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How to Source, Vet, and Oversee Medical Product Development Contractors

Ensuring efficient, timely, and high-quality studies and data for regulatory submissions

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Goals of Presentation

Demonstrate the importance of selecting “fit-for-purpose” contractors

- Contract Research Organizations (CROs)
- Contract Development and Manufacturing Organizations (CDMOs)

Delineate the critical role of being actively involved with outsourced activities

Provide an example of the steps in selecting and contracting outsourced activities

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Importance of Active Involvement in Outsourced Activities

Importance of Active Involvement

- **Your Study is Very Important to You**
  - **You have more personal investment in the success of the product than the CRO/CDMO**
  - **Your reputation is linked to the success of the study**
    - Not necessarily the results, but the quality of the study
  - **You want the highest chance of regulatory acceptance**
    - GLP, GCP, and GMP compliance
    - Scientific quality (design, data integrity, results)
  - **You, the granting organization, and the company are relying on a successful study**
    - You cannot guarantee the results, but you can influence the quality

Importance of Active Involvement (cont.)

- **You Know Your Product Best**
  - **Historical data and product background**
    - CMC: synthesis process and potential hurdles, stability, desired formulation
    - Nonclinical: study design, dose setting, animal welfare issues
    - Clinical: dose setting, study population, potential safety issues
    - Target Product Profile (TPP) and Development Plan
      - Can determine which CRO/CDMO provides medical product development services that best align with the development plan
  - **Physical/chemical properties**
    - Possible formulations, analytical approaches, local irritation, worker safety, etc.
  - **Play a key role in helping the CRO/CDMO be efficient, cost-effective, and successful**
    - Many questions need to be answered before, during, and after the work

Importance of Active Involvement (cont.)

- **CROs and CDMOs Are Typically Very Busy**
  - **Multiple competing studies**
    - “Squeaky wheel gets the grease”
  - **Employee turnover**
    - “Getting up to speed”, experience
  - **GMP, GLP, and GCP compliance**
    - GxP compliance does not guarantee a sound scientific study or regulatory acceptance
  - **Protocol amendments**
    - Ensuring everyone is aware of changes

Importance of Active Involvement (cont.)

- **You, the Granting Organization, and the Company/Management Will Likely Want Timely and Reliable Updates**
  - **Pivotal studies can make or break a drug development program (or company)**
    - Will likely need to provide continuous updates
  - **Updates from CRO/CDMO**
  - **Remote monitoring of activities/studies/data**
  - **Onsight monitoring of activities/studies/data**

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Examples of Outsourcing Issues

Examples of Outsourcing Issues

Nonclinical

GLP rat oral gavage carcinogenicity study

Very senior Study Director did not go to the study room or review raw data for 6 months

GLP Seg II rabbit IV teratogenicity study

Many animal deaths and injection-site-related reactions that the study director never mentioned and were not identified until an on-site morning visit

Drug exposure in control animals

Topical drug product for dogs and animal care staff causing cross-contamination

Examples of Outsourcing Issues

Nonclinical (cont.)

Study director changed during middle of a 6-month repeat dose rodent study and technician turnover was high

Many dosing errors and some key study functions were skipped, particularly after protocol amendments and on weekends

Understand who is conducting study functions

During teleconference, it was determined that on weekends, untrained security personnel were going to conduct clinical observations

Examples of Outsourcing Issues

- **CMC**
  - **Synthesis**
    - Theoretically, an easy synthesis route; however, multiple published routes and CDMO used wrong publication to develop method
      - Also used entire 100 g allotment of starting material in first attempt at synthesis and failed
  - **Stability**
    - Stability studies on toxicology batch drug substance did not cover duration of toxicology study
      - Also applies to GMP batches for clinical work
    - GMP stability work indicated potential precipitation issues for oral mucosal spray
      - Issue was not addressed and in the middle of pivotal chronic GLP toxicology non-rodent study, pumps clogged

Examples of Outsourcing Issues

- **CMC (cont.)**
  - **Analytical**
    - CDMO developed HPLC-MS/MS method where a simple HPLC-UV method would have been easier, more cost-effective, and more robust for various immediate and long-term needs
  - **Component selection**
    - Glue selected by CDMO for preparation of tubing set (combination product) was cytotoxic

Examples of Outsourcing Issues

- **Clinical**
  - **Study design**
    - Inclusion/exclusion criteria were very restrictive and required discussions with the FDA to revise so recruitment was more reasonable
  - **Sample collection and storage**
    - Pharmacokinetic (PK) samples required special processing
      - Required providing special instructions (collection, processing, storage, and shipping) but too complex for most sites
  - **Study data**
    - PK profiles at one site were the same for multiple healthy volunteers
      - Overseas study site was never monitored before or during the study

