Shayne C. Gad · Charles B. Spainhour

Contract Research and Development Organizations

Their Role in Global Product Development

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To my brother Scott Michael Gad and sister-in-law Rosa Gad, who left us too soon.

Shayne C. Gad

To my beloved wife, Joan, who is my best friend and who has been very devoted and supportive in all that I do; my good friend Shayne Gad, an outstanding professional and even more admirable human being for his friendship and always being there for me; and finally the Big Black Boys Amos, Andy, Tim, Jinkx, and Mike whose cold noses, wagging tails, and wild tongues make life tolerable.

Charles B. Spainhour

Preface

Dr. Gad was privileged to start his career in toxicology more than 30 years ago in a testing laboratory that was a hybrid of a company lab and a contract testing lab. The Chemical Hygiene Fellowship of Carnegie Mellon Institute of Research (later known as Bushy Run Labs) was a near perfect environment to learn the practical aspects of regulatory toxicology testing while also being pushed to stay abreast of the then rapidly flowering science of toxicology. Though he has not worked in the contract research environment full time since then, the insights, work ethic, and friendships from those days have been invaluable.

Alternatively, Dr. Spainhour started his career working for a small ethical pharmaceutical company by the name of Smith, Kline & French Ltd. During his tenure there managed to work in a variety of different disciplines in drug development, providing opportunities to understanding the mechanics of how drugs were discovered and developed. Eventually, Dr. Spainhour opted for an opportunity to work for a very small CRO, Pharmakon Research Laboratories and learned first-hand what contract research is all about and successfully grew and developed that business. The things that he learned along the way and the relationships that he established have been of critical importance in formulating his current views and strategies today.

At least through the point of completion of initial studies in humans, most pharmaceutical and medical device development is performed by one form or another of contractor. It is only because of contract research organizations (CROs) that the recent advances in basic science have been translated to the medical wonders that have become available the last 10 years, with the CROs providing the essential regulatory compliant underpinnings of science and technology. Success in pharmaceutical and medical device development requires many things, but the probability of a positive outcome is vastly improved if the individuals and companies seeking to develop these new products truly understand the "tools" before them. Improving that understanding is the objective of this book.

Cary, USA — Shayne C. Gad
Clarks Summit, USA — Charles B. Spainhour

Contents

Chapter 1
Introduction

The research-driven components of the global healthcare industry represent an enormous economic and societal force in the world, and even at the primary (new product developer) levels are composed of an incredibly diverse set of component organizations. These range from huge multinational corporations to "virtual" organizations, which have only a few part time employees, but are now truly global in scope. While primarily in the private sector, there are also those which are partially or fully funded by various government organizations (there is probably even room for a separate volume on funding models and means of funding for such organizations and the impact of such on development processes). There are "for pay" directories of these available (Drug Information Association (DIA) 2010 for example), but these are by no means either comprehensive or objective (being compendiums of paid testing).

For the purposes of this volume, the resulting products from all of the efforts of this sector of the global economy include drugs (pharmaceuticals, biological, nutraceuticals, vaccines and so forth), medical devices, and diagnostics. All of these are highly regulated during their development and marketing, both in the US and overseas. Though many of the service organizations referred to in this volume also do work for other industries, our focus will concentrate on their activities in the more limited pharmaceutical and medical device industrial sectors. While there was always an element of outsourcing of the research, development, and even manufacturing of these healthcare products, the twenty-first century has seen such "virtual" approaches become the majority approach. Currently, it is estimated that more than 1,100 CRO organizations worldwide serve just the nonclinical and clinical development needs of these industries.

CROs (also called CSOs – contract service organizations or PDOs – pharmaceutical development organizations) span an amazing range of areas of expertise. Though there are some organizations which present themselves as turn-key "we do it all" (none truly do), and many present themselves as "full service CROs," most offer

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distinct niche services and at best can readily subcontract other needed services. These include:

Biological: Pharmacology (in vitro screening, efficacy modeling, safety pharmacology, candidate in vivo screening for final selection), toxicology (genetic toxicology, animal toxicology – with many subsets), pharmacokinetics, and metabolism.

Chemistry: Synthesis, API manufacture, radiolabeled synthesis, analytical methods, and bioanalytical methods.

Clinical: Phase I centers, CRA identification and training, statisticians, data and site management, report writing services, and for profit Phase II/III sites. Centerwatch.com currently lists more than 800 of these for the US alone.

Dosage form aspects: Formulation developers, drug product manufacturers CTM (clinical trial material) manufacturers (oral, topical and parenteral, labeling, patient kit preparation).

Regulatory: IND, NDA, IDE, 510(k), PMA, CTD, DMF and annual update writers, and regulatory advisors.

A more detailed breakdown of the scope and types of activities of CRO's is provided in Chap. 4. Literally, the services provided cover the entire range of activities involved in discovering, selecting leads, developing candidates, and securing market approval for manufacturing, distributing, and marketing the products in these industries. We will limit this volume to those involved in taking an idea or molecule forward through candidate selection development to the point of getting regulatory approval to market a product.

The authors must also state that most of our careers have been spent in the aspects involved in insuring the safety of products, and therefore we will tend to use the CRO's ("toxicology labs") and activities in this area as examples. While such have been the subject of limited directories in the past (Jackson 1985; Texas Research Institute 1986; Freudenthal 1997), these references have been limited to larger US toxicology facilities. More recently, there has been publication of annual directories (by *Contract Pharma*, and DIA, for example) which are actually compendiums of paid advertisements.

We should start by considering the history of such commercial labs. The oldest in the US (Food and Drug Research Laboratories or FDRL) opened in the 1930s, moved from suburban New Jersey to rural upstate New York, and went out of operation (under the FDRL name) in the late 1980s, though the facilities are still utilized by some of the staff who still work at Liberty Laboratories, which specializes in felines (domestic cats) for and in research.

From the second half of the 1970s a number of toxicology laboratories (Industrial Biotest – IBT, the University of Miami operated lab, Cannon Laboratories, Bioassay Systems, Lilton Biometrics, Tegaris Labs, Bushy Run (in earlier years called the Chemical Hygiene Fellowship of Carnegie Mellon Institute and perhaps the second oldest contract toxicology laboratory), Borriston/Midatlantic Laboratories, Primate

Research Institute (PRI), Utah Biomedical Testing Laboratory (UBTL), HTI, and Oread Laboratories – to name a few) of significant size thrived but subsequently have gone out of existence. Additionally, just as in the industries they serve, there has been a continued series of acquisitions, mergers (the current Charles River Laboratories includes what were once Sierra Biomedical, Bio-Research, Pathology Associates Incorporated, Argus Research, Redfield Laboratory (site now closed), Springborn Laboratories and TSI Mason (also until site closed) among its parts), and renaming (Hazleton becoming Corning changing to Covance, for example). These same trends and forces have been active in the other types of CROs. There have been noticeable trends where protracted periods of acquisition would be followed by fragmentation into separate labor. As has continued shifting (and generally) expansion of services offered to expand market, revenues, and profitability. In extreme cases, this has lead to the evolution of some organizations (such as Quintiles, Covance, and MDS Pharma) which offer to "do it all" for the pharmaceutical industry. Periodic economic changes also have served to reshape the "population" of CRO's.

An ever decreasing number of companies seeking to develop a new regulated product (though the focus of this book is on drugs, devices and diagnostics, this also applies to dietary supplements, pesticides, cosmetics and many other products) have the capability to perform the required technical (and in many cases, regulatory) work needed to bring a product to market. From this point such companies will be generally referred to as clients or sponsors. Alternatively, although some or all of the capabilities may exist theoretically, the company's laboratory schedule may in actuality not be able to accommodate all required work in the desired time frame. At some time, for various reasons, industry will need to contract work to external facilities, whether they are commercial contract laboratories, university laboratories, or even a member company's laboratory as in the case of a consortium study. As with all contractual arrangements, careful planning and coordination coupled with thorough preparation is required in order to obtain the desired product or service, to avoid confusion and misunderstanding, and to produce a timely and cost-effective result. This is a practical guide for those organizations that need to outsource some or all of their activities at external facilities. Here, we shall attempt to present how of such activities take place and a source book (directory) of those that are available.

The needs for (and means of accessing) CRO support services are different for the majority of client organizations (smaller companies which have no or only one marketed product) and larger organizations (sometimes referred to as "big pharma," comprising truly fully integrated companies with multiple products on the market). Issues of timing, cash flow and objectives (get the product to a point where a "partner" will buy or at least heavily support the continued development of a product vs. taking products all the way to market) as well as what contract resources are needed and how they are to be managed as parts of a development program tend to be very different. But the majority of the concerns and issues of individual contractory selection, monitoring, and management as presented in this book are common (FDA 1984).

Consultants

While consultants have existed and been active in the pharmaceutical and medical fields for many years, the changes in how development is done (particularly the shift to many smaller and "virtual" companies) and the thinning out of staff by established larger companies have transformed consultants to inherent and critical parts of the process.

From the consultant side, this has meant a shift from consulting being either something done between other jobs or late in a career (while transitioning to retirement) to a legitimate long-term career.

Consultants may be either narrow or broad in focus, and may operate as individuals, with small support staffs, as members of small group, or as employees of large consulting companies. There are, as yet, few associatiations of such consultants. One such is the Roundtable of Toxicology Consultants (RTC – see http://www.toxconsultants.com), in which an international gets more than 140 (currently) individuals who have associated to both better market themselves and to be able to draw on mutual knowledge and experience in meeting client needs.

Defining the Project

Development of the Study Record

The objective of a study or any research is to evaluate theories and hypotheses and to produce results supporting or disproving the theories. The written evidence of this work is called the study record and includes all records, documentation, and results of the development effort. Let us now consider the logical progression of such research activities and the development of the study record.

Research Plan

The development project begins with developing the study or project plan, or simply thinking through what needs to be done and when. Whether the worker is performing internal research, concept evaluations, or work in support of regulatory requirements, this plan should be written down. When written, the research plan becomes the framework for the protocol or contract for the project and includes the hypothesis, the proposed methods, observations to be made, and the expected results. Researchers should pay special attention to the level of detail in this plan. For example, in regulatory research environments there are mandated requirements for inclusion of particular details in the protocol and a specified format. Optional experimental methods may

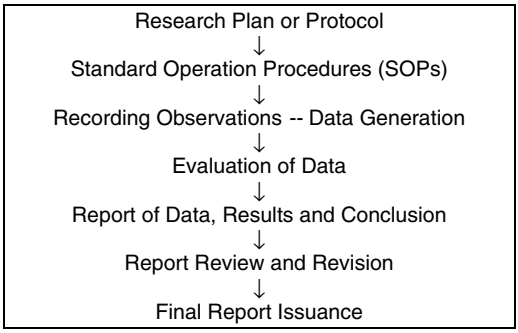

Fig. 1.1 Progression of a contracted study or project

be included in the protocol or amended into it as needed, but (again) they must be recorded. Even if a written protocol or detailed contract is not specifically required for the project, it is useful to develop the habit of producing a protocol because it requires you and your colleagues to think clearly through the experimental design, resources required, and any potential issues. It also provides guidance for the actual conduct of the work and promotes consistency in performance (Fig. 1.1).

General Considerations

There are a number of general aspects to be considered in the operations of a CRO in the regulated industries with which we should be concerned. Most of these, of course, have to do with how things are documented. We will generally use USFDA's Good Laboratory Practices (FDA 2002a) as our model in this volume, but the principles are the same internationally (Gad 2001, 2010) and for Good Manufacturing Practices (GMPs) (FDA 2002c) and Good Clinical Practices (GCPs).

Standard Operating Procedures

Some of the procedures performed during the study are routine for the laboratory. CRO's formalize the documentation of these routine procedures into written standard operating procedures (SOPs). SOPs are detailed descriptions of such things as animal handling, equipment operation, methods for taking and recording data, and procedures for reagent receipt, storage, and preparation – the types of procedures that are common to all laboratory operations. SOPs should be written in sufficient detail as to promote consistency in performing the procedures, but not in such detail as to make implementation cumbersome from a quality assurance perspective. Having SOPs and insisting that they are followed provides the researcher with a measure of control over potential variables in the experiment.

Regulatory Performance

A good place to initiate an evaluation of any regulated facility is to examine its record of previous inspection results and responses to these. For FDA, these are easy to obtain (FDA 2002b).

Data Recording

Once the study initiates, as each procedure is performed, it is essential to, write down what one did, and record the observed results. The level of detail of any written record should enable someone else with equivalent technical training to repeat your experiment exactly as you did. Why? *Reproducibility*. That experimental results must be reproducible is a basic covenant of science. It is the process through which scientific conclusions and discoveries are confirmed. Reproducibility is promoted by the specific data-recording requirements for data that are submitted to FDA and, equivalent non-US regulatory agencies. Reproducibility is also required in research performed to support a patent request.

