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CONTRACTS AND REGISTRATION STUDIES

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ABSTRACT: Public and governmental concerns about the health, safety, and environmental impacts of pesticides have led to increased regulatory requirements to determine the hazards and risks associated with their manufacture, distribution, and use. Vertebrate pesticides are regulated by the U.S. Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended. Much of the data required for registration of these pesticides will be generated by commercial testing laboratories under contract to the product registrants or sponsors. In this paper, we address aspects of the contract research process including: 1) an overview of FIFRA requirements, 2) the nature of the contract research process, 3) guidelines for setting up and administering a contract for this type of work, and 4) several case studies to illustrate some of the "pitfalls" that may be encountered. The information presented is based on the collective experience of the authors' involvement with 49 contracted studies over a three-year period.

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INTRODUCTION

The registration or reregistration of vertebrate pesticides entails the generation of chemical and biological data to satisfy Environmental Protection Agency (EPA) requirements under the Federal Fungicide, Insecticide, and Rodenticide Act (FIFRA), as amended. The law requires EPA to weigh the benefits derived from the use of a pesticide against any potential risks to public health and the environment. FIFRA requires that pesticides be registered by EPA and authorizes the Agency to require submission of data to facilitate the benefit-risk assessments (Conner et al. 1991). EPA data requirements are set forth in the U.S. Code of Federal Regulations at 40 C.F.R. part 158 (Giles 1991) and are divided into 12 categories which are designed to identify the composition of the pesticide and to reflect the effects of the pesticide on humans, non-target wildlife, and the environment. The test data are intended to demonstrate that the product will perform its intended function without unreasonable adverse effects as defined within the FIFRA § 3(c)(5) or 3(c)(7). Several of the more significant categories of data requirements affecting vertebrate pesticides and the reasons for the requirements are the following. Product Chemistry data provide a profile of the physical and chemical characteristics of the product and associated impurities. Toxicology studies are intended to show the toxicological properties of the pesticide based on the route of exposure (oral, dermal, inhalation, ocular), the duration of exposure (acute, subchronic, chronic), and the types of effects (neurotoxicity, teratology, oncogenicity, reproduction, mutagenicity, etc.). Wildlife and Aquatic tests are aimed primarily at determining toxicity to non-target species of birds, mammals, fish, or aquatic invertebrates. Residue Chemistry data are required for pesticides used on a food or feed crop and are used to set and enforce pesticide tolerances. Environmental Fate studies determine rates of hydrolysis, photodegradation, leaching, dissipation, and metabolism in soil or water. Product Performance data provide efficacy information; these are useful for labeling the product or refining the instructions for its use.

Generation of these data is both time-consuming and costly (Fagerstone et al. 1990, Ramey et al. 1992, Poche 1992). Studies must be done according to standards and protocols that are acceptable to EPA - hence, the risks (e.g., failure to meet deadlines, rejection of a study, cancellation of registrations, fraud, etc.) involved in trusting these studies to a commercial laboratory can be great. Consider, for example, the plight of several registrants who, as clients of Craven Laboratories, a commercial testing laboratory, lost an estimated $11 million because of the fraudulent practices of that laboratory (Anonymous 1993). In this case (U.S. v. Craven Laboratories, DC WTexas, No. A 92 CR 152, plea agreement reached 12/2/93), the laboratory owner, the quality assurance officer, and two of the laboratory's employees were indicted by a federal grand jury in September 1992 on criminal charges that they tampered with pesticide tests conducted for 11 major manufacturers and the EPA in violation of the FIFRA. The indictment also alleged that the defendants tried to cover up a federal investigation of the laboratory's practices, and, in addition, that the laboratory's falsification of test data defrauded pesticide manufacturers of money they had paid for the tests and caused false information to be submitted to the EPA. Care and diligence in the contract research process is imperative.

CONTRACTS AND THE CONTRACTING PROCESS

Registrants basically have two ways to fulfill EPA data requirements: 1) they can use the knowledge, skills, and expertise of their own staff, their own equipment, and their own facilities to write the protocols, conduct the studies, prepare a final report for submission to EPA, archive the raw data and specimens, and assure that all Good Laboratory Practice (GLP) standards have been met throughout the process; or 2) they can hire someone else to do it for them. The first option may not be practical because the staff, facilities, equipment, and special expertise needed are not available; this will likely be the case for some of the required studies because of their specialized nature. Hence, option 2--hiring a commercial

or "contract" testing laboratory--is mandated.

