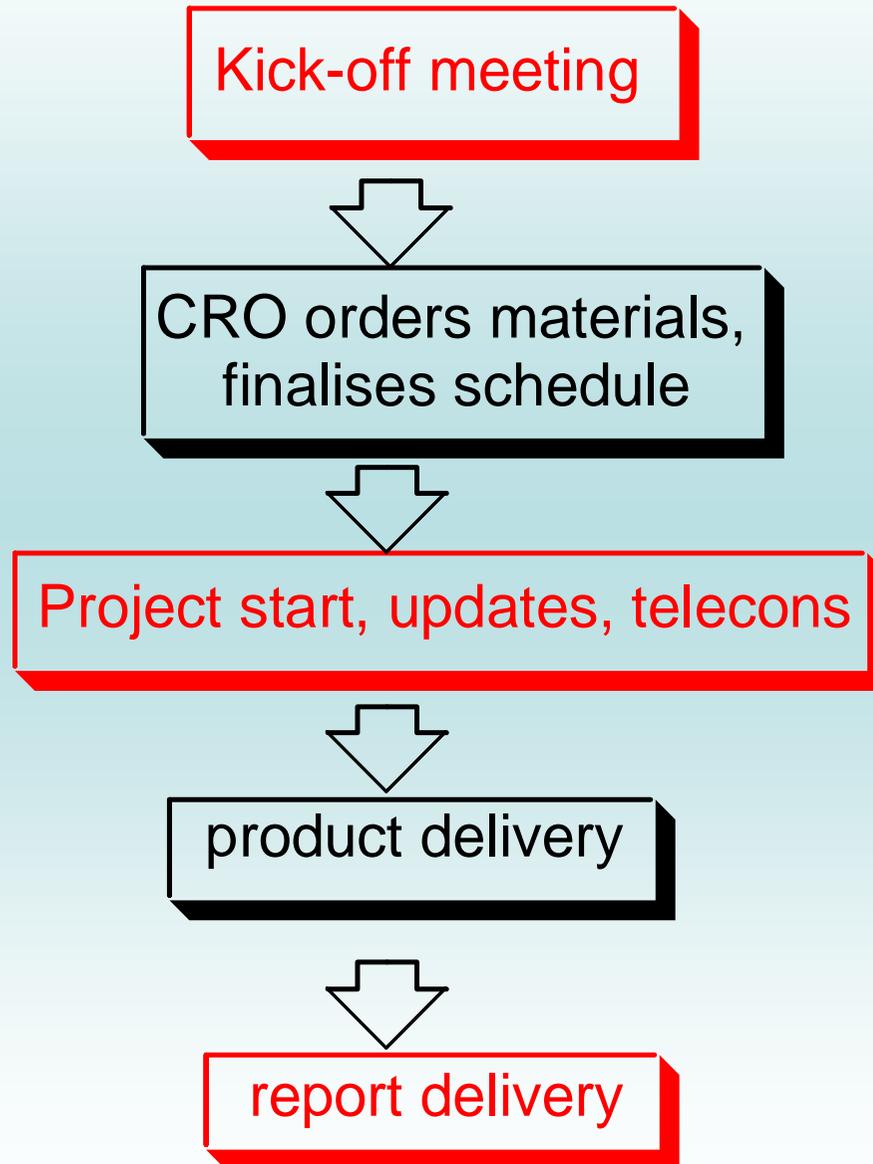
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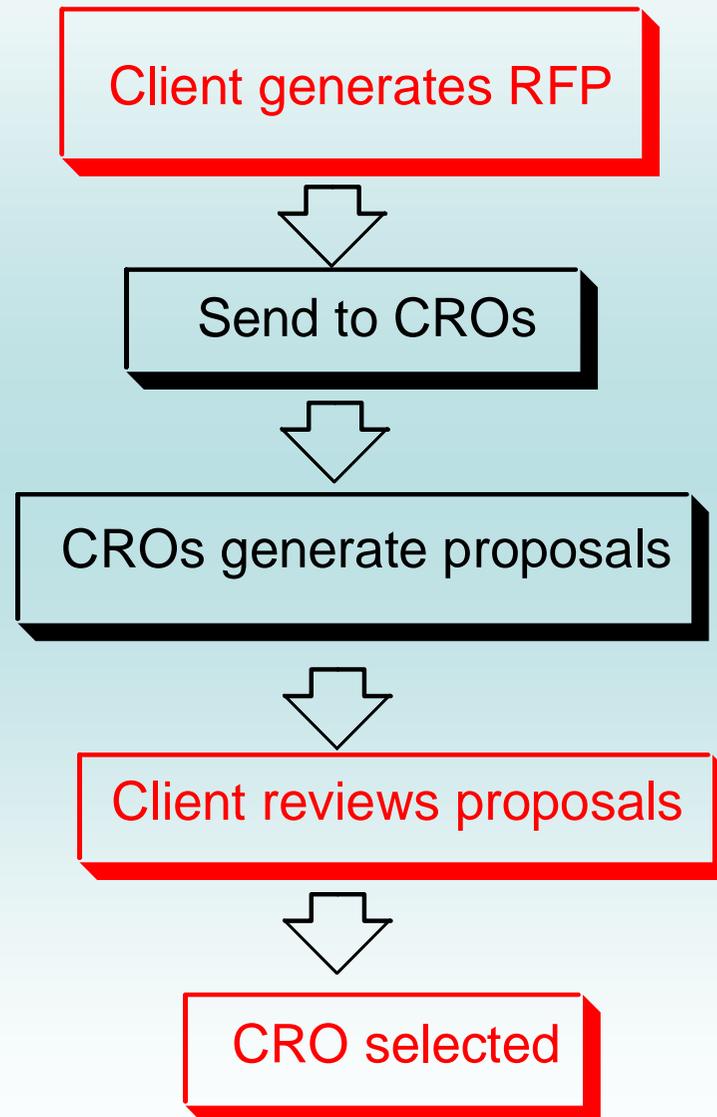
# Sequence of events – consultants can help