For now, we wish to introduce you to the concept of "if you didn't write it down you didn't do it." You, the researcher, have the burden of proof in regulated research, in protection of patent rights, and in defense of your work in professional circles. The issue is *completeness* of your records. The study record must be a complete documentation of all data and procedures performed. If you did not write it down, you did not do it as far as regulatory agencies and patent offices are concerned. In the experimental record, there are however some accepted shortcuts. Here, some of the hard preparatory work pays dividends. In the written record, one may include references to previously described methods and SOPs, state that they were followed exactly, or describe amendments to or deviations from them. Efficient ways of collecting data may be developed to encourage the complete recording of all required data. Later in this chapter, methods for recording procedures and observations will be discussed in detail.

The *accuracy* of recorded data is another important consideration because any observed result, if not recorded immediately, may not be recorded accurately. Do not lose data because of some rationalization about time, money, or one's ability to remember what happened. All data should be recorded directly into a notebook or onto a worksheet at the time of the observation. Keep in mind that transcribed data – data copied by hand or entered by a person into a computer – often is subject to errors. If data are copies to a table or a spreadsheet, the entered data should be checked for complicity against the original data to ensure accuracy. In a regulated research work, all such work and data will also be audited and the accuracy and conformance to all procedures verified.

Analysis of the Data

When the laboratory work is done, the analysis of the data begins. Observed data are entered into formulae, calculations are made, and statistical analyses are performed. All these manipulations must be carefully recorded, because from these data the conclusions for the study will be drawn. The manipulations of the data are the link between the original observations and the conclusions. Consistency between the data and the result is controlled by monitoring all transcription, manipulation, and correlations of the data in generation of the final manuscript.

Reporting of Results and Conclusions

Finally, a draft final report is provided for review, to the client and/or their agent. It will receive critical review before acceptance. The final version will then be provided to others and again will receive critical review by other scientists or some skeptical governmental or public audience. In all cases, it will be essential to be able to justify the integrity of the data. Additionally, the methods, initial data, the calculations and statistical analysis, and the conclusions must be defensible, meaning complete, accurate, internally consistent, and repeatable to withstand scientific criticism.

Types of Data

Earlier we mentioned different elements of the study record research plan or protocol, observations, calculations and statistical output, and conclusions. For ease of explanation, the terminology from the GLPs, GMPs, and GCPs (here on GLPs will be used to stand for all three in the general case) – protocol, raw data, statistical analysis, and final report – will be used to describe the components of the study record.

According to the GLPs, the protocol is a written document that is approved by the study director (person responsible for the technical conduct of the study) and sponsoring organization. The protocol is the research plan, or the project plan in a management sense. It clearly indicates the objectives of the research project and describes all methods for the conduct of the work. It includes a complete description of the test system, the test article, the experimental design, the data to be collected, the type and frequency of tests executed, and the planned statistical analysis. Financial considerations should not be included in a protocol, which should be restricted to scientific details. An amendment may be included specifying important milestone dates, but this is not an essential feature and such a schedule can be specified outside of the protocol.

The protocol needs to be strictly followed during research. "What," you say, "no experimental license, no free expression of scientific inquiry?" Of course there is, as long as the changes in procedures or methods are documented along the way as amendments to the protocol. If the work you are doing is governed by strict contractual or regulatory guidelines, you may not be able to express much creativity, but remember the objective, in this case, is to provide consistent and reliable data for comparisons for regulatory purposes. Even the GLPs make provisions to amend the protocol and document any deviations from it. During all research, except perhaps during the most routine analysis, there may be changes in experimental methods and procedures, rethinking of design, decisions to analyze data in new or different ways, or unexpected occurrences that cause mistakes to be made. An important concept to apply here is that these variances from the plan must all be documented. Amendments to a protocol are "planned" changes to the protocol that are documented before they are implemented. Deviations address mistakes or events that are exceptions to the protocol and are documented after the fact.

Raw Data

"Raw data" is the term used to describe the most basic element of experimental observations. It is important to understand fully the concept of raw data. There are unique standards for recording raw data that do not apply to other types of data. These will be discussed later in the chapter. For now, let us look at what constitutes raw data. In the FDA and EPA GLPs raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof that are the result of original observation and activities of the study and are necessary for the reconstruction and evaluation of the report of that study. All terms must be taken in the most literal sense and must be interpreted collectively to apply this definition to the data generated during a study or experiment. There are two key phrases: "are the result of original observations and activities of the study," and "are necessary for the reconstruction and evaluation of the report of that study." Raw data includes visual observations, direct measurements, output of instrumental measurements, and any activity (room temperature, room humidity, room airflow, light period, etc.) that describes or has an impact on the observations. Indeed anything that is produced or observed during the study that is necessary to exactly reconstruct (know what happened) the study and evaluate (analyze or, for regulatory purposes, assess the quality of) the reported results of the study and its conclusions is raw data. This definition of raw data has been carefully designed to encourage the development of data that is defensible and reproducible.

Included in the scope of raw data may be data that results from calculations that allow the data to be analyzed, for example, the results of gas chromatography where the raw data are defined as the curve that was fitted by the instrument software from individual points. The individual points on the curve are essentially meaningless by

themselves, but the curve provides the needed basic information. The area under the curve, which is used to calculate the concentration, is an interpretation of the curve based on decisions made about the position of the baseline and the height of the peak. This is not "raw data" since it is not the original observation and may be calculated later and, practically, may be recalculated. For the researcher to completely understand the results, the curve with the baseline, the area under the curve, and the calculations are required to be performed and recorded, but only the curve itself is "raw data." The distinction is that the curve is the original observation and must be recorded promptly. The current advance of the "section" of the GLP, governing how electronic (automated) data is collected, manipulated, audited, verified, stored, and provided to the FDA (section 11) adds another entire dimension to consideration of there issues.

Other Types of Data

Other types of data that are not typically viewed as raw data may be included with the study or experimental records. For example, correspondence, memoranda, and notes that may include information that is necessary to reconstruct and evaluate the reported results and conclusions. While these are not records of original experimental observations, they do represent documentation of the activities of the study and can help with its reconstruction. They often contain approvals for method changes by study management or sponsoring organizations, instructions to laboratory staff for performing procedures, or ideas recorded during the work. Here are some examples of raw data that are generated during a toxicology study:

Test article receipt documents	Equipment use and calibration
Animal receipt documents	Equipment maintenance
Records of quarantine	Transfer of sample custody
Dose formulation records	Sample randomization
Sample collection records	Animal or sample identification
Dosing records	Assignment to study
Animal observations	Necropsy records
Blood collections and analysis	Analytical results
Euthanasia records	Histology records
Pathologist's findings	

For government-regulated research, all records that are documentation of the study conduct are treated as raw data. From the perspective of the scientific historian, the original notes, correspondence, and observations tell the story of the life and thought processes of the scientist being studied. From the mundane to the extreme, these records are important, a fact which will more than be appreciated when an audit might occur or challenge to the data might develop.

Computerized Data Collection

Special attention must be dedicated to computer-generated raw data. Automated laboratory instrumentation has come into widespread use. In hand-recorded data, the record of the original observation is raw data. But what is considered raw data in computerized systems? In this case, raw data are the first recorded occurrence of the original observation that is readable by a human. This definition treats computer-generated data as hand-recorded data. It documents the "original observations and activities of the study and is necessary for reconstruction and evaluation of the report of that study" (FDA 1987; EPA 1989a, b). However, we must pay special attention to this type of data. The validity of hand-recorded data is based on the reliability of the observer and on well-developed and validated standards of measurement. For computer-generated data, the observer is a computerized data collection system, and the measurements are controlled by a computer program. These are complex systems that may contain complex flaws. Just as the principles behind measurements with a standard thermometer were validated centuries ago and are verified with each thermometer produced today, so must modern computerized instrumentation be validated and its operation verified. This causes a real dilemma for many scientists who are proficient in biomedical research but not in computer science. Because of the size and scope of this issue, we can only call your attention to the problem and refer you to the literature for additional guidance.

Finally moving to promulgation and clarification of requirements of GLP section 11 (21 CFR 11) compliance, multiple points must be considered. Though it is still not completely clear exactly what all will be required, seven elements are certainly involved: Software validation, logon security, existence of audit trails, authority controls (over entries and changes), storage of data, backup and archival, and training for users and administration. Again, this is a very complex area and no more than a superficial perspective is presented here.

Statistical Data

Statistical data result from descriptive processes, summarization of raw data, and statistical analysis. Simply put, these data are not raw data but represent manipulation of the data. However, during this analysis process, a number of situations may affect the raw data and the final conclusions. For example, certain data may be rejected because they are shown to be experimentally flawed, an outlier believed to have resulted from an error, or not be plausible. We will leave it to other texts to discuss the criteria by which decisions like these are made. Here, we will say only that any manipulation of raw data is itself raw data. For example, a series of organ weights is analyzed. One of the weights is clearly out of the usual range for the species, and no necropsy observations indicated the organ was of unusual size. The preserved

tissues are checked, and the organ appears to be the same size as others in the group. The statistician then may decide to remove that organ weight from the set of weights. The record of this action is raw data. The analysis is not, because it can be replicated by simple data handling techniques. It is a fine distinction that matters only to QA people in the context of recording requirements for raw data since both the analyses and record of the data change are required to reconstruct the report.

Statistical analysis is part of the study record. Documentation of the methods of statistical analysis, statistical parameters, and calculations is important. Critical evaluation of conclusions often involves discussion of the statistical methods employed. Complete documentation and reporting of these methods, calculations, and results allows for constructive, useful critical review.

Results and Conclusions

The study record includes the results and conclusions made from review of the data produced during the scientific investigation. The data are summarized in abstracts, presented at meetings, published in journals, and, with all previously discussed types of data, are reported to government agencies. However, it is the scientist's interpretation of the data that communicates the significance of the experimentation. In all scientific forums, scientists present their interpretation of the data as results and conclusions. Results and conclusions are separate concepts. This is an important distinction not only because it is the required format for journal articles and reports, but because it is important to separate them. Results are a literal, objective description of the observations made during the study, a statement of the facts. Conclusions, on the other hand, represent the analysis of the significance of these observations. They state the researcher's interpretation of the results. If results are presented clearly and objectively, they can be analyzed by any knowledgeable scientist, thereby testing the conclusions drawn. This is the process by which the body of scientific knowledge is refined and perfected.

For regulatory purposes, the results presented to the regulatory agencies (FDA or equivalent) must be complete. Included in such regulatory reports for submission must be tables of raw data, all factors that affect the data, and summaries of the data. In journals, the results section usually is a discussion with tabular or graphical presentations of what the researcher considers relevant data to support the conclusions. Conclusions presented in either case interpret the data, discuss the significance of the data, and describe the rationale for reaching the stated conclusions. In both bases, the results are reviewed and the conclusions evaluated by scientific peers. The functions of the peer review process are to question and dispute or confirm the information gained from the experiment. Objective reporting of results and clear discussion of conclusions are required to successfully communicate the scientist's perspective to the scientific community.

Development of Study Data

We have just discussed the types of data that make up the study record. The following discussion addresses quality characteristics for the study record, requirements for recording raw data, and methods for fulfilling the quality characteristics and raw data requirements by using various recordkeeping formats.

Quality Characteristics

There are four characteristics the study record must have: completeness, consistency, accuracy, and reconstructability. *Completeness* means the information is totally there, self-explanatory, and whole. *Consistency* in the study record means that there is "reasonable agreement between different records containing the same information" (DeWoskin 1995). *Accuracy* is agreement between what is observed and what is recorded. The final characteristic is *reconstructability*. Can the data record guide the researcher or someone else sufficiently so as to reproduce the events of the study? These characteristics are goals to meet in developing the study record and will be used in Chap. 4 to evaluate the quality of these records. They must be built into the study from the beginning and considerable attention to these goals will be required as the study progresses to produce a complete, consistent, accurate, and reconstructable study record. Quality cannot be put in at the end of the study or experiment.

Recording Raw Data

Raw data may be recorded by hand in laboratory notebooks and worksheets or entered into a computerized data management system. Today, more and more data are computer generated and recorded as paper outputs or are electronically written to magnetic media, stored on microfiche, or other electronic storage media. This section will discuss how raw data in both forms are recorded.

General Requirements for Raw Data Recording

Raw data must be recorded properly to preserve and protect them. The following is excerpted from the FDA GLPs:

> All data generated during the conduct of a study, except those that are generated by automated data collection systems, shall be recorded *directly, promptly*, and *legibly in ink*. All data entries shall be *dated on the date of entry* and *signed or initialed by the person entering the data*.