The contracting process is, essentially, an incorporation of the elements of a contract. Briefly, a contract is an agreement enforceable by law. Certain elements must be present in order for a contract to exist--these are:

- Offer - a proposal of the terms of the transaction to another party.
- Acceptance - the party receiving the proposal must agree to the terms and conditions offered.
- Consideration - both parties must give up something of value to the other party.

In order for the contract to be valid (enforceable), the following additional elements must also be present:

- Capacity of the parties - for an agreement to be a contract, both parties must be legally competent to enter into a contract.
- Legality of the subject matter - a valid contract must be for a lawful purpose; an agreement to do something prohibited or not authorized by law will not be enforced.
- In writing if required by law.

Figure 1 illustrates the contracting process and the formation of a contract in the context of pesticide registration research based on the following scenario: the registrant or sponsor (one of the competent parties) has a need to generate data to meet a data call-in requirement issued by EPA (the legal purpose); after unsuccessful attempts to have the requirement waived by EPA, the registrant makes plans to hire a contract laboratory to do the study; the registrant or sponsor issues a solicitation to potential contractors asking for proposals; various testing laboratories send in proposals (the offers) to do the study; the sponsor evaluates the proposals and selects (the acceptance) one of the laboratories (the other competent party) to do the study; the contract laboratory conducts the study under the supervision of the sponsor; the registrant gets the needed report for submission to EPA and the laboratory gets paid (mutual consideration). It sounds simple--but it is complex.

The specific sequence of events which a registrant will follow to hire a contract laboratory depends on several factors. For example, is the registrant a government agency, a commercial business, or a member of a data-gathering consortium? A government agency will have to follow a more restrictive, time-consuming sequence than will a private business or a data-gathering consortium because of internal regulations and procedural requirements. Private industry or consortia can deal directly with any source and need not be concerned with competition; government agencies are required to seek full and open competition. This makes the selection process longer and more complicated, but it offers a slightly greater degree of protection should a dispute or breach arise. The time factor must be considered because the data requirements established by EPA generally have submission deadlines associated with them.

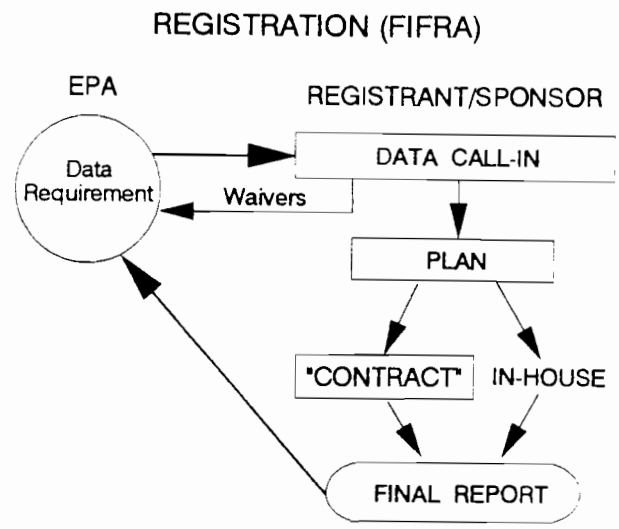

Figure 1. Schematic illustration of the contracting process within the context of a pesticide registration research scenario.

CONTRACT LABORATORIES - SOURCES

There are numerous commercial testing laboratories, both in this country and abroad. Locating a contract laboratory to meet specific needs is not a difficult task; but to do it effectively can be time-consuming and requires diligence. There are published directories of commercial testing laboratories (e.g., ASTM 1990, Regulatory Assistance Corp. 1991, Freudenthal 1992). These provide diverse information on the capabilities and specialties of each laboratory, species used, associated support capabilities, equipment, staff, accreditation information, and key contact persons. Although the directories can be a valuable aid in contract laboratory selection, they should be used only as an initial step--sort of like looking through the yellow pages. Following identification of a number of potential candidates, additional information should be sought about these specific laboratories and their operations. Key steps should include the following:

- Literature/Brochures - ask for literature; much can be learned about a laboratory even from a cursory review of the material provided (e.g. is it of professional quality or of a "desk-top" publisher quality?; does it include a listing and qualifications of principal staff?; does it provide a description of the facilities, support capabilities, etc.?)
- Protocols - ask for generic protocols of the studies you are interested in; compare these with the EPA Pesticide Assessment Guidelines to see if they conform.
- Price Estimates - ask for price estimates (if not included in the literature); compare these with estimates from other laboratories. Although prices will vary, estimates should be roughly comparable; be wary of relatively very high or very low estimates.