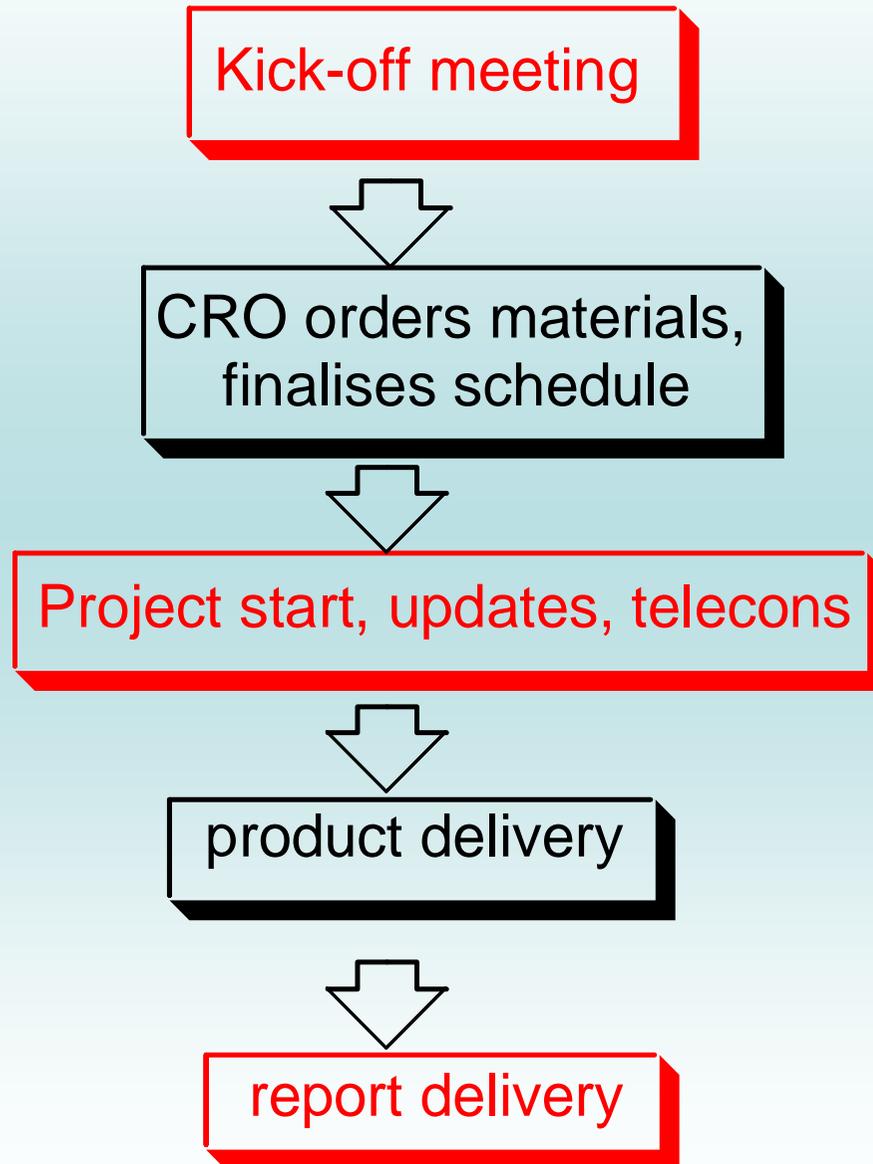
# Sequence of events – consultants can help