All introductory laboratory courses teach the basic techniques for the recording of raw data. Even though these standards are published as regulations for only certain types of research, we believe that there is never an instance when these minimum standards do not apply. There may be researchers who "get by" writing in pencil or scribbling data on paper towels, but they often ultimately suffer the consequences of their carelessness when data are lost or their records are unintelligible. Also, if these same researchers attempt to patent a product or method, or to submit their data to regulatory agencies, their submissions are simply not acceptable, because their data is flawed. In fact, if the regulatory data are incomplete or obscured in some way, the scientist involved may even be subject to civil or criminal penalties. It is always best to establish good habits early, especially for scientific recordkeeping.

For hand-recorded data – "directly, promptly, and legibly in ink" – means to write it down in the notebook or on the worksheet as soon as you see it, so that it is readable and in indelible ink. The purpose is to accurately preserve the observation. Notes on paper towels, post-it notes, or scratch paper may be lost. Prompt recording promotes accuracy and chronologically correct records. Legibility assures that at a later time you will understand what is written. This does not necessarily mean neat. If you are recording directly and promptly, neatness may have to be forgone. It does, however, mean readable and understandable.

The use of ink preserves the record from being erased or smeared illegibly. It is commonly understood that the ink should be indelible, meaning it cannot be erased and can withstand water or solvent spills. Some organizations may require a specific color of ink to be used, usually black or dark blue. This requirement originated because black ink was the most permanent and could be readily photocopied. Even without such requirements, the ink used in the lab should be tested to see how it withstands common spills and to see if its imaged copies from a standard photocopier are of good quality. Some colors of ink and some thin line pens may not copy completely. There are a number of reasons why data may need to be copied, and that these copies are 'exact' copies is a very practical issue. Inks should not fade with time. Some analytical instruments produce printed data on heat sensitive paper, which tends to fade in time. To preserve these data, laboratories will make photocopies. This is an issue that will be discussed more fully in Chap. 3.

The requirements to sign and date the data record flow from practical and legal considerations; it is often useful to know who made and recorded the observation. In many research labs, graduate assistants or research technicians are responsible for recording the raw data. If questions arise later, the individual responsible may be sought out and asked to clarify an entry. For GLP studies, the signature represents a legal declaration meaning the data recorded here are correct and complete. The data must be dated at the time of entry. This attests to the date of the recording of the observation and the progression in time of the study conduct. Some lab work is time dependent and in this case the time and date must be recorded. There is never any instance when data or signatures may be backdated or dated in advance.

Signatures and dates are crucial when documenting discovery and in supporting a patent claim. For studies conducted under the GLPs, the signature and date are legal requirements for the reconstruction of the study conduct. Falsely reported data

may accordingly result in civil or criminal penalties to the person recording the data and his/her management for making false and misleading statements.

In some types of research, additional signatures and dates may be required. Data used to support a patent and data generated during the manufacture of drugs or medical devices must be signed and dated by an additional person – a witness or reviewer thus corroborating the stated information. An important point here is that the witness or reviewer can in the simplest form attest to nothing more than the signing and dating of the data entry and not to the integrity of the data collection methods or the data itself unless marked "read and understood," in which case the witness or reviewer is actually attesting to the integrity of the data as it has been generated.

Error Correction in Data Recording

What happens when there is a mistake in recording data or an addition that must be made to the data at a later time? Well the FDA GLPs address this.

> Any changes to entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed at the time of the change.

All changes to the written record of data must be explained and signed and dated. Doing so provides justification for the correction and again provides testimony as to who made the change and when it was done. To make corrections to the data, the original entry is not obscured. A single line is drawn through the entry. Then, the reason for the change is recorded with the date the change is made and the initials of the person making the change. For simplicity and ease of recording, a code may be established and documented to explain common reasons for making corrections to data. A simple example may be a circled letter designation like:

S = sentence error
E = entry error
C = calculation error

This is easy to remember and use. Any other types of errors or corrections must be described in sufficient detail to justify the change. A compendium of these symbols and abbreviations must be a matter of record, like in a suitable SOP.

Raw data may be generated by computer programs and stored on paper or magnetic material. Most laboratories approach this kind of data as they would hand-generated data. The GLPs state:

> In automated data collection systems, the individual responsible for direct data input shall be identified at the time of the data input. Any changes to automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for the change, shall be dated and the responsible individual shall be identified.

For automated data collection systems, there are similar standards to hand-recorded data (FDA 1987). All raw data should be recorded promptly and directly. Whereas the requirement for hand-collected data is that the records be written legibly

and in ink, but the requirement for computer-collected data is permanence and security. However, there may be special considerations for how signatures and dates are recorded. The physical signature of data may not be possible when using electronic storage media. Electronic signature or the recording of the operator's name and the date are often a function provided in the software and are recorded and embedded with the data. When the data are printed in a paper copy, this information should be included. Some labs have adopted a policy requiring that the paper printout must be signed and dated by the operator. Some instruments produce a continuous printout or strip chart. In this case, the chart should be signed by the operator and dated on the date the data are retrieved. If the data are maintained on electronic media, the operator's name and date must be recorded on that medium.

Because computer security and risk of corruption or destruction of computer-stored data are a major concern, many laboratories maintain computer-generated data in paper printouts because the means for maintaining this data are traditional and easy to implement. As long as the printout represents a verified exact copy of the original raw data, it is acceptable and often even preferable to designate the printout as the raw data. This point should emphasize again the importance of proper validation of information technology systems and software, so that there is confidence in a print out being an exact copy of the electronic files.

When changes to the electronically stored raw data are made, the original observation must be maintained. This is accomplished in several ways. Newer software packages allow these changes to be made and properly documented. To do this, the original entry is not erased, and there is a way of recording the reason for the change along with the electronic signature of the person authorized to make the change and the date of the change. However, some data collection systems still do not have this capability. If this is the case, the original printout may be retained with the new printout that contains the change, the reason for the change, the signature of the person authorized to make the change, and the date of the change. Some computer programs allow for footnotes and addenda to be added to the record. These additions to the record, if made later, should also include a handwritten or computer-recorded signature and date.

Formats for Recording Data

We will now begin to construct the study record. The format for the study record may be determined by the preferences of the researcher. Some researchers prefer to maintain all study records in laboratory notebooks. In private industry, research and development labs may be required to use lab notebooks because of potential patent documentation requirements. Many chemists have become accustomed to the use of lab notebooks. However, handwritten data may be maintained in laboratory notebooks, on worksheets and forms, or one may use computer-generated printouts and electronic storage media. The remainder of this section discusses guidelines for recording data using all formats.

Laboratory Notebooks

Laboratory notebooks are usually bound books with ruled or girded pages that are used to record the events of an experiment or study. Organizations may order specially prepared notebooks that are uniquely numbered on the cover and spine. They have consecutively numbered pages, and some come with additional carbonless pages to make exact copies of the entries. Organizations may have strict procedures in place for issuing notebooks to individuals for use on specific research projects. After the glassware is cleaned, all that remains of a study is the notebook; its value is in the cost of repeating all the work because it could not be recreated. Therefore, SOPs should be written to control the assignment, use, and location of these records.

The pages may be designed to contain formats for recording information. In the header, there may be space for the title and date. In the footer, space may be allocated for signature and date of the recorder, and signature and date of a reviewer or witness. When beginning to use a laboratory notebook, set aside the first few pages for the table of contents. Then a few pages may be held in reserve for notes, explanations, and definitions that are generally applicable to the contents.

The remainder of this section discusses the rules for recording data in the notebook. First, each page should contain a descriptive title of the experiment that includes the study designation and the experimental procedure to be performed. The date the procedure was performed is also recorded. Often a complete description of the experiment will require several pages. After the first page, subsequent pages should indicate, at least, an abbreviated title and cross-reference to the page from which it was continued.

The body of the experimental record should include the following sections:

- Purpose of the experiment
- Materials needed, including instruments, equipment, reagents, animals used, etc.
- Reagent and sample preparation
- Methods and procedures
- Results

The *purpose* may be recorded in a few sentences. The *materials section* is a list of all the things you need for the experiment – the instruments to be used, the equipment, and chemicals. When recording the analytical instruments, include the make, model number, and serial number, the location of the instrument; and all settings and conditions for the use of the instrument. Remember one needs to be able to provide sufficient detail that the experiment or study can be reproduced at any time in the future. The description of the chemical used should include a complete description including name, manufacturer, lot or serial number, concentration, expiry date if applicable, and stability profile. *Reagent and solution* preparation must be described in detail with a record of all weights and measurements. It is extremely important that sample identification and sample preparation be completely documented in detail. The *methods and procedures* section is a step-by-step description of the conduct of the experiment.

If SOPs are in place that describes any of the above information in sufficient detail, they may be referenced rather than writing or entering all of the tedium of the procedure again. Information recorded in the notebook is all weights and measurements, and any information that is unique to this experiment or not is specifically discussed in the SOP. SOPs often are written for more general applications. An SOP may state that the pH will be adjusted using a buffer or acid as required. The notebook should indicate what was used to adjust the pH and the volume that was used. An SOP may describe the formulation of a compound in a certain amount, when the experiment requires a different amount. The mixing procedures may be cross-referenced, but it will be necessary to describe in detail the conversion of the SOP quantities and any changes in procedure resulting from the change in quantity. Study-specific SOPs can be very useful when properly written, used, and referenced.

The *experimental results* section must contain all observations and any information relating to those results. It should include any deviation from established methods, from SOPs, and from the protocol. Failed experiments must be reported even though the procedure was successfully repeated. Justification for repeating the procedure and a description of what may have gone wrong is recorded. All calculations should be shown in detail and include a description of the formula used.

Remember, all entries are recorded directly and promptly into the notebook at the appropriate time in the experiment and are recorded legibly and in indelible ink. Some information may be entered at the beginning of the day, some entered at the end of the day, but all weights, measurements, and recorded observations must be entered into the notebook directly and promptly as the information is generated.

For a complete record, it is often necessary to insert such information as shipping receipts, photographs, and printouts into the lab notebook. In doing so, do not obscure any writing on the page. The following are tips for inserting information into the notebook.

- Glue (e.g., glue stick) the loose paper in place. (We do not recommend using tape because tape over time loses its holding power).
- Inserts may be signed, dated, stapled, and cross-referenced to the notebook and page so that they can be replaced if they become loose.
- Make verified (stamped: “Exact copy”) copies of data that is too large for the page, shrinking it to fit the notebook page. Reference the location of the original.
- If, by some chance, data are accidentally recorded on a paper towel or other handy scrap of paper, these should be signed, dated, and glued into the notebook. It is not wise to transcribe data thereby, introducing the possibility of error or opening oneself to the criticism of potential of data tampering.

The bottom of each page must be signed by the person entering the data and dated at the time of entry. The date at the top of the page – the date of the activity – in most cases will be the same as the date at the bottom of the page. A few exceptions are appropriate. The most legitimate exception to this rule occurs when a page is reserved for the results printout. The printout may not be available to insert until the following day. The printout should indicate the date when the data were first recorded

which should in turn match the top date. The date at the bottom of the page indicates when it was glued into the notebook.

Occasionally, a scientist will forget to sign and date the page. When this happens, there is no quick fix. The only remedy is to add a notation: "This page was not signed and dated on ____, the time of entry," Then, sign and date this statement using the date that this entry was made.

This discussion has been detailed because the signature and dates on the pages are very important. They are legally required for regulatory purposes. Data used to support patents and specified data produced under the FDA current GMPs and GCPs require the signature and date of a witness or reviewer. For example, the GMPs require that all materials weighed or measured in the preparation of the drug be witnessed, signed, and dated. Patent applications are supported by witnessed experimental records. Some institutions may require supervisory review of notebook entries with accompanying signature and date. This is to say that you should be aware of the uses your data and any requirements for this additional signature. These additional signatures should be embedded in the following statement: "Read and understood by ____ on ____."

An important concept to remember is that bound, consecutively page-numbered notebooks are used to demonstrate the progression of the research and to document the dates of data entry and the chronological nature of the work performed. To prevent the corruption of this record, unused and partially used pages may be marked out so no additions may be made. A suggested method is to draw a "Z" through the page or portion of the page not used. At the end of the project, there may be unused notebook pages. These pages may be marked with Z's or the last used page may indicate that this is the end of the experimental record and no additional pages will be used.