- Schedule - ask when your study could be started. Since you may have a deadline to meet with EPA, scheduling of the study to allow sufficient time for completion of all phases (and some unanticipated delays) is important. Allow at least one month for review/revision of final reports. Some laboratories tend to sign up more clients than they can serve in a timely and effective manner.
- Site Visits - ask if the laboratory permits sponsor or sponsor's representative site visits. If they discourage this or seem hesitant about it, take your business elsewhere.

These steps will give you an initial idea about which laboratories you may be interested in and which ones should receive a copy of the solicitation or request for proposals. The amount of time and resources dedicated to laboratory selection will depend on the nature of the studies to be conducted. Selection of a qualified laboratory to conduct comparatively simple acute toxicity studies or product chemistry studies is far less critical and involved than the selection of a laboratory to conduct a complex series of environmental fate studies, a long-term neurotoxicity study, or a multi-generation reproduction study.

CONTRACT LABORATORIES - SOLICITATIONS

Before a contract lab can submit a study proposal to the registrant or sponsor, they must know what the needs of the sponsor are. It is the sponsor's responsibility to define its requirements in the "solicitation" or "request for proposals" (also referred to as the terms-of-reference, statement-of-work, or specifications). The more detailed and specific this document is, the easier it is for the laboratory to respond and the less likely that a misunderstanding will occur which may not be realized until later.

The terms-of-reference or statement-of-work included in the solicitation tells the prospective contractor what work will be required, the conditions under which the work must be conducted (e.g., it must be done in compliance with Good Laboratory Practice Standards and other appropriate regulations), how the proposals will be assessed (i.e., the evaluation criteria including the relative importance attached to each criterion), and what the obligations will be. It enables the contractor to assess its capabilities in light of the contract requirements.

General guidelines for developing the terms-of-reference are as follows:

- Describe the scope of work to be done as a clearly defined task or tasks with a definite goal, objective, or target.
- Establish meaningful parameters of measure.
- Allow sufficient flexibility to permit proposers some degree of latitude in structuring a technical approach to solve the problem.
- Avoid the use of abstract or vague words or words with multiple meanings.

One item that will be prominent in the selection process is cost. However, if cost or price is not to be the primary selection factor (i.e., technical merit may be considered more important), this must be clearly stated in the solicitation.

As a basic rule, the solicitation should be explicit enough to give offerors reasonable notice of what factors are actually going to make a difference in selecting the contractor for the job. There are at least two reasons for this: first, if the offerors must guess about what you want, you risk inviting proposals from inadequately qualified sources and proposals which do not reflect what you need. Secondly, some offerors may correctly guess what you want while others may not. Those who fail to do so may contest the acquisition process in court. The EPA publishes Pesticide Assessment Guidelines that set forth standards and protocols for testing that are acceptable to the Agency. These guidelines are helpful to the sponsor in drafting the terms-of-reference and to the laboratory in designing the study protocol.

Once the sponsor's needs are known by the contract laboratories, they prepare proposals. Depending on the laboratory and the nature of the study, these can vary from a relatively simple, unassuming document to multi-volume, state-of-the-art productions that are intimidating by their sheer volume and mass. And each one must be carefully read and evaluated.

CONTRACT LABORATORIES - EVALUATION/SELECTION

Technical evaluation is the consideration of the technical merit of the proposals. It is best done by an evaluation panel using an evaluation plan and scoring system designed before release of the solicitation. An example of such a plan is shown in Figure 2. In order for the evaluation of proposals received in response to a solicitation to be legally valid, the evaluation must be conducted in accordance with the "rules of the game;" these are the evaluation criteria announced in the solicitation. For example, if two competitors' proposals were judged equal in technical merit on the basis of criteria announced in the solicitation but the winner was selected because it was located in the same city as the sponsor (a criterion not made known to the competitors), the unsuccessful offeror would have a valid basis for protesting the selection and award of the contract to the other offeror. Evaluation panelists should document their rationale for the ratings reached on each proposal (Figure 3). This demands time and effort but it is important for several reasons. When a panelist reaches a conclusion, the rationale or basis for it is clear at the time but it may be unclear or forgotten days, or weeks, or several other proposals later. If individual evaluators cannot remember how they arrived at their ratings, it will be difficult to develop a written rationale for the final panel evaluation report; this may become a critical point in the event of a protest. Unsuccesful offerors are entitled to a "debriefing" as to why they were not selected. If substantiated reasons cannot be offered, the award may be subject to protest on the grounds that it was made arbitrarily. The technical evaluation of proposals will yield a ranking of the offerors and may eliminate some from further consideration.