# But consultants can also hinder!



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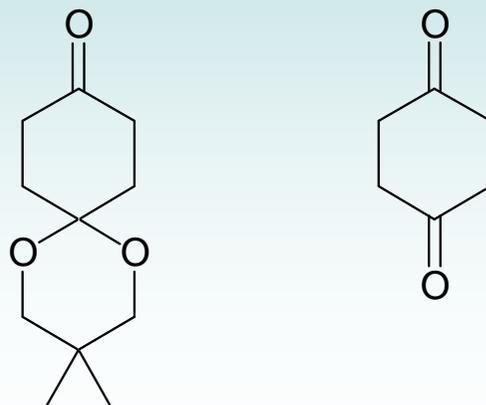


# Challenges faced by CRO

- ❖ Raw materials supply
- ❖ Changes in scope from the client
- ❖ Client's consultant
- ❖ We just don't get on!

# Raw materials supply – case 1

- ❖ We needed the mono-protected diketone, which comes from the diketone
- ❖ I had 3-4 separate companies quoting
- ❖ Issue: the diketone was made by only one manufacturer in limited number of campaigns per year and one wasn't due
- ❖ Outcome: there seemed to be sudden large interest in the diketone – it all funnelled back to me!



# Raw materials supply – case 1

## ❖ Outcome:

- We secured one supplier able to supply sufficient for the next campaign
- Through dialogue with our client we got commitments to material needs for next 6 months
- This enabled us to secure sufficient interest to reserve existing diketone stocks
- A further manufacturing run was planned so we had secured materials for the future demand

## Raw materials supply – case 2

- ❖ The project goal was to make 10kg API to cGMP standard for PI trials
- ❖ We had to do process development to render the process safe and operable at plant scale
- ❖ There was sufficient material available for the laboratory development work
- ❖ The client informed us they had the bulk quantity on order and had dual sourced it from China
- ❖ 2 weeks before campaign start we asked about the delivery – we needed it on site for QC release testing
- ❖ Client contacted his suppliers.....

## Raw materials supply – case 2

- ❖ Supplier 1: there's been a typhoon in the area and the manufacturer has been delayed owing to building damage
- ❖ Undeterred, our client called his second supplier
- ❖ Supplier 2:.....any guesses?

## Raw materials supply – case 2

- ❖ Supplier 2: there's been a typhoon in the area and the manufacturer has been delayed owing to building damage
- ❖ Two agents, one manufacturer

# Raw materials supply – case 2

## ❖ Outcome

- The project was delayed by about 6 weeks
- We were able to adjust our plant schedules and bring another project forwards
- If we had not been able to fill the plant slot, we were entitled to charge the client anyway

❖ CROs are looking for high plant occupancy and may not have spare capacity sitting around

❖ Be aware of this when retaining responsibility for raw materials supply

## Raw materials supply – case 3

- ❖ We needed an aryl hydrazine and did not have capacity to produce it
- ❖ We provided a 10kg scale process and asked for quotes from 3 suppliers for 75kg
- ❖ Supplier A gave best price and lead time – simple choice
- ❖ Supplier A turned out to be a European agent using Indian manufacturer
- ❖ Owing to persistent containment failures, 3 operators ended up in hospital and the Indian manufacturer refused to work on the project
- ❖ My supposed European supplier cancelled the order

## Raw materials supply – case 3

- ❖ Returned to one of the previous quotes
- ❖ Confirmed they would be manufacturing – the site was in Europe
- ❖ They manufactured a quantity of material reported to be >95% purity by HPLC
- ❖ I got a pre-shipment sample
- ❖ Assay by NMR showed 9-10%w/w with the remaining 90% comprised of water and NaCl
- ❖ I asked why they hadn't noticed a theoretical molar yield of over 500%!

## Raw materials supply – case 3

- ❖ We were lucky, we could actually use the 10% assay material directly
- ❖ We took the full shipment and paid based on assay content
- ❖ We changed suppliers for the next campaign!