Forms and Worksheets

While many analytical laboratories continue to use lab notebooks, other labs may use forms and worksheets to record their data. The purpose is to provide an efficient format for recording data that are routine in nature. The basic concept is that forms and worksheets should be designed to be easy to use and to provide a complete record of all relevant data. They may be used in combination with lab notebooks as described earlier or kept in files or loose-leaf binders. Explanatory footnotes may be preprinted or added to explain abbreviations and/or the meaning of symbols. Additional space for comments and notes should be incorporated into the format.

Computer spreadsheets and word processing make forms and worksheets easy to design and produce.

The advantages of using forms and worksheets include the following:

- They may be customized and formatted to prompt for all necessary information.
- They are easy to follow, complete, and well-organized.
- Header information, title, study designation, sample numbers, etc. may be filled out in advance, thus saving time.

- Cross-references to applicable SOPs may be included on the worksheet.
- They help to standardize data collection.

Disadvantages of using forms and worksheets include the following:

- They must be carefully designed and should be pretested for completeness and ease of use.
- They may encourage a tendency not to write more information than is specifically requested when designed space is allotted for notes and comments only.
- Forms and worksheets that are designed for general use may contain blanks that are not necessary for the current study. Yet all blanks must be completed. If not needed, "n/a" (not applicable) should be written in the blank or a dash put in the space or when the form is printed "blacked out."
- Forms and worksheets create a routine that can become mindless; individuals need to take care to properly complete the form.

  Example 1: Necropsy forms often contain a complete list of tissues to be checked by the technician. When only some tissues are inspected or retrieved, it may be too easy to check inappropriate boxes.

  Example 2: Animal behavioral observation forms contain blanks to record all observations. The observer must record something in the blank space. A check or "OK" may be used to describe normal behavior if such is defined on the form or in an SOP. A problem occurs when these designations are used automatically without proper attention being paid to observing and recording the behavior of each animal, particularly when most animals are behaving normally.

In discussing the earlier given disadvantages, we are not trying to discourage the use of worksheets. However, one must be careful to institute procedures and practices that assure that forms and worksheets are properly used.

As in any data record, the signature and the date of entry are recorded at the time of the entry, and represent and attest to the accuracy of the information. Any changes to the data or additional notes made after completion of the form or worksheet are made as previously described. Any unused lines on the form or worksheet should be crossed or "Z'd" out. If the signature of a witness or reviewer is required, there should be a line allocated for this purpose.

Forms and worksheets can be a useful and practical way to record and preserve raw data – if you pay attention to the rules of data recording.

Automated Data Collection Systems (Laboratory Information Management Systems)

This is the hottest, most fluid and most difficult topic in this book. Application of data collection rules to computer systems has been the topic of numerous seminars, books, journal articles, government policy committees, and regulatory interpretation.

As an example of the electronic data policy difficulties, the FDA has spent several years trying to reach a consensus on a policy for electronic signatures (US FDA, 1997a, b being the formal latest guidance but the new Current Standard for the Exchange of Non-clinical Data (CSEND) standards are starting to take form in 2011).

Two major issues surround automated data collection systems: validation of the system and verification of the system's proper operation.

Validation asks whether the system is properly designed and tested so that it performs as it should to measure and record data accurately, completely, and consistently. In other words, are all the bugs worked out so that the system does not lose, change, or misrepresent the data you wish to obtain? We recollect, from many years ago, a software program for recording animal weights. If a particular animal had died on study and was not weighed at a weigh session, a "0" was entered for the weight. It was discovered that the software would automatically reject the 0 and record in its place the next animal's weight. This was totally unacceptable. The system was inadequately designed to properly handle commonly occurring data collection exceptions.

The second issue is the verification of the system's operation. Have you tested and proven that the data produced and recorded by the system are accurate, complete, and consistent, meeting all the date quality standards discussed under handwritten data?

Validation and verification are processes that involve hardware and software development and acceptance testing, laboratory installation procedures and testing, computer security, and special recordkeeping procedures, to name a few. There are numerous publications on this topic. If you are working in a research area subject to FDA or its equivalents, we suggest starting with the following: the FDA Computerized Data Systems for Nonclinical Safety Assessment – Current Concepts and Quality Assurance, known as the Red Apple Book and the FDA Technical Reference on Software Development Activities.

The following sections will discuss the defining of raw data for automated data collection systems, what should be recorded in the raw data, electronic signatures, and report formats and spreadsheets.

Computer-Generated Raw Data

It was Dr. Gad's privilege to work a team of experts during the later stages of finalization of the GALPs (Good Automated Laboratory Practices). One of the most difficult tasks was deciding how to define raw data for laboratory information management systems (LIMS). Hours and days were spent on this issue alone. Here is the definition that was ultimately adapted:

> LIMS Raw Data are original observations recorded by the LIMS that are needed to verify, calculate, or derive data that are or may be reported. LIMS raw data storage media are the media to which LIMS Raw Data are first recorded.

From these discussions, we have developed a broader-based alternative definition of computer-generated raw data. For automated data collection systems, "raw data"

means the first record on the system of original observations that are human readable and that are needed to verify, calculate, or derive data that are or may be reported. The GALP definition was designed to fit the scope of the GALPs.

The real issue is how to apply the definition. Hand-recorded raw data is easy to define. What you see is what you write. Automated systems are much more complex. Analytical instruments may perform several functions. For example, the transmittance of a light beam is measured, then converted into an electronic signal, this signal is transmitted to a computer, the software on the computer converts the signal to a machine-readable representation, this representation is translated into a value, this value is recorded into a reporting format that performs calculations and a summary of the input data, and the reported number or numbers are sent to an electronic file or to a printer.

The question is when do we have raw data? It is when an understandable value is first recorded. If the human readable value is saved to a file prior to formatting, this is raw data. If the first recording of the data is in the report format, this is raw data. Some labs have declared the signal from the instrument to the computer to be raw data, but it is then very difficult to use the signal as a means for verification of the report of the data. This example represents only one situation of the possible variations in instrumentation. Each automated data collection system must be assessed to determine when the output is "raw data." What exactly is raw data for electronic instruments and for computers needs to be openly and unambiguously stated and defined to avoid confusion.

Why is the definition of raw data for computer applications so important? One obvious reason is to meet regulatory requirements. Behind these requirements are the same data quality characteristics that apply to hand-recorded data: accuracy, completeness, consistency, and reconstructability. As mentioned earlier, transcription of data can cause errors. Each time data are translated or reformatted by a software application, there is the potential for the data to be corrupted or even worse, lost. When the data are recorded and human readable *before* these downstream operations, these "raw data" can then be used to verify any subsequent iterations.

Here is the type of information that should be included in the automated raw data record:

- The instrument used to collect the data
- The person operating the instrument
- The date (and time) of the operation
- All conditions or settings for the instrument
- The person entering the data (if different from the operator)
- The date and time entered or reported
- The study title or code
- Cross-reference to a notebook or worksheet
- The measurements with associated sample identification
- All system-calculated results

If the system does not allow the input of any of the information given here, it may be recorded by hand on the printout or on cross-referenced notebook pages or worksheets.

Automated raw data may be stored in soft copy (e.g., magnetic media) or in hard copy (e.g., paper printout, microfiche, and microfilm). However, soft copy storage of raw data presents a unique set of problems that are often avoided by printing it in hard copy. Many labs choose to print out raw data, because it assures the data are available and unchanged. More about storage on magnetic media is discussed in Chap. 3.

Many software applications for instruments record the data in a worksheet format. The same rules as those for hand-generated worksheets should apply for automated formats. However, some raw data may not yet be formatted when they are first recorded. In this case, a key to the formatting of the raw data must accompany the data.

Why do we not designate the final formatted report as raw data in all cases? Remember, in the definition of raw data, the phrase, "first recorded occurrence of the original observation." Since steps occur between the collection of the data and the final reporting of the data in a final report, the final report cannot be raw data. This is important because the data should have undergone as little manipulation and transfer as possible over different software applications. This prevents corruption and loss and allows the raw data to be used to verify additional operations performed on it. Also, why not designate the signal read by the instrument or transmitted by the instrument as the raw data? This is because this event cannot be understood by humans and therefore is not useful to verify the results and conclusions. Testing should be performed on this signal, however, to validate the operation of the instrument and its communication functions (e.g., positive controls or adequate standards).

Electronic Signatures

Electronic signatures are the recorded identity of the individual entering data and are input through login procedures – presumed to be secure. One of the issues regarding electronic signatures is the validity of a computer-entered signature because it is not traceable by handwriting analysis to the person signing, and presumably anyone could type in a name. One of the charges years ago against Craven Labs was that the lab changed the clock on the computer to make it appear that samples were analyzed on an earlier date. Currently, the FDA is accepting electronically recorded names or initials as signatures although the policy has not been made official at this writing.

Until a policy statement is made, two criteria may be used to justify the use of electronic signatures. All individuals who operate the instruments or associated software must be aware of the meaning and importance of the entry of their name (or unique personal code) and the computerized date stamp. That is what constitutes a legal signature. Second, the electronic signature is best justified when access to the system is strictly controlled. Controlled access usually involves some sort of password or user identification system that must be activated before an authorized person may perform an operation. Some automated systems have levels of access that may control different operations by allowing only certain individuals to perform certain tasks.

Access levels may include read only, data entry, data change authorization, and system level entry or change. When these controls are in place, the system may automatically record the persons name into the file based on the password entered. Some systems use voice recognition, fingerprint, or other biometric recognition. This discussion only begins to touch on the complexities of computer security-related issues.

Spreadsheets

Spreadsheet use to the modern lab is what invention of the printing press was to publication. Although spreadsheets make recording, processing, and reporting data easy and quick, some special considerations are important to the use of these powerful programs. Whether data are keyed into spreadsheets or electronically transferred to them from existing data files, the entry of the data must be checked to assure the data record is complete and correct. Commonly, mistakes occur in calculations and formulae, in designating data fields, and in performing inappropriate operations on the data. Because of the versatility of spreadsheets, take special care in validating the spreadsheet. When you perform calculations, check the spreadsheet formulae and be sure that the arithmetic formula is defined on the spreadsheet. The way the program rounds numbers and reports significant digits is important to the calculation of results and the reporting of the data. When you try to recalculate or evaluate the processes performed by the spreadsheet program, be sure to define all functions used.

Most recently, FDA has announced plants to promulgate a standard (CSEND) for the electronic submission of such data in support of regulatory submissions. This is a part of the efforts by the CDISC (Clinical Data Interchange Standard Consortium) team.

Reporting the Data

This final section suggests ways to generate data tables and figures for the final report or manuscript. Here are some guidelines:

- The title of the table or figure should be descriptive of the data.
- Column and row headings should be understandable, avoiding undefined abbreviations.
- Units of measure should be included in the column headings or axes of charts.
- For individual data, all missing values must be footnoted and explained.
- All calculations used to derive the data should be defined step-wise and, when the calculation is complex or nonstandard, given in a footnote.
- Statistical summaries or analyses should be clearly defined including the type of process performed. Statistically significant values may be identified with a unique symbol that is footnoted.

- All abbreviations or acronyms should be clearly defined.
- Continuing pages should contain at least a descriptive portion of the title and indicate "continued."
- The data should be easy to read and be uncluttered. The font should not be too small.
- Charts should contain a legend of any symbols or colors used, and the labels of the axes should be descriptive and easily understood. Keep in mind that black and white copies of these charts and graphs may be made at some time and a method to identify the colored components as black and white components should be identified and stated.
- The text of the report should include references to the tables or figures when the data is presented.
- The text of the report should exactly match the data in the tables or figures. Any generalization, summarization, or significant rounding should be designated as such in the text.

Distinguishing Essential from Negotiable Study Elements

An important step in managing and executing studies and experiments is to determine which parts of the study or experiment must be included and how they should be included. It is desirable to maximize the amount of information to be obtained, while also considering time, numbers of animals, and use of other resources. It may not be realistic to try to accomplish all the objectives which can be stated during the early stages of study design. Remember the "KISS" principle (keep it simple, stupid). Simple experiments provide simple results. Complex experiments produce chaos. This distinction of essential and negotiable study elements is a critical step which will enable the study sponsor to select a suitable laboratory as well as to negotiate the specific components of the study.

Designating the Study Monitor

Another early aspect to consider in external placement concerns personnel, specifically, the study's director. In the past, it was not uncommon that the employee or consultant who functions as a study monitor on behalf of the sponsor would be called the "study director." This is now a difficult concept to grasp, since the responsibilities of the study director imply being intimately involved with and overseeing the day-to-day activities of the study. These actions can only be discharged by an employee of the laboratory contracted to perform the study. Regardless of what the on-site study director is called, the sponsor needs to provide sufficient authority to allow important decisions to be made without prolonged discussions on the telephone, or worse yet, emergency site visits by the sponsor and for clean lines of authority for any potential changes. For example, if an animal is judged by the veterinary staff to be

in pain, the study director needs to be able to consult with the attending veterinarian to make a timely decision with regard to the fate of the animal and not be delayed by time zone differences or lack of availability of the sponsor via phone or email.