Case Study

Process of Outsourcing GLP Nonclinical Studies

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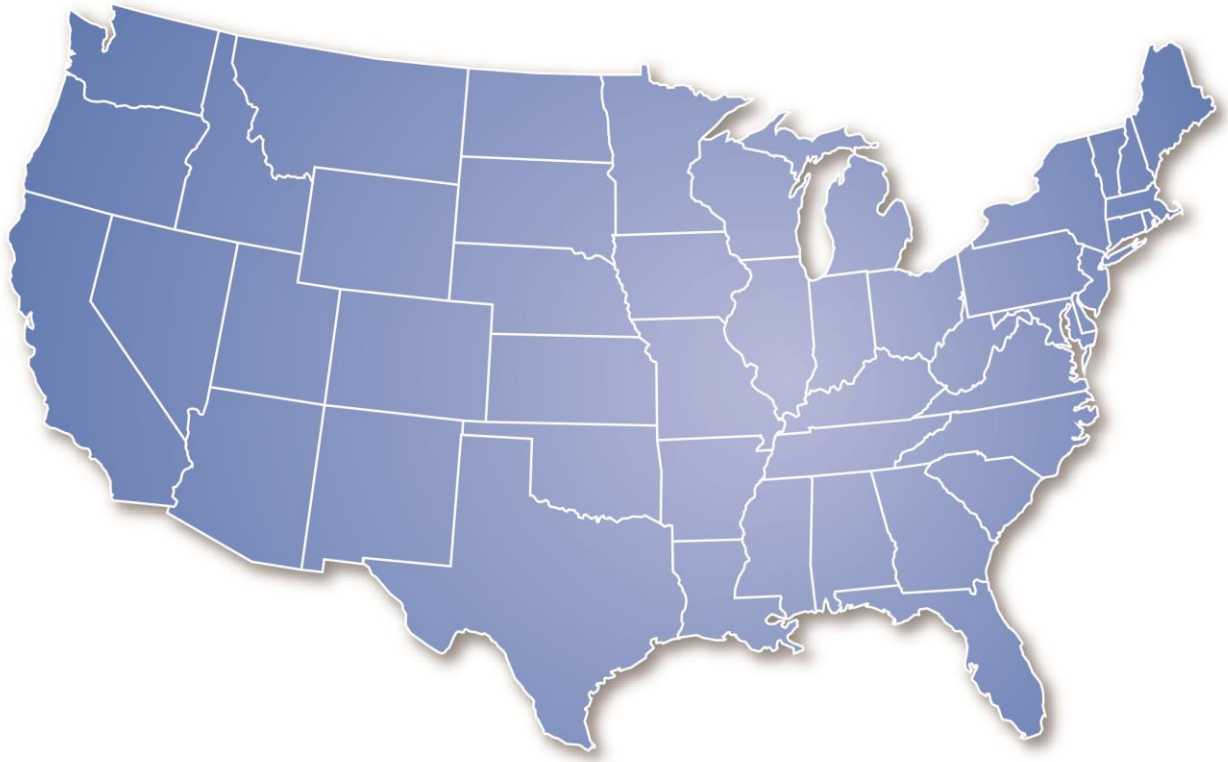
Selecting a Laboratory to Run a Nonclinical Study

Location of the CRO

USA

- Typically, very familiar with FDA GLPs and inspections
  - Laboratory is not “pre-certified” as GLP compliant
- Easy to monitor
- Similar time zones
- Cost of study can be higher than outside USA



Location of the CRO (cont.)

- **Outside the USA**
  - **May or may not be familiar with FDA GLPs and inspections**
    - Many ex-USA laboratories are approved as “GLP Facilities” and it is assumed (by the local monitoring authority, but not necessarily the FDA) that studies conducted at the laboratory are GLP-compliant
  - **More difficult to monitor**
  - **Widely varying time zones**
  - **Can be very good pricing**

Types of Laboratories

Academic

- Typically non-GLP
- Difficult contract negotiations
- Problematic Institutional Animal Care and Use Committee (IACUC) approvals

Government

- GLP and non-GLP
- Typically, do not conduct research for private firms unless part of a consortium or independent research agreement

Types of Laboratories (cont.)

Private and Not-for-Profit

(aka Contract Research Organization [CRO])

Will focus on CROs that run GLP studies

- GLP and non-GLP
- Easier contract negotiations and IACUC approvals
- Responsive
- Established GLP SOPs

Screening Potential CROs

- **Search Out Potential CROs**
  - Online research
  - Meet with sales representative
  - Scientific conferences and scientific organizations
  - Colleague recommendations and experience
  - Personal experience

Screening Potential CROs (cont.)