Guidelines for Technical Evaluation of Proposals

The proposals will be evaluated by a three-member panel. Each panelist will read each proposal completely and carefully, evaluating the proposal on the basis of the following criteria which appeared in the solicitation as the factors to be used to determine the most technically competent proposal:

- The offeror's understanding of the terms-of-reference as evident from the logic, clarity, and thoroughness of the proposal.
- The approach proposed to accomplish the scientific and technical objectives.
- The availability and competence of experienced scientific technical personnel.
- The offeror's experience in the field.
- The availability of the necessary research facilities and equipment.

Scoring:

Panelists will score each criteria by assigning a numerical value based on the following scale.

.....5.....	.....4.....	.....3.....	.....2.....	.....1.....	
O	E	A	F	P	U

O = Outstanding (5.0-5.9); E = Excellent (4.0-4.9); A = Average (3.0-3.9); F = Fair (2.0-2.9); P = Poor (1.0-1.9); U = Unacceptable (0.0-0.9).

Narrative:

In addition to assigning a numerical score to each factor, evaluators will prepare a narrative statement explaining their reasons for scoring the criteria as they did. The narrative statements should be concise but contain sufficient detail to fully explain the score.

Ambiguities:

Evaluators may not contact any offeror to obtain clarification of language in the proposal that may be ambiguous; in such instances the item should be identified as a possible item for discussions but the offeror should be downgraded for lack of clarity.

Inadequate Substantiation:

Evaluators may not contact any offeror for additional information because the proposal fails to provide adequate substantiating information; identify the item as a possible item for discussion and downgrade the offeror for lack of adequate substantiation.

Strengths and Weaknesses:

Evaluators should identify the strengths and weaknesses of proposals.

Deficiencies:

Evaluators should identify each aspect in which an offeror, or what is offered, is inadequate to meet the sponsor's minimum requirements. For each deficiency identified the evaluator should provide: an explanation as to why it is felt that one or more minimum requirements will not be met; an opinion (with supporting rationale) as to whether the deficiency can be remedied; an opinion (with supporting rationale) as to whether remedying the deficiency would amount to allowing submission of a second proposal.

Competitive Range:

Evaluators should identify any proposal that does not have a reasonable chance of being selected and explain why they believe that to be the case.

Ranking:

The sum of the criteria scores = the proposal score. The sum of the proposal scores = the ranking score with the high score ranked No. 1.

Figure 2. Sample guideline for technical evaluation of proposals; the evaluation criteria will be the same as those included in the solicitation.

Technical Evaluation of Proposals

Company Name_____

Panel Member_____

1) The offeror's understanding of the terms-of-reference as evident from the logic, clarity, and thoroughness of the proposal.

   Numerical Rating: _____

   Narrative Statement:

2) The approach proposed to accomplish the scientific and technical objectives.

   Numerical Rating: _____

   Narrative Statement:

3) The availability and competence of experienced scientific and technical personnel.

   Numerical Rating: _____

   Narrative Statement:

4) The offeror's experience in the field.

   Numerical Rating: _____

   Narrative Statement:

5) The availability of the necessary research facilities and equipment.

   Numerical Rating: _____

   Narrative Statement:

General Comments/Observations:

Figure 3. Sample technical evaluation rating form to be used by each panel member to document his or her evaluation of each proposal.

The final step in the selection process is the site visit or pre-award survey. This may involve visiting only one laboratory if the technical evaluation revealed it to be a clear winner, or it may involve visiting several if they were very closely ranked on the basis of technical merit. The purpose of the site visit is to meet the personnel who will be involved in the project, to see the facilities and operations firsthand, to "get a feel" for the laboratory and staff, to verify claims made in the proposal, and to finalize the selection. The pre-award survey should be as extensive as possible and focus on the offeror's "capability" and "capacity" as reflected by its facilities, equipment, staff qualifications, standard operating procedures, quality assurance procedures, audit history, accreditation, etc. It will be helpful to design a checklist of items to review during the site visit; a sample checklist is shown in Figure 4.