# Challenges faced by CRO

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# Scope changes

- ❖ Client placed an order for 2kg for GLP toxicology study
- ❖ Calculation based on the average weight of rats
- ❖ The study was to be done in part in dogs
- ❖ Having started the work, client requested manufacture of 5kg
- ❖ Same timeline!
  
- ❖ Outcome
  - We were lucky - raw materials readily available
  - Client was lucky - it was lab-based
  - We could juggle teams and work shifts to meet timelines

# Scope changes

- ❖ We were commissioned to prepare 2kg of API in salt form for toxicology study
- ❖ Client had provided lab-based methods for free base
- ❖ Client said they would
  - Identify the preferred salt version
  - Develop analytical impurities method for API
  
- ❖ Outcome
  - Client failed to keep up with project schedule
  - No salt form was forthcoming within agreed plan
  - No method was forthcoming
  - We agreed to supply free base and release using our method

# Challenges faced by CRO

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# Client's consultant

- ❖ We were working with a Biotech company
- ❖ They employed a development/CMC consultant
- ❖ Joint telecons
- ❖ Consultant would follow-up directly with my project leader and instruct work to be done
- ❖ Project leader would disagree as some items were outside agreed scope of the project
- ❖ Project leader came to me for arbitration

# Client's consultant

## ❖ Outcome

- I spoke with our client to inform her of the issue
- I said we were happy to do as the consultant requested but,
- This would burn through our allotted internal budget for the project without achieving the requested goals
- I would then stop the work and invoice and/or ask for more money
- Client reigned in their consultant to ensure work was as per agreed project proposal

## ❖ Communication is critical of course

## ❖ Client does need to keep a check on their consultants' activities

# Challenges faced by CRO

- ❖ Raw materials supply
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# We don't get on!

- ❖ Not all marriages are made in heaven!
- ❖ I have changed project leader in the past owing to crippling disagreements in approaches
- ❖ Communication is critical of course
- ❖ As client, you need someone outside of the technical team to talk to
  - Technical manager
  - Commercial contact
  - Honest about the issues to resolve it early
- ❖ As CRO one needs to be flexible and accommodating.....even tolerant!

# Client – CRO- consultant interface

- ❖ What do consultants bring to the party?

# Generation of request for proposal

- ❖ Consultants can assist in their preparation or review
- ❖ A key first step in establishing a correct approach and understanding
  - Key aspect to mitigate against failure
- ❖ Responses to the RFP are a measure of both the quality of the RFP and the person/group asking the questions
  - Consultants can assist in the review of proposals

# Proposal from CRO

- ❖ Responses from several CROs will vary
- ❖ Ensure the RFP is clear about not only the chemistry but the work breakdown and costings
- ❖ It is often very difficult to compare proposals in detail
  - Assumptions are poorly defined
  - No clear picture on the 'production plan'
    - Single batch throughout or multiple batches?
  - No schedule is included
  - CRO has failed to respond to the cost details required
    - Don't ask for too much detail
    - You need enough for effective comparisons
    - Break out project components such as lab development, analytical development, manufacturing

# Generation of proposal – know the process

- ❖ RFP is subject to a preliminary review to place the work
  - Lab
  - Plant
  - Not suitable – decline
- ❖ Detailed technical review
  - Is there a route?
  - Is development needed or is it a tech transfer?
  - Environment, Health and Safety considerations
    - Operating licence may require permissions from the regulators
  - Do we have appropriate kit?
    - Is the kit going to be available at the predicted time?
  - Raw materials availability?

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- ❖ **Client often wants proposal in 5 business days**

# Quality of proposal

- ❖ Directly related to the quality and experiences of the team putting it together
- ❖ Reliability of raw materials information may be suspect
- ❖ The proposal should state the assumptions, check them!
  - The assumptions can demonstrate great understanding, so may well reflect the likely competency
  - How much overage has been allowed for?
  - Do you get the overage without extra charge?

# Are you getting the 'B' team?

- ❖ Who generated the proposal?
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- ❖ Was he/she at the kick-off meeting?
- ❖ Will he/she be part of the project team?
  