For complex or long-term studies, the laboratory should provide an alternate or deputy study director to ensure both continuing internal oversight as well as a contact for the sponsor if the primary study director is unavailable.

Having defined the work to be done i.e., ranked the elements of the study as essential or negotiable and selected a study monitor from within the sponsor's organization, a laboratory must be found which can do the necessary work.

Shifting Paradigms

The twenty-first century up until 2007 was the third golden age of contract toxicology, the first two having been in the mid-1970s until the early 1980s and the second having been from the early until the mid-1990s. To a degree, for all contract research organizations, each of these has seen expansion of facilities, marked prosperity, and changes in practice services offered and technology utilized. The first and last of these also saw both new ("green grass") facilities build and opened. Each has also been followed by an economic contraction, with reductions in costs charged to clients (and corresponding reductions in profit merging for the CROs), reductions in staff, and closing of some facilities.

As this is written, we are still in the period of contraction of the economy and of spending in R&D, especially by the many smaller pharmaceutical companies which are the bread and butter of the work stream for CRO's.

These changes from the perspective of those seeking the services of CRO's have been viewed as generally positive changes. (1) Pricing by CRO's is quite competitive, and (2) Study start times are quite short.

There are also negative aspects of the current situation primarily that staffing and organizations are frequently changing (Snyder 2009a, b, 2010). Contributing to this state of change is the entry of multiple new CRO's in China, India, and the broader world. This is further discussed in Chap. 6.

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Chapter 2
Pharmaceutical Development

The process by which a new therapeutic entity is discovered and developed to the point that it is available to patients in the marketplace is complex, expensive, and long. We will not pretend to present or analyze this process in any detail here, but rather to give a basic understanding of the process and of the components that may be outsourced to a contract organization. There are no current or comprehensive volumes describing this process, though there are some volumes on the area (Guarino 1987; Mathieu 2000; Smith 1992; Sneader 1986; Spilker 1994).

As explained at the beginning of this volume, the pharmaceutical development process is a long (13–16 years from drug inception to market approval) and costly ($250–$800 million, depending on how one allocates costs) process, even when successful. It is shaped by medical needs, regulatory requirements, economics, finances, ethics, legal considerations, our understanding of sciences and diseases, and limitations of technology. All of these interact to shape a process that serves to iteratively reduce risks (to both economic and human safety), with the probability of failure being reduced in a stepwise fashion (Matoren 1984; Zbinden 1992). Figure 2.1 briefly summarizes this process, while Fig. 2.2 presents a more detailed summary of the process and activities up to the filing of an INDA (Investigational New Drug Application) and Fig. 2.3 is an alternative presentation. We will use the six categories of activities in Fig. 2.2 (Safety, Pharmaceutical Development, Pharmacology, Analytical, Clinical, and Regulatory) as a framework to discuss activities throughout the development process. The major pharmaceutical companies have their research and development expenses well documented (Tables 2.1 and 2.2). These figures are impressive, as are the sales of their products (Table 2.3). It should be kept in mind, however, that there are more than 2,500 smaller pharmaceutical development companies (both "small molecule" and biotech) in the United States, which have an even higher proportion of their budgets invested annually in research and development.

For our purposes (i.e., from the development to market perspective), the purpose of all nonclinical (animal and in vitro) development is to reduce the risks and probability of adverse events while optimizing the potential for therapeutic efficiency in humans.

S.C. Gad and C.B. Spainhour, *Contract Research and Development Organizations: Their Role in Global Product Development*, DOI 10.1007/978-1-4614-0049-3_2,

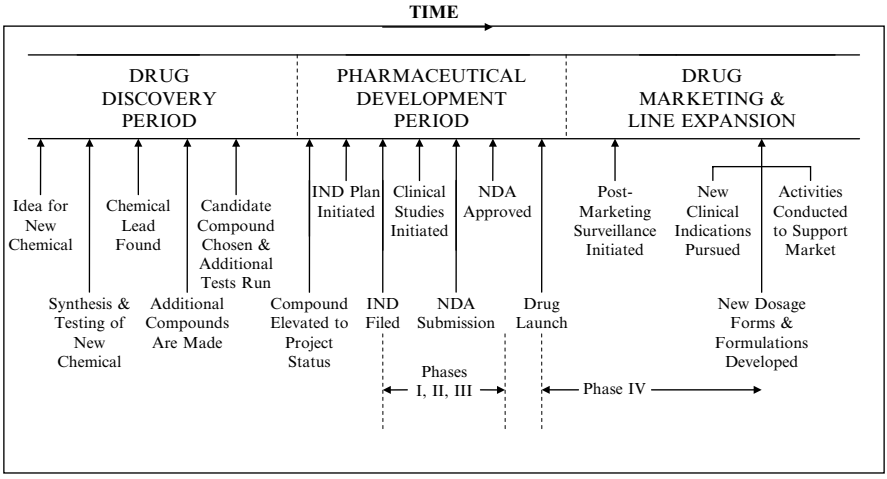

Fig. 2.1 Generalized flow of pharmaceutical development

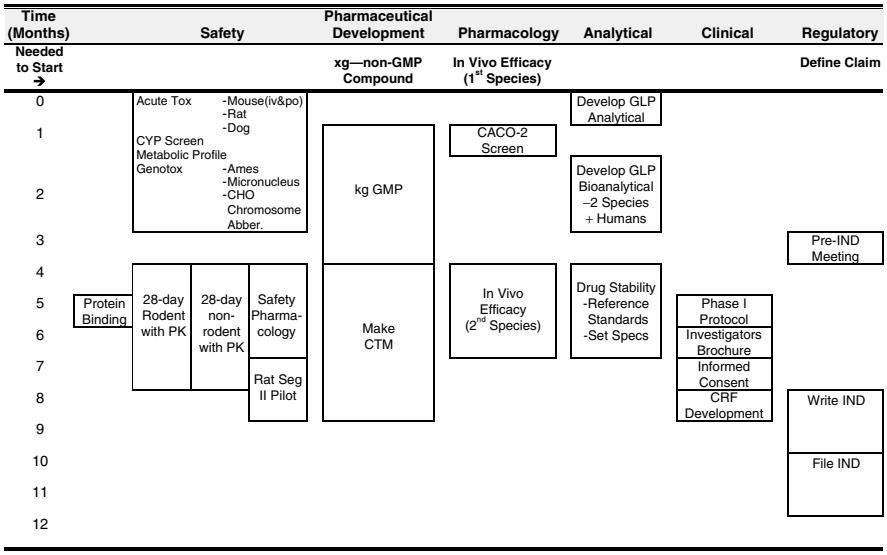

Fig. 2.2 Components of development to the filing and opening of an IND

But between initial nonclinical testing (and concurrent with additional animal testing) and a drug reaching the marketplace, the potential for having adverse effects in the general patient population, it is intended for is further guarded against by a scheme of increasingly more powerful human ("clinical") trials (Piantadosi 1997; Nylen 2000). How a drug is moved through this process is the subject of this chapter.

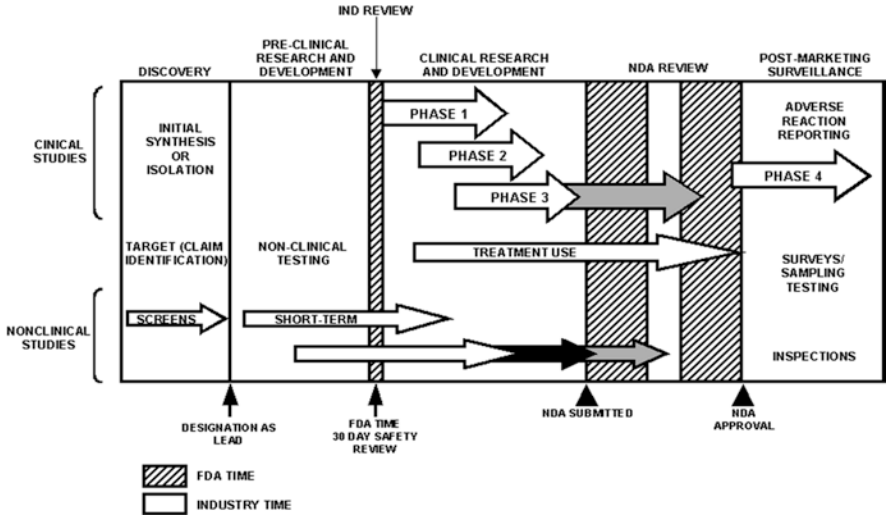

Fig. 2.3 The pharmaceutical development process, viewed as four stages (discovery, preclinical development, clinical development, and NDA review) as well as the important postmarket surveillance phase

Table 2.1 R&D, PhRMA member companies growth in domestic R&D and R&D abroad, ethical pharmaceuticals, PhRMA member companies, 1970–2009

Year	Domestic R&D ($)	Annual percentage change (%)	R&D abroad[a] ($)	Annual percentage change (%)	Total R&D ($)	Annual percentage change (%)
2009[b]	34,806.0	–2.2	10,976.1	–7.1	45,782.1	–3.4
2008	35,571.1	–2.8	11,812.0	4.6	47,383.1	–1.1
2007	36,608.4	7.8	11,294.8	25.4	47,903.1	11.5
2006	33,967.9	9.7	9,005.6	1.3	42,973.5	7.8
2005	30,969.0	4.8	8,888.9	19.1	39,857.9	7.7
2004	29,555.5	9.2	7,462.6	1.0	37,018.1	7.4
2003	27,064.9	5.5	7,388.4	37.9	34,453.3	11.1
2002	25,655.1	9.2	5,357.2	–13.9	31,012.2	4.2
2001	23,502.0	10.0	6,220.6	33.3	29,772.7	14.4
2000	21,363.7	15.7	4,667.1	10.6	26,030.8	14.7
1999	18,471.1	7.4	4,219.6	9.9	22,690.7	8.2
1998	17,127.9	11.0	3,839.0	9.9	20,966.9	10.8
1997	15,466.0	13.9	3,492.1	6.5	18,958.1	12.4
1996	13,627.1	14.8	3,278.5	–1.6	16,905.6	11.2
1995	11,874.0	7.0	3,333.5	[b]	15,207.4	[b]
1994	11,101.6	6.0	2,347.8	3.8	13,449.4	5.6
1993	10,477.1	12.5	2,262.9	5.0	12,740.0	11.1
1992	9,312.1	17.4	2,155.8	21.3	11,467.9	18.2
1991	7,928.6	16.5	1,776.8	9.9	9,705.4	15.3

(continued)

Table 2.1 (continued)

Year	Domestic R&D ($)	Annual percentage change (%)	R&D abroad[a] ($)	Annual percentage change (%)	Total R&D ($)	Annual percentage change (%)
1990	6,802.9	13.0	1,617.4	23.6	8,420.3	14.9
1989	6,021.4	15.0	1,308.6	0.4	7,330.0	12.1
1988	5,233.9	16.2	1,303.6	30.6	6,537.5	18.8
1987	4,504.1	16.2	998.1	15.4	5,502.2	16.1
1986	3,875.0	14.7	865.1	23.8	4,740.1	16.2
1985	3,378.7	13.3	698.9	17.2	4,077.6	13.9
1984	2,982.4	11.6	596.4	9.2	3,578.8	11.2
1983	2,671.3	17.7	546.3	8.2	3,217.6	16.0
1982	2,268.7	21.3	505.0	7.7	2,773.7	18.6
1981	1,870.4	20.7	469.1	9.7	2,339.5	18.4
1980	1,549.2	16.7	427.5	42.8	1,976.7	21.5
1979	1,327.4	13.8	299.4	25.9	1,626.8	15.9
1978	1,166.1	9.7	237.9	11.6	1,404.0	10.0
1977	1,063.0	8.1	213.1	18.2	1,276.1	9.7
1976	983.4	8.8	180.3	14.1	1,163.7	9.6
1975	903.5	13.9	158.0	7.0	1,061.5	12.8
1974	793.1	12.0	147.7	26.3	940.8	14.0
1973	708.1	8.1	116.9	64.0	825.0	13.6
1972	654.8	4.5	71.3	24.9	726.1	6.2
1971	626.7	10.7	57.1	9.2	683.8	10.6
1970	566.2	–	52.3	–	618.5	–
Average		*11.6%*		*15.5%*		*12.2%*

[a]Estimated

[b]R&D abroad affected by merger and acquisition activity

Notes: (1) R&D expenditures for ethical pharmaceuticals only. (2) Domestic R&D includes expenditures within the United States by PhRMA member companies. (3) R&D abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by U.S. divisions of foreign-owned PhRMA member companies. (4) Increases in R&D expenditures are likely due to a more rigorous data collection methodology

Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2009

Safety

The safety component of the development of a new drug has both a nonclinical (i.e., not in human beings) and a clinical component. Until an IND is opened, all safety evaluation is classified as nonclinical (also properly called, to this point, preclinical). After an IND is opened, both clinical and nonclinical components of safety evaluation are required. The timing of the nonclinical components, particularly after an IND is opened, is susceptible to a fair degree of judgment. The details of the components of this process are beyond the scope of this volume (see Gad 2009 for such details).