- **Types of studies** (for example, pharmacology, PK, or toxicology)
- **GLP vs. non-GLP**
- **What study functions are conducted in-house vs. subcontracted?**
- **Does the CRO have all the capabilities and experience required for the study?**
- **How many studies have they run of the type you are requesting?**
  - Availability of Historical Control Data
- **Do you want to monitor the study with on-site visits?**

Selecting the CRO to Run Your Study

- **Establish a Non-Disclosure Agreement (NDA) with the Laboratory**
  - Typically, a 2-way agreement because CROs do not like you giving out their pricing to other CROs
- **Provide a Detailed Study Outline to the CROs for Accurate Pricing**
  - Provides a good opportunity to see how well the CRO pays attention to the details and their responsiveness
- **Determine which of Price, Payment Schedule, Quality, Responsiveness, Reputation, etc., Are Most Important**

Selecting the CRO to Run Your Study (cont.)

- **Deeper Dive to Determine if the CRO Has Specific Capabilities or Expertise Critical to the Success of the Study**
  - Does the CRO have a full-time, onsite, board-certified veterinary pathologist to oversee necropsies for in-life animal moribundity/mortality?
  - Who does ocular examinations? And is a board-certified veterinary ophthalmologist needed?
  - Are BSL facilities required for an infectious agent?
  - Is the scientist conducting pharmacokinetic or toxicokinetic modeling trained at interpreting the data or just entering the data and running the modeling software?
  - Does the study require complex statistical analyses and is this offered by the CRO?
  - Can the CRO obtain and handle the species and strain of animal required for the study?

Selecting the CRO to Run Your Study (cont.)

- **Conduct an On-site Audit of the Facility If This Is the First Time Working With This Specific CRO**
  - Could also be the same CRO but a separate test site
  - Tour facility and review SOPs
  - Establish relationships with study director, management, technicians, and scientists

- **FDA Warning Letters**
  - Ask laboratory for recent FDA inspection reports

- **If Everything Is Acceptable, Sign a Contract to Run The Study**
  - Legal negotiations can take time
  - Pay attention to payment schedule, study room reservation cancelation or delay penalties, other Sponsor obligations that incur financial or scheduling penalties, etc.

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Designing a Scientifically Sound Nonclinical Study

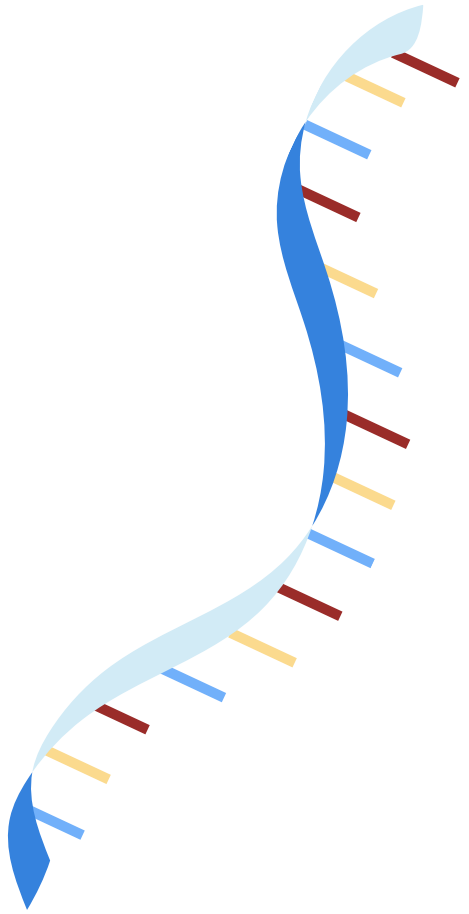
The Importance of Active Study Involvement

Scientific Needs, Logistical Feasibility, and Regulatory Compliance

- **These Three Factors Do Not Always Align**
  - The study design requires an excessive number of animals
  - Not enough cages, rooms, technicians, time, etc.
  - Animals need to be singly housed for clinical observations; however, animal welfare requirements specify group housing
  - Setting the high dose
    - Matching clinical dosing vs. Maximum Tolerated Dose (or other high-dose setting options)
    - Dosing dogs with 10 large capsules 5 times per day

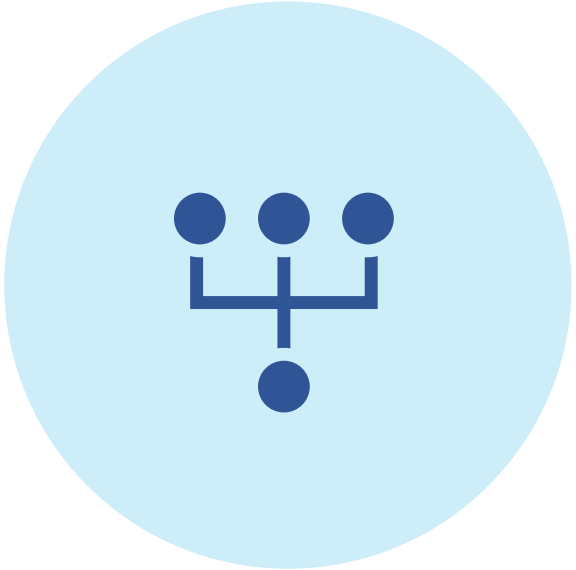
Scientific Needs, Logistical Feasibility, and Regulatory Compliance (cont.)