- ❖ The proposal is great, the kick-off meeting was brilliant
- ❖ The project gets underway but the updates and telecons are appalling and understanding is poor
  
- ❖ You've got the 'B' team!
- ❖ You will have to stay very close to the project or pay more to have a consultant do so

# Common project challenges

- ❖ Raw materials delivery delay
- ❖ Raw materials quality issue
- ❖ Yields are not holding up as against the assumptions so predicted product quantity will fall below order quantity
- ❖ Chemistry does not work/technology transfer problem
- ❖ New impurity profile
- ❖ Unable to dry below ICH solvent levels
- ❖ Different physical form
- ❖ Particle size and distribution differences

# Common project challenges

- ❖ The analytical support is not yet available and/or lagging behind
- ❖ Previous project has been delayed impacting your project
- ❖ Crucial information from another source is not forthcoming
- ❖ Packaging
- ❖ Storage stability
- ❖ Transportation challenges
- ❖ Working around international holidays and festivals

# Common project challenges – Yields not holding up or chemistry not working

- ❖ Consultant can perform an independent, objective review of the supplied information and CRO performance
- ❖ There could be valid reasons
  - Don't change CRO mid-project unless you need to!
- ❖ Consultant can assist in the trouble-shooting
- ❖ Consultant can assist with revised project plans

# Common project challenges – Yields not holding up or chemistry not working

- ❖ Consultant can assist with an objective view of the work carried out such that appropriate payments are negotiated
- ❖ Consultant can assist by suggesting alternative CRO options and when to switch, or, as can often be the case
- ❖ Make recommendation the existing CRO performed well

# Common project challenges – New impurity profile

- ❖ A validated process being transferred to lower cost manufacturer in Asia
- ❖ Chemistry well established over 10 years previously
- ❖ All transfer was going well until at one step a known impurity was seen at about 6% vs typically <0.2% in a qualification run
- ❖ It transpired that it was not common practice at the destination plant to use nitrogen blanketing unless a flammable solvent was in use
- ❖ This failure to use inert atmosphere resulted in aerial oxidation and elevated impurity level
- ❖ Easy to fix, but attention to detail was crucial

# Common project challenges – helping to manage cultural differences

- ❖ America and England, two countries separated by a common language!
- ❖ ‘Okay’ or ‘fine’
  - In England it means exactly that – it meets the requirements
  - In America – it barely meets the standard, I’ll accept it if I have to, but you’re not really doing well enough
- ❖ Different cultural approaches
  - How do you say ‘no’ to someone?
  - How do you ask a question to find out a negative result without compromising the respondents position?
- ❖ Different approaches to development
  - What is a developed process?

# Working for the CRO

- ❖ Major Pharma client requested 100kg of an intermediate (non-GMP) with a defined delivery time
- ❖ CRO quoted and won the business
- ❖ Due to an oversight, the key raw material was not ordered immediately
- ❖ Due to a further oversight, the project manager did not inform the client of likely 2 week delay
- ❖ Outcome.....

# Working for the CRO

- ❖ Ensured the client was informed of the delay
  - Bad news must always be communicated promptly
- ❖ Worked with the CRO to establish what the options were to expedite delivery and develop an alternative plan
  - Suggested working on the basis of 2 x 50kg batches, the first on time
- ❖ Advised the CRO project manager to set up a telecon with client purchasing person, client internal technical team (*ie* the actual end user), CRO technical teams
- ❖ Client end user made it clear that of the 100kg, 50kg was absolutely required at the original time, the subsequent 50kg was not required for at least 2-3 weeks later
- ❖ The CRO had a plan that could meet this

# Working for the CRO

- ❖ Communication
- ❖ Accessing the end-user can be critical
- ❖ Larger companies generally have a purchaser who does not know the full details
- ❖ In my view, the purchasers will inevitably be motivated by securing best price and on-time delivery and can lack flexibility

# Communication

- ❖ The key to success and crucial in all of the above complications
- ❖ Maintain project focus – don't allow personal frustrations to get in the way
- ❖ Take great care to ask questions in a way that can be replied to
- ❖ All projects need a parallel communication channel so commercial and technical discussions can be held without conflicting each other
  - As client, you need to scientists on your side
  - As CRO, you may need the consultant on your side

# Concluding remarks

- ❖ Thanks for your time and attention
- ❖ Learning is a two-way process
- ❖ Successful outsourcing requires the client to learn from their service provider and so enable smoother working interactions
- ❖ It takes time to develop trust and openness, but in my view the effort is rewarded
- ❖ CROs should be prepared to provide accurate and honest feedback; some clients will definitely be wanting to see you have an opinion and will apply your expertise to their project/problem

# Concluding remarks

- ❖ And finally.....
- ❖ There are many excellent scientists working within CROs
- ❖ Don't assume they're all there because they failed in some way to make the grade to get into a blue chip multinational company!
- ❖ I've had people treat me like a second-class citizen.....check my cv, it was my choice to work in the CRO arena