Table 2.2 Domestic R&D by function, ethical pharmaceuticals, PhRMA member companies, 1998–2000 (dollar figures in millions)

	1998		1999		2000	
Function	Dollars	Share (%)	Dollars	Share (%)	Dollars	Share (%)
Synthesis and extraction	2,066.7	12.07	1,763.1	10.0	987.7	9.3
Biological screening and pharmacological testing	2,600.5	15.1	2,508.1	14.2	2,582.9	12.1
Toxicology and safety testing pharmaceutical dosage	895.5	5.2	802.1	4.5	872.1	4.1
Formulation and stability testing	1,550.0	9.0	1,290.6	7.3	1,081.3	5.1
Clinical evaluation: phase I, II, and III	4,873.9	28.3	5,139.5	29.1	5,464.6	25.6
Clinical evaluation: phase IV	998.9	5.8	2,060.5	11.7	1,882.3	8.8
Process development for manufacturing and quality control	1,705.0	9.9	1,463.4	8.3	1,4999.9	7.0
Regulatory: IND and NDA	757.7	4.4	730.3	4.1	644.2	3.0
Bioavailability	413.4	2.4	321.6	1.8	327.8	1.5
Other R&D	1,265.9	7.9	1,594.3	9.0	2,693.7	12.6
Uncategorized ethical pharmaceutical R&D[a]	0.4	0.0	797.6	4.3	2,327.2	10.9
Total	*$17,127.9*	*100%*	*$18,471.1*	*100%*	*$21,363.7*	*100%*

[a]Represents companies that provided total R&D expenditure figures, but not individual details

Notes: (1) Company-financed R&D expenditures for ethical pharmaceuticals only. (2) Domestic R&D includes expenditures within the Unites States by PhRMA member companies

Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2002

Table 2.3 Top pharmaceutical companies

Company	Annual revenue (2009 global pharma sales) ($)	R&D expenditures (2009) ($)
Pfizer	44.2 Billion	7.9 Billion
GlaxoSmithKline	43.0 Billion	5.2 Billion
Sanofi-Aventis	38.7 Billion	6.5 Billion
Novartis	36.0 Billion	7.2 Billion
AstraZeneca	31.6 Billion	5.1 Billion
Johnson&Johnson	24.6 Billion	5.1 Billion
Merck	23.6 Billion	4.8 Billion
Roche	21.0 Billion	7.2 Billion
Eli Lilly	19.3 Billion	3.8 Billion
Wyeth	19.0 Billion	3.4 Billion
Bristol-Myers Squibb	17.7 Billion	3.6 Billion
Abbott	16.7 Billion	2.7 Billion
Bayer	15.1 Billion	2.5 Billion
Amgen[a]	14.7 Billion	3.0 Billion
Schering-Plough	14.2 Billion	3.5 Billion
Boehringer Ingelheim	13.6 Billion	2.9 Billion
Takeda	12.2 Billion	2.7 Billion
Teva	11.1 Billion	786 Million
Genentech[a]	10.5 Billion	2.8 Billion
Astellas	9.7 Billion	1.3 Billion
Daiichi Sankyo	8.8 Billion	1.6 Billion
Novo Nordisk	8.6 Billion	1.5 Billion
Merk KGaA	7.6 Billion	1.5 Billion
Eisai	7.2 Billion	2.2 Billion
Otsuka	6.5 Billion	1.0 Billion
Baxter International	5.3 Billion	868 Million
Servier	5.2 Billion	N/A
Gilead Sciences	5.1 Billion	722 Million
Mylan	4.3 Billion	317 Million
UCB	4.3 Billion	1.1 Billion

[a]Indicates biopharmaceutical companies

All the safety evaluation components have in common that they are heavily regulated and subjected to either GLPs (Good Laboratory Practices) or GCPs (Good Clinical Practices). The nonclinical components include genotoxicity (a minimum of three studies, usually an *Ames* assay (in vitro) and CHO chromosome aberration or unscheduled DNA synthesis in vitro and a mouse micronucleus in vivo), safety pharmacology (with evaluations of cardiovascular, central nervous system, and respiratory pharmacologic activities being required prior to the filing of the IND (pre-IND) and others before large clinical trials in patients are initiated), immunotoxicology (just now coming into being specifically required), systemic toxicity (single and multiple dose studies in two or more species with a pharmacokinetic (PK) component or arm to the multi-dose pre-IND, then longer multiple dose studies in concert with clinical development), developmental and reproductive toxicities,

carcinogenicity evaluations (if the drug is intended to be for chronic use), and any special studies that may be of interest to the reviewing agency or specific to the class of drugs or the intended use of the potential drug. Also generally required are determinations of degree of protein binding, the pharmacokinetics and disposition of the drug in animals and man, metabolic activation and inhibition, and the nature and level of significant metabolites in man (Ozdemir et al. 2001).

Pharmaceutical Development

The chemical development process also stretches through most of the length of the pharmaceutical development process. The needs to be met include the following:

- Manufacture of increasing amounts of quantities of active pharmaceutical ingredient of suitable purity and stability. Early lots are in gram (or tens of grams) quantities for small molecules. Such are produced under GLPs but not GMPs. Frequently, the first upscale produces lots of hundreds of grams. Finally, lots of kilo or greater sizes are produced. Keep in mind that the purities of these different lots are important. There are no specific guidelines written with regard to the levels of purity of test article material for nonclinical studies. Under any circumstances, do not produce material that is of extremely high purity for nonclinical studies. You can back yourself into a corner. If the material that is used in preclinical studies is of higher purity than that used in clinical studies, then the preclinical studies will have to repeated, because of the unfavorable impurity difference. This does not mean that the purities of preclinical and clinical lots have to be the same or identical. Typically the purity of any preclinical material should be about 95% or within 5% of the intended purity of the clinical trial material (CTM). It is acceptable and desirable to use material in nonclinical studies that is of lesser purity than the CTM. As synthetic scale up proceeds, the impurity profile of the test article will more than likely adversely change as a direct result of the scale up and the kinetic qualities of side reactions. Although such problems can be addressed, such activity consumes money, time, and resources and can readily be avoided with proper planning. Somewhere in here (typically late in the process), the most stable (and possibly soluble) form (frequently a salt) is produced under GMP's. Later efforts still may seek to identify and optimize the most economical production process.
- Human dosage form(s) must be developed and produced. When used in clinical trials, these are labeled CTM (Clinical Trials Materials). If for an oral drug, a simple formulation (such as a stable, simple capsule) may be used for phase I studies, but more elegant formulations are produced for later studies. If the route is parenteral, simple sterile, stable, and isotonic solutions are explored.
- Formulations must be developed, first for preclinical studies and then for clinical studies. Lots of considerations come into such formulations including bioavailability, stability, use of allowed excipients, and patient acceptability.

Swarbrick and Boylan (2002) provide an excellent overview of the range of skills and technology involve here.

Pharmacology

Pharmacology studies (other than safety pharmacology) initially serve to identify candidate compounds for development that is to identify and optimize "leads." Such studies (particularly in appropriate "gold standard" models of the specific disease to be treated – or predictive of efficacy) are essential both in making decisions to go forward with development of a compound and in helping estimate or model the dose to be used in the clinic. Dose selection or "target identification" for clinical trials is best performed based on achieving an effective concentration of therapeutic entity at the target site (receptors or organs in vivo), but should also at least have achieved plasma levels at efficient doses driving the target concentration for clinical studies.

Additionally, it is important to evaluate the specificity of action at the target sites. This means that activity and or binding at other receptor sites must be characterized quantitatively (e.g., K_i, K_d, K_a, etc.), as such may limit the actual target concentration and potential utility of a drug.

Since 2006, the FDA has started to require formal laboratory evaluation (with formal reports) to support the claims and/or assumptions of pertinent pharmacodynamics – that is desired therapeutic activity in a suitable animal model.

Analytical

It is clearly essential to be able to both identify and quantitate the actual drug entity itself in a range of biological and nonbiological milieu. These include the lots of drug produced (where purity and the identity of any accompanying impurities also is important), stability study samples, dosage preparations for preclinical studies, and fluid and tissue samples from in vivo studies.

The last of these tasks usually mean being able to accurately and sensitively quantitate the levels of the drug entity in serum, blood or plasma, and urine, and possibly in target tissues. Such methods need to be developed and validated not only for humans but also for the principal species used in nonclinical studies (usually rats and either dogs or nonhuman primates (NHP), plus in rabbits to verify exposure in developmental toxicology studies).

It also becomes important at some point to be able to identify and quantitate the levels of significant metabolites, particularly if they are pharmacologically active. The limit of detection (LOD) needs to be in the picogram (pg/mL) range to satisfy regulatory agencies. This LOD is not documented in any guideline, but has slowly evolved over the recent years as analytical technology has increased to permit such a level of detection. What exactly does a pictogram level of detection mean? Well certainly 1 pg/mL is a highly desirable level, and 1,000 pg/mL is not ideal. In method development, try to get as close as one can to the 1 pg/mL level, but if the final result is 495 pg/mL, it will be acceptable to the agency. A level such as 500 ng/mL will not be acceptable, providing that there is not sufficient documentation to PROVE and support that number as a methodological endpoint.

Clinical

Generally, the single most expensive (and time consuming) portion of any pharmaceutical development timeline is the clinical evaluation portion (Spilker 1994). Initially these studies (Phase I) are intended primarily to evaluate the safety (tolerance) and pharmacokinetics of a drug, and unless the drug is intended to treat life threatening conditions, such studies are performed in healthy volunteers and not patients. Patients can be used in life-threatening conditions. Although it should generally be possible to perform such work with just three (single dose escalating, multi-dose tolerance and a single dose escalating) or four studies (validation of achieved dose by an optimized formulation/dosage form), many more may need to be performed.

Subsequent to the completion of the Phase I studies, a series of phase II studies are generally performed in patients, first and very importantly to give confidence in efficacy. Finally, it should be noted that regulatory approval generally requires the completion of two successful "pivotal" studies. These are generally phase III studies, but may be phase II studies. The requirements are as follows: adequate numbers of patients to achieve unequivocal statistical proof of efficacy of an accepted a priori endpoint, and adequate numbers and exposure of a representative patient population to identify the potential occurrence of any significant safety concerns when the drug is on the market. All this is done while protecting trial subject safety and confidentiality to the fullest extent possible (Willman 2000; Wechsler 2001).

The phase III testing phase is almost always both the longest and the most expensive segment of the drug development process. From the earliest point, sponsors/investigators seek to gain first any reliable hint that the drug works (see Biomarkers Definitions Working Group 2001) while also worrying about previously undetected safety concerns such as hepatic damage (Kaplowilz 2001).

Regulatory

In parallel with (Gad 2010) all of the technical activities in the pharmaceutical development process, there is an accompanying string of activities which must be conducted to fulfill the regulatory requirements for successfully completing the market approval (NDA) process. Such usually start with bringing about a successful pre-IND meeting with FDA. Subsequent to this interaction, the following generally must occur:

- An INDA must be assembled, paginated, and submitted. Any resulting questions raised by the FDA must be answered effectively and in a very timely manner.
- The "opening" of the IND (Investigational New Drug (Application)) must be verified (the FDA does not usually provide any such verification).
- Necessary IND amendments (documenting changes in formulation; significant findings as to safety; changes in clinical study protocols, facilities or personnel, or new protocols) must be to the FDA submitted in a timely manner.
- An end of phase II meeting with FDA should be effectively executed.

- Assembly and submission of an NDA, with effective and timely response to any subsequent FDA queries.
- An effective quality monitoring and auditing program of vendors performing GLP, GMP, and/or GCP regulated tasks.