Check-List of Items to Review During Site Visit

Personnel:
- Qualifications, experience, training for their assigned function.
- Current job description and current summary of training.
- Sufficient number of personnel for the timely and proper conduct of study.
- Adequate safety practices and equipment.

Study Director:
- Scientist or other professional with appropriate education or training assigned.
- Single point of study control.
- Responsible for all aspects of the conduct of the study.

Quality Assurance Unit:
- Independent.
- Reports to management.
- Master schedule.
- Inspections.
- Good Laboratory Practices.
- Audit history.

Facilities:
- Suitable size, construction.
- Separation of functions.
- Equipment suitaable in design, capacity, and function - properly maintained.
- Security.
- Operations - SOPs/Test substance control.
- Animal care - food, water, bedding, pest control, IACUC, veterinary care.

Reports and Records:
- Storage and retrieval.
- Archives - limited access/preservation/inventory control/fragile materials.
- Final reports - format/content.

Figure 4. Sample checklist for site visits. These are some of the major items that should be reviewed. An actual checklist can (and probably should) be much more detailed.

The selection of a contract laboratory is critical for several reasons:
- Economics - the various toxicology, environmental fate, and other kinds of tests, along with associated services such as chemical analysis, can be expensive; therefore, there is a definite economic consideration.
- Acceptability - the results of the study (i.e., the final report) must be acceptable in both form and content to the EPA or other regulatory agency to which it will be submitted. Regardless of the scientific merit of the study results, if it is not presented in proper format, the regulatory agency will reject it outright.
- Timeliness - the availability of the study results in time to meet the established deadline for submission is requisite. EPA is operating under a deadline imposed by Congress for registration of pesticides, hence they are not very sympathetic about delays of required submissions.

CONTRACT ADMINISTRATION

Once the contract laboratory has been selected and the contract awarded, administration of the contract is the responsibility of the sponsor's representative. This individual will have signatory responsibility for approval of the final study protocol and any amendments thereto as the study progresses. It is the representative's job to get the required amount of the test substance to the study director, and to coordinate other activities as necessary to facilitate initiation and completion of the study. The most important step of contract administration is to review the requirements and specific obligations set forth in the contract. The terms-of-reference or contract specifications contain the details of these requirements and obligations. Although the sponsor's representative may have written the specifications, it is imperative that the entire contract package be read and reviewed in order to properly discharge the responsibilities of contract administration. It is a fundamental rule of contract law that the obligations of the parties are established and governed by the language of the contract. During the selection and pre-award process, discussions and negotiations may have involved a number of revisions, changes, additions, or deletions; but what actually governs is precisely what was agreed to by both parties in the contract. The final written contract words are taken to mean exactly what they say.

Contract administration or contract monitoring is intended to ensure that the sponsor obtains the following performance elements from the contractor:
- Delivery of the specific item(s) called for in the contract.
- Avoidance of waste of time and/or money.
- Good quality.
- Performance in a timely fashion.
- Performance within the budget.

Monitoring may be done by on-site inspection, progress reports, and telephone conversations. The sponsor has the right to inspect and check the work

(e.g., audit of raw data) as the study progresses. The contractor's written progress reports can be of significant help in providing a picture of work progress under the contract. Ideally, a combination of inspections, written progress reports, and ongoing communications between the contractor's study director and the sponsor's representative will contribute to a successful project. Contract monitoring does not, however, mean taking charge and usurping the authority of the study director; the laboratory and the study director were hired because of their particular knowledge and skills in a specific scientific field. Contract monitoring means:

- Keeping well-informed of what the contractor is doing.
- Using technical expertise (if needed) to identify the contractor's actions or failures to act that clearly affect the quality of the work underway (and hence the quality of the end result).
- Calling the contractor's attention to deficiencies.
- Working out appropriate action to deal with deficiencies.

Care and diligence in the contracting process will contribute to selection of the best contract laboratory to conduct the required studies and careful administration of the contract, once awarded, will contribute to a successful completion of the project and to the mutual satisfaction and benefit of the parties to the contract.