- **These Three Factors Do Not Always Align (cont.)**
  - Blood collection volume is too high or too frequent
  - A required endpoint or analytical instrument is not validated by the laboratory (non-GLP)
  - Too many samples are being collected during necropsy
    - Samples are very labile and require special handling (for example, RNA)



General Study Design Issues That Require Input/Involvement (cont.)

- **Animal Procurement and Selection**
- **Quarantine and Pre-study Health Assessment**
- **Animal Identification**
- **Animal Housing**
- **Water and Feed**
- **Environmental Controls**
- **Number and Types of Groups and Subgroups** (i.e., Staggered Start)
- **Randomization to Groups**



General Study Design Issues That Require Input/Involvement (cont.)

- **Dosing**
- **In-life Evaluations**
  - Physical exam
  - Clinical observations
  - Body weight
  - Feed and water consumption
  - Ophthalmology exam
  - Electrocardiogram
  - Clinical pathology (hematology, clinical chemistry, clotting time, urinalysis)
  - Toxicokinetics
  - Many other possible assessments depending on the study requirements (for example, ocular pressure)

General Study Design Issues That Require Input/Involvement (cont.)

- **Terminal Procedures**
  - Clinical pathology (hematology, clinical chemistry, clotting time, urinalysis)
  - Gross necropsy
  - Organ weights
  - Tissue preservation and histopathology
  - Other possible assessments depending on the study requirements
    - For example, tissue preservation for subsequent gene expression analysis using NextGen sequencing

Protocol and Standard Operating Procedures (SOPs)

- **The Study Protocol Must Specify All Study Details Unless Covered by Laboratory SOPs**
- **The Study Design (Protocol) Must Meet GLP and Animal Welfare Requirements**
- **The Study Design Should Meet:**
  - Applicable regulatory guidance (for example, FDA or ICH nonclinical guidance documents)
  - Necessary regulatory requirements (for example, advice provided by the FDA during a pre-IND meeting)

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Ensuring GLP, Regulatory, and Scientific Compliance

Key Determinants of Success

- Laboratory Selection
- Study Design (Protocol)
- Study Monitoring
- GLP Compliance
- Animal Welfare Compliance

GLPs

- **Helps Ensure:**
  - The study is conducted in compliance with the protocol and SOPs
  - The study (and data) is thoroughly documented so it can be reconstructed and there is confidence that the collected data are accurate

- **GLP Compliance Does Not Ensure Regulatory and Scientific Compliance**
  - You can have a fully GLP-compliant study that does not address a specific request from the FDA
  - You can have a fully GLP-compliant study that does not have adequate control groups and consequently does not provide relevant scientific data

GLPs (cont.)

- **FDA Has Proposed to Revise the GLPs to:**
  - Enhance the existing quality system approach
  - Address multisite studies
  - Closer alignment with other GLPs (for example, OECD)

Animal Welfare

- **The Study Protocol Will Be Reviewed by the Laboratory's Institutional Animal Care and Use Committee (IACUC)**
  - Ensure that the study complies with appropriate federal, state, and local animal welfare regulations or guidelines
  - Similar requirement for animal welfare protocol review by outside-the-USA CROs; however, animal welfare regulations may be stronger or weaker

Animal Welfare (cont.)

- **Potential Conflicts**
  - Under the GLPs, the study director has overall responsibility for the conduct of the study (single point of control)
    - However, under the USA animal welfare regulations, the Attending Veterinarian makes the final determination on animal care and use
  - Inclusion of humane endpoints (for example, early animal termination) may conflict with scientific requirements
  - Use of sedatives, analgesics, or anesthetics may confound the scientific interpretation of the study
  - Animal housing (group vs. single) and environmental enrichment

Conclusions

Conclusions

- Determine how your study/work fits into your overall development plan
- Determine which CROs or CDMOs can provide the medical product development services you need
- Once the list is narrowed down, further screen the CROs or CDMOs
- Select a CRO or CDMO that best meets the goals of your development plan
- Design the study/work so that it meets the relevant scientific and regulatory requirements
- Be actively involved with your study

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Q&A