Except for those cases where there is substantial potential to save or extend lives (such as anticancer and anti-AIDS drugs) or where the intended target diseases are chronic and severe (e.g., Parkinson's or MS) or the routes of administration are invasive (e.g., intrathecal), the initial evaluations in humans are performed in "normal," healthy volunteer with the primary objective being limited to defining the limits of tolerance (safety) of the potential drug and its pharmacokinetic characteristics. These trials may also seek to detect limited (usually surrogate or indirect) indicators of efficacy, but are severely limited in doing so (Biomarkers Definitions Working Group 2001). Later trials look at the drug's actions on carefully defined and selected groups of patients.

With the number of drugs withdrawn from the marketplace since 1990 (or, perhaps, the degree of media coverage of such withdrawals), public concern with and media coverage of the workings of the drug safety evaluation aspects of the development process have risen sharply (Granter 1999; Wechsler 2001). It is currently estimated that in the United States, adverse drug reactions (ADRs) rank between the fourth and sixth leading cause of death (Eikelbom et al. 2001). Although improvements in the nonclinical procedures of drug safety assessments are possible and even likely, clearly the clinical aspects are likely to be where the most relevant improvements in trials and a better understanding of individual or subpopulation differences in human responses to drugs are to be found.

Although there is much press about the concern that the "increased pace of drug approval" has caused the release onto the market of less safe drugs (Willman 2000), the causes are more mundane and of much longer standing. The most common "unexpected" (from nonclinical trial results) safety findings in initial trials involve the skin (dermatitis of one form or another) and the liver (Kaplowilz 2001).

An important reason for the high incidence of serious and fatal ADRs is that the existing drug development paradigms do not generate adequate information on the mechanistic sources of marked variability in pharmacokinetics and pharmacodynamics of new therapeutic candidates, precluding treatments from being tailored for individual patients with their physiologic, biochemical, and genetic idiosyncrasies (Ozdemir et al. 2001).

Pharmacogenetics is the study of the hereditary basis of person-to-person variation in drug response. The initial focus of pharmacogenetic investigations has traditionally been unusual and extreme drug responses resulting from a single gene effect. The Human Genome Project and recent advancements in molecular genetics now present an unprecedented opportunity to study all genes in the human genome, including genes for drug metabolism, drug targets, and postreceptor second messenger mechanisms, in relation to variability in drug safety and efficacy. In addition to sequence variations in the genome, high throughput and genome-wide transcript profiling for differentially regulated mRNA species before and during drug treatment

will serve as important tools to uncover novel mechanisms of drug action. Pharmacogenetic-guided drug discovery and development represent a departure for the conventional approach, which markets drugs for broad patient populations, rather than smaller specifically targeted groups of patients in whom drugs may work more effectively and optimally. To date, these new tools have not brought a product to market. But their use is in demand, as are the older receptor-binding screening services intended to determine the specificity of action of a potential drug.

Putting It All Together

While integrative project management is not a separate or distinct segment of pharmaceutical development, its proper use and incorporation in the development pathway is essential to ensure that in the end all of the steps and pieces fit together in a coherent fashion. Extensive options are available in contract research are available to ensure that this happens. In the large pharmaceutical companies (Table 2.3), these skills historically have been to a large part internal. For the vast majority of the smaller 3,500 pharmaceutical/biotech companies (in the US and Canada), this is not the case and the services must be contracted at least in part or more commonly in the whole from either a large ("meta") CRO, a smaller CRO, a provider specializing in niche services, or a "fatigue" organization, which serves only a few clients at a time. Keep in mind that there are about an equal number of drug companies located all over the world that are not located in the US or Canada.

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Chapter 3
Medical Device Development

The medical device industry in the United States and worldwide is immense in its economic impact (sales in 2009 were $260 billion worldwide, $120 billion in the United States alone, $64 billion in the European Community, and $45 billion in Japan; in 1998 the US medical equipment trade surplus was $18.2 billion). Between 87,000 and 140,000 different devices are produced in the United States annually by approximately 8,200 different manufacturers employing some 311,000 people. Furthermore, it is believed that more than 1,000 of these manufacturers are development-stage only companies without products yet on the market. Medical devices are or extreme importance to the health of the citizens of the world (Nugent 1994; The Wilkerson Group 1999) (see Table 3.1). While it is true that the large companies dominate the market in terms of sales and revenue, just as with pharmaceuticals it is the small companies that dominate innovation. The assessment of the safety to patients using the multitude of items produced by this industry is dependent on schemes and methods that are largely peculiar to these kinds of products, are not as rigorous as those employed for foods, drugs, and pesticides, and are in a persistent state of flux. Regulation of such devices is, in fact, relatively new. It is only with the Medical Device Amendments (to the Food, Drug and Cosmetic Act of 1976) that devices have come to be explicitly regulated at all, and with the Safe Medical Devices Act of 1990, the Medical Device Amendments Act of 1992, and subsequent laws that the regulation of devices for biocompatibility became rigorous (see Table 3.2). According to section 201(h) of the Food, Drug and Cosmetic Act, a medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory that is:

> Recognized in the official National Formulary, or the United States Pharmacopeia (USP 2000), or any supplement to them.
>
> Intended for use in the diagnosis of disease, in man or other animals.
>
> Intended to affect the structure or any function of the body of man or other animals, and that does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals, and that is not dependent upon being metabolized for the achievement of any of its principal intended purposes (CDRH 1992).

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Table 3.1 The largest US medical device markets (2001)

US medical device markets (2001) (US $ in billions)	
Diagnostics (in vitro)	20.5
Surgery (min. invasive)	16.4
Orthopedic	14.7
Wound care	13.0
Cardiovascular	12.5

Table 3.2 FDA classification of preamendment medical devices

Part number	Title	Date of publication
21 CFR Part 862	Clinical chemistry and clinical toxicology	May 1, 1987
21 CFR Part 864	Hematology and pathology devices	May 11, 1987
21 CFR Part 866	Immunology and microbiology	November 9, 1982
21 CFR Part 868	Anesthesiology devices	July 16, 1982
21 CFR Part 870	Cardiovascular devices	February 5, 1980
21 CFR Part 872	Dental devices	August 12, 1987
21 CFR Part 874	Ear, nose, and throat devices	November 6, 1986
21 CFR Part 876	Gastroenterology–urology devices	November 23, 1983
21 CFR Part 878	General and plastic surgery devices	June 24, 1988
21 CFR Part 880	General hospital and personal use	October 21, 1980
21 CFR Part 882	Neurological devices	November 4, 1979
21 CFR Part 884	Obstetrical and gynecological devices	February 26, 1980
21 CFR Part 886	Ophthalmic devices	September 2, 1987
21 CFR Part 888	Orthopedic devices	September 4, 1987
21 CFR Part 890	Physical medicine devices	November 23, 1983
21 CFR Part 892	Radiological devices	January 20, 1988

- FDA determines that the device is substantially equivalent to another device that was not in commercial distribution before such date but that has since been classified into class I or II (through the 510(k) process).
- FDA reclassifies the device into Class I or II.

The procedures for reclassifying a "postamendment" class III device are codified in 21 CFR section 860.134(b) (1)–(7).

The device classification process continues to this day. As FDA becomes aware of new devices that require formal classification or pre-1976 devices that were somehow overlooked in the original classification procedures, the agency initiates new classification proceedings, again requesting the recommendation of one or more of the appropriate advisory panels.

Under this definition, devices might be considered as belonging to one of nine categories (North American industrial classification): surgical and medical instruments, ophthalmic, dental, laboratory apparatus, irradiation, specialty devices, medical/surgical supplies, in vitro diagnostics, and electromedical. There were (in 2000) 16,170 companies involved in these sectors – 6,750 of them manufacturers worldwide.

Table 3.3 The ten projected biggest growth device products (in 2000)

Rank	Product	Percentage revenue growth rate (years)	Specialty
1	Fibrin sealants	174.6 (1995–2002)	Wound care
2	Solid artificial organs	141.2 (1995–2002)	Transplant/implant
3	Left ventricular assist devices	96.0 (1995–2002)	Cardiovascular
4	Skin substitute products	63.1 (1997–2004)	Wound care
5	Refractive surgical devices	54.4 (1998–2005)	Ophthalmic
6	Gynecologic fallopscopes	49.5 (1995–2000)	Endoscopic/MIS
7	PTMR products	47.8 (2000–2004)	Cardiovascular
8	Bone growth substitutes and growth factors	47.0 (1997–2004)	Orthopedics
9	Growth factor dressings	46.0 (1997–2004)	Wound care
10	Vascular stent-grafts	46.0 (1997–2004)	Cardiovascular

This is a global industry with a $260 billion annual market. The US market alone is $120 billion, or 42% of this (MDDI 2000) (see Table 3.3).

The top 20 medical devices in terms of revenues in 1999 were the following:

1. Incontinence supplies
2. Home blood glucose-monitoring products
3. Wound closure products
4. Implantable defibrillators
5. Soft contact lenses
6. Orthopedic fixation devices
7. Pacemakers
8. Examination gloves
9. Interventional cardiovascular coronary stents
10. Arthroscopic accessory instruments
11. Prosthetic knee joint implants
12. Lens care products
13. Prosthetic hip joint implants
14. Multiparameter patient-monitoring equipment
15. Mechanical wound closure
16. Wound suture products
17. Absorbable polymers
18. Hearing aids
19. Wheelchair and scooter/mobility aids
20. Peritoneal dialysis sets (The Wilkerson Group 1999)

The steps and processes involved in developing and bringing to market a new medical device are significantly different than those in pharmaceutical development (Gad 2010). This process, while less complex, less expensive, and shorter than that for a drug, is also less well defined and less profitable if successful. But the fundamental objectives in development and approval are the same as for a drug – to have a product that can be profitably marketed with proven therapeutic efficacy and safety.

There are two significant routes to regulatory approval (and therefore development) for a device (Kahan 2000), 510(k) and PMA (premarket approval). The 510(k) route is less rigorous but requires that the device be either Class I or II (the lower two categories of risks) and that there already be a similar ("predicate") device on the market. Such devices may or may not require clinical studies (efficacy and safety may be adequately established in nonclinical studies). Suitable materials must be utilized (and analytical data must be available to establish that the levels of purity and nature of impurities in said materials are acceptable), and the resulting actual product must be sterilized, packaged, and labeled in accordance with regulatory requirements. Also a 510(k) application must be assembled, submitted, and approved by CDRH (Center for Devices and Radiological Health). Such applications account for roughly 98% of new devices, with only 10% of such applications requiring some sort of clinical testing (*Note*: There is a 510(j) route of approval, but it is very rare and will not be discussed here).

The other route for approval requires a PMA. Devices coming to market by this regulatory route include all of those in Class III and also those in Class II that either do not have a predicate or are of some specified category. Clinical studies must always be performed for these to both demonstrate efficacy and evaluate safety in clinical use.

Biocompatibility

The year 1990 saw the passage of the Safe Medical Devices Act, which made premarketing requirements and postmarketing surveillance more rigorous. The actual current guidelines for testing originated with the USP guidance on the biocompatibility of plastics. A formal regulatory approach springs from the Tripartite Agreement, which is a joint intergovernmental agreement between the United Kingdom, Canada, and the United States (with France having joined later). After lengthy consideration, the FDA announced acceptance of International Standards Organization (ISO) 1993 guidelines for testing (ASTM 1990; FAO 1991; MAPI 1992; O'Grady 1990; Spizizen 1992) under the rubric of harmonization. This is the second major trend operative in device regulation: the internationalization of the marketplace with accompanying efforts to harmonize regulations. Under the efforts of the ICH (International Conference on Harmonization), great strides have been made in this area.

Independent of FDA initiatives, the USP has promulgated test methods and standards for various aspects of establishing the safety of drugs (e.g., the recent standards for inclusion of the levels of volatiles in formulated drug products), which were, in effect, regulations affecting the safety of both drugs and devices. Most of the actual current guidelines for the conduct of nonclinical safety evaluations of medical devices have evolved from such quasi-agency actions [e.g., the USP's 1965 promulgation of biological tests for plastics and ongoing American National Standards Institute's (ANSI) standard promulgation].

A medical device that is adequately designed for its intended use should be safe for that use. The device should not release any harmful substances into the patient that can subsequently lead to any adverse biologic effects. Some manufacturers believe that biocompatibility is sufficiently indicated if their devices are made of

medical grade material or materials approved by FDA as direct or indirect additives. The term medical grade does not have an accepted legal or regulatory definition and therefore can be misleading without appropriate biocompatibility testing.

There are no universally accepted definitions for biomaterial and biocompatibility, yet the manufacturer who ultimately markets a device will be required by the Parenteral Drug Association (PDA) to demonstrate biocompatibility of the product as part of the assurance of its safety and effectiveness. The manufacturer is responsible for understanding biocompatibility tests and selecting methods that best demonstrate the following:

- The lack of adverse biological response from the biomaterial.
- The absence of adverse effects on patients.