CASE STUDIES

The following case studies illustrate some of the kinds of things that can occur during the contract research process. These are not exhaustive, only representative of different problems or events that have occurred during our contracting experience; they are presented for their value as learning experiences.

CASE #1:

Situation - Studies of acute avian dietary toxicity (LC_{50}) in quail and duck were required. An analytical method for measuring the levels of test substance in the diets presented to the test birds was needed before the studies could be done. Two contracts to two different laboratories were set up - one for the toxicity study, and one for the method development. It took more than three years before final reports on these eight-day studies were available for submission to EPA.

Analysis - This case involves numerous points: 1) unwise division of responsibility and concomitant lack of control, 2) lack of definition of specific needs, 3) multiple changes of sponsor's representative, and 4) lack of continuity of responsible parties resulting in general confusion and delay.

Point - Assign a single permanent sponsor's representative to coordinate all aspects of a contract study. Avoid separate contracts for sub-portions of the work. If technical advise is needed, assign a technical advisor to assist the representative.

CASE #2:

Situation - This involved a primary eye irritation study in rabbits. Severe irritation was noted by day 3 of a planned 14-day test. The study director recommended stopping the study for reasons of humaneness. The sponsor's representative, acting on the belief that EPA would reject the study if observations were not continued for 14 days, instructed the study director to continue the test (EPA had been asked for permission to terminate but had not responded). The test was continued until day 8 when a veterinary ophthalmologist was consulted. Based on his recommendation, the test was terminated and EPA later concurred with this decision.

Analysis - The EPA Guideline for this test does not specify a duration for the observation period and in fact states that it "... should not be fixed rigidly but should be sufficient to of the effects observed." Among the regulations applicable to toxicology studies in addition to FIFRA, and 40 C.F.R. parts 150 to 189, are the Animal Welfare Act (AWA), as amended, and associated regulations in 9 C.F.R. parts 1, 2, and 3. A basic aim of the AWA is to minimize pain and distress. In this case, the animals underwent the effects of the test substance for five more days after the study director recommended termination. Several factors contributed to this situation; the laboratory did not have a staff veterinarian, and, although EPA was contacted, the EPA respondent may or may not have been knowledgeable of the AWA requirements. Termination or continuation was a judgement call on the part of the sponsor's representative who was concerned with the integrity of the study and EPA's reaction to termination.

Point - Be thoroughly familiar with all applicable regulations and act accordingly.

CASE #3:

Situation - This case involved a single environmental fate study, accumulation in fish. The contract laboratory's study director subcontracted the biology portion (i.e., exposure of fish to the test substance in both range-finding and definitive studies) to another laboratory. The draft final report received from the contract laboratory basically consisted of a one-paragraph explanation that the study had been done in three phases as described in three separate study reports (i.e., an acute toxicity study [the range-finding], a bioconcentration and elimination of residues study [the definitive exposure], and a report on the metabolite identification in fish tissues. The separate reports were, in fact, three separate studies, each with its own study director.

Analysis - This was a violation of Good Laboratory Practice standards and the EPA format guidelines for submission of data. It would have been rejected outright by EPA. Apparently, the study director did not make clear that the studies to be done by the subcontractor were sub-parts or phases of a larger study for which he was the study director; multiple study directors is a violation of 40 C.F.R. §160.33.

Point - Don't assume that the contractor's study director or even the Quality Assurance representative are familiar with the requirements and procedures for sub-contracting parts of studies which will be submitted to a regulatory agency. Discuss these matters in detail with the contract before the study begins.

CASE #4:

Situation - A contract was awarded to a laboratory for an acute toxicity study. Tentative arrangements for a site visit were reluctantly agreed to by the laboratory's director. Following persistent phone calls from the sponsor's representative in an effort to finalize arrangements, the visit was refused by the contractor one day before it was to take place. Various reasons were given, subsequent calls were not returned, finally the phone was disconnected.

Analysis - The contract was awarded without adequate investigation of the laboratory, its history, staff qualifications, etc. It was later learned that the laboratory had gone out of business.

Point - Check out the laboratory's reputation. Contracts should not be awarded solely on the basis of written information or verbal assurances from laboratory staff nor on the basis of cost alone. Site visits should be arranged before contract award and any reluctance to allow a visit should be considered reason not to award.

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