The diversity of the materials used, types of medical devices, intended uses, exposures, and potential harms present an enormous challenge to the design and conduct of well-designed biocompatibility testing programs. The experience gained in one application area is not necessarily transferable to another application. The same applies to different or sometimes slightly different (variable) materials. Biodegradation and interaction of materials complicate and confound the assessment.

Biocompatibility describes the state of a biomaterial within a physiological environment without the material adversely affecting the tissue or the tissue adversely affecting the material. Biocompatibility is both a chemical and physical interaction between the material and the tissue and the biological response to these reactions.

Biocompatibility assays are used to predict and prevent adverse reactions and establish the absence of any harmful effects of the material. Such assays help to determine the potential risk that the material may pose to the patient. The proper use of biocompatibility tests can reject potentially harmful materials while permitting safe materials to be used for manufacturing the device.

Any biocompatibility statement is useful only when it is considered in the proper context. A statement such as “propylene is biocompatible” lacks precision and can lead to misunderstanding. Any statement of biocompatibility should include information on the type of device, the intended conditions of use, the degree of patient contact, and the potential of the device to cause harm. Manufacturers should avoid using the term “biocompatible” without clearly identifying the environment in which it is used and any limitations on such use.

The need for biocompatibility testing and the extent of such testing that should be performed depends on numerous factors. These factors include the type of device, intended use, liability, degree of patient contact, nature of the components, and potential of the device to cause harm. There are no universal tests to satisfy all situations, and there is no single test that can predict biological performance of the material or device and reliably predict the safety of the device. The types and intended uses of medical devices determine the types and number of tests required to establish biocompatibility. Biological tests should be performed under conditions that stimulate the actual use of the product or material as closely as possible and should demonstrate the biocompatibility of a material or device for the specifically intended use. These tests will be more extensive for a new material than for those materials that have an established history of long and safe uses.

All materials used in the manufacture of a medical device should be considered for an evaluation of their suitability for intended use. Consideration should always be given to the possibility of the release of toxic substances from the base material(s), as well as any contaminants that might remain after the manufacturing process or sterilization. The extent of these investigations will vary, depending on previously known information (prior art) and initial screening tests.

Fundamentals of Biocompatibility Tests

Biocompatibility is generally demonstrated by tests utilizing toxicological principles that provide information on the potential toxicity of materials in the clinical application (Gad 2002). Many classical toxicological tests, however, were developed for a pure chemical agent, and are not applicable to biocompatibility testing of materials. In addition, medical devices are an unusual test subject in toxicity testing. A biomaterial is a complex entity of multiple components, and the material toxicity is mediated by both its physical and chemical properties. The toxicity from a given biomaterial often comes from its leachable components, and the chemical composition of a material is often not known or not known with precision. Toxicological information on the material and its chemical composition is seldom available, and the possible interactions among the components in any given biological test system are seldom known.

Accordingly, biocompatibility should not be defined by a single test. It is highly unlikely that a single parameter will be able to ensure biocompatibility; therefore, it is necessary to test as many biocompatibility parameters as appropriate. It is also important to test as many samples as possible, therefore suitable positive and negative controls should produce a standard response index for repeated tests.

Additionally, the use of exaggerated conditions, such as using higher dose ranges and longer contact durations or multiple insults that are more severe by many factors than the actual condition(s) of use, is important. Adopting an acceptable clinical exposure level that is multiple factors below the lowest toxic level has been a general practice.

Most of the biocompatibility tests are short-term tests designed to establish acute toxicity. Data from these short-term tests should not be extrapolated to cover the areas with longer periods of exposure in which no test results are available.

Biocompatibility testing should be designed to assess the potential adverse effects under actual use conditions or specific conditions close to the actual use conditions. The physical and biological data obtained from biocompatibility tests should be correlated to the device and its use. Accuracy, reproducibility, and interpretability of tests depend on the method and the equipment used and the investigator's skill and experience.

There are several toxicological principles that the investigator must consider before planning biocompatibility testing programs. Biocompatibility depends on the tissue or tissues that contact the device. For example, the requirements for a blood-contacting device would be different from those applicable to a urethral catheter.

Also, the degree of biocompatibility assurance depends on the involvement and the duration of contact with the human body. Some materials, such as those used in orthopedic implants, are meant to last for a long period of time in the patient. In this case, a biocompatibility testing program needs to show that the implant does not adversely affect the body during the long period of use. The possibility of biodegradation of material or device should not be ignored. Biodegradation by the body can change an implant's safety and effectiveness. The leachables from plastic used during a hemodialysis procedure may be very low, but the patient who is dialyzed 3 times a week may be exposed to a total of several grams during his or her lifetime, therefore the cumulative effects (chronic exposure) should be assessed.

Two materials having the same chemical composition but different physical characteristics may not induce the same biological response. Also, past biological experiences with seemingly identical materials have their limits, too. Toxicity may come from leachable components of the material due to differences in formulation and manufacturing procedures.

Empirical correlation between biocompatibility testing results and actual toxic findings in humans and the extrapolation of the quantitative results from short-term in vitro testing to quantitative toxicity at the time of use are controversial. Such accumulation of data needs a thorough, cautious, careful, and scientifically sound interpretation and explanation within the boundaries of the information at hand. The control of variation in the assessment of biological susceptibility and resistance to obtain a biological response range for a toxic effect needs careful attention as does an assessment of the host factors that determine the variability of susceptibility in a toxicological response adjustment to susceptibility. The variability in human populations also needs careful attention.

The challenge of the assessment of biocompatibility is to create and use knowledge to reduce the degree of unknowns in the development process and in turn use this information to help make the best possible decisions pertaining to actual conditions of use. The hazard presented by a substance, with its inherent toxic potential, can only be manifested when fully exposed in a patient. Risk, which is actual or potential harm, is therefore a function of toxic hazard and exposure. The safety of any leachables contained in the device or on the surface can be evaluated by determining the total amount of potentially harmful substance, estimating the amount reaching the patient's tissues, assessing the risk of exposure, and then performing a risk vs. benefit analysis. Then the potential harm from the use of biomaterial is completely identified from the biocompatibility analyses and data of an alternate material.

Clinical Testing

Current data indicate that large medical device developers are conducting fewer studies at fewer locations, but the sheer number of products in the pipeline is providing significant opportunities for investigative sites and CROs with experience conducting

Table 3.4 Clinical grant spending for medical device trials in the United States

1994	$100
1998	$250
2002	$530

Table 3.5 Original investigational device exemptions (IDEs) approved

Number of IDEs	
1991	220
1993	248
1995	210
1997	272
1999	305
2001	284
2002	307
2003	246
2004	217
2005	238
2006	234
2007	214
2008	215

device trials. Indeed, spending on clinical medical device studies remains one of the fastest growing segments (see Table 3.4).

Whereas spending for clinical studies of drug therapies grew 14% annually over the past several years, spending for devices grew by more than 20% annually in that same period. It is estimated that sponsors will spend more than half a billion dollars on clinical research for medical device trials in 2002. Sponsor's use of CROs to manage device trials is also growing substantially. The driver of growth in medical device trials is not regulatory pressure, as is often the case. It is the medical community. "Doctors are clearly the ones driving most of the research," said Charlie Whelan, an industry analyst in the medical device group of San Jose, CA based Frost and Sullivan. "They're conservative by nature and won't use something until they feel there's sufficient clinical evidence to support its use. Some doctors want more data than the FDA requires. They want longer-term data or want answers to more specific questions."

The persistent pattern of filings in this market is expected to continue and possibly grow with enhanced physician demand for clinical trial evidence and a rich pipeline of potential new devices (Table 3.5).

Although the number of original investigational device exemption (IDE) applications dropped slightly between 2000 and 2001, the numbers of PMAs and PMA supplements have been increasing steadily. These devices are novel and present

potentially higher risk. They also require more pre- and postmarketing clinical research studies. “There is no shortage of opportunity in this market segment,” said Whelan. “Many hundreds of new device companies have been created in each of the past five years, fueled by an aging population and new technologies.”

Market Characteristics

The global medical device market, excluding imaging and clinical diagnostics, is valued at over $150 billion annually. Product lines are numerous and diverse, ranging from latex gloves and wheelchairs to hearing aids and artificial hearts. About 80% of the medical device market is composed of small companies with fewer than 50 employees. Nearly one-fourth of the 13,000-plus medical device and diagnostics manufacturers are startup companies with no source of revenue. This fragmentation mirrors the multitude of small markets for a widely diverse range of devices used in medical interventions.

The strategy for most manufacturers is to get a 510(k), then do a clinical study. It is not an “investigation device” anymore, and the FDA never sees the data. The studies are still subject to Part 56 and Part 50 regulations regarding IRB approval and informed consent, but the FDA has no tools or means to effectively monitor and insure compliance.

Europe is again seeing a healthy portion of the activity, largely because devices are far less regulated across the Atlantic than in the United States. The only ethical regulatory strategy that makes sense is to first do a clinical study in Europe and get approval and then come to the United States. Most often clinical trials are conducted in Europe where they tend to be larger projects with an average of 531 subjects per study vs. 172 on average in the United States. Companies specifically conduct five clinical studies to bring a device to market in Europe, more than twice the US average. Unlike the increasingly global nature of clinical trials for ethical pharmaceuticals, medical device trials are becoming less international.

Device companies are placing their studies in many of the same places where drug studies are conducted. Typically, clinical studies go to leading academic institutions where the prevalence of disease in the patient population is most representative.

According to Frost and Sullivan, medical device companies contract out less than 5% of their clinical research projects to CROs (see Table 3.6). “They use CROs a lot less than drug companies,” said Whelan. “Our forecast suggests that, in coming years, the medical device industry is likely to outsource more of its R&D, but not very much – i.e., up to maybe 7% by 2005.” Most of the research that needs to be done can typically be done in-house. Doing research through a CRO also exposes the company to a lot of risk, including patent infringement. There are an estimated half dozen CROs in the United States and another half dozen in Europe that cater mostly, if not exclusively, to medical device companies. Many of them are boutique CROs that specialize in particular types of devices. All of them are fairly small, with

Table 3.6 Increasing use of CROs for medical device trials

Percentage of device companies who report using CRO for the years 1998 and 2001

	1998 (%)	2001 (%)
Protocol design	0	11
CRF design	0	12
Monitoring services	13	29
Regulatory services	8	11
Statistical services	8	33

between 5 and 30 employees. The big, multipurpose CROs, like Quintiles and Parexel, also assist sponsors with device trials. About 96% of medical device manufacturers utilize CROs most frequently for statistical and monitoring services.

Changing Focus, Changing Oversight

The US device industry is continuously developing new and innovative techniques in areas such as molecular diagnostics (including test for infectious diseases, inherited and metabolic diseases, and cancer), minimally invasive surgery, biocompatible materials used for cardiovascular purposes, and orthopedic implants.

Combination products, gene therapies, and imaging technologies and devices that can be linked to bioterrorism are among the hottest areas of medical device research currently.

A recent report by Frost and Sullivan named digital radiography and molecular diagnostics as two sectors worth watching for new developments in the months ahead. As healthcare providers shift to digital radiography techniques, image integration will gain in importance. Financial simulation will gain in importance. The simultaneous shift toward home health care and nursing home care is also bound to spur demand – and thus the launch of even more new products – ranging from ambulatory aids to orthopedic supports. "Products focusing on self-care, the geriatric population and women are likely to experience impressive growth," a recent report has stated.

Regulations are as stringent for devices as for drugs, claim FDA officials (see Table 3.7). Submission-to-decision review times, however, are now worse for original PMAs than for New Drug Applications – 411 vs. 365 days – and the highest since the passage of FDAMA. Review times on 501(k)s, meanwhile, are falling. Third-party review of eligible Class I and II 510(k) devices, paid for by the manufacturer, is very small – but growing – contributor to review spending. The CDRH's Office of Device Evaluation (ODE) received only 107 510(k)s reviewed by third-party organizations in FY 2001, which amounted to about 16% of all eligible 510(k). However, that is a 128% increase over the 47 such submissions received the prior year. Expansion of the pilot program in March 2001 more than tripled the number of eligible devices to 670.

Table 3.7 Improving development performance

Percentage of IDEs approved by FDA in first review cycle	
1997	69%
1999	68%
2001	80%

As the FDA itself reports, the frequency and consequence of hazards resulting from medical use error far exceed those arising from device failures. So the FDA is paying far more attention to device design and labeling. The Office of Health and Industry Programs (OHIP) assists CDRH's ODE by providing "human factors reviews" for PMA and 510(k) devices. This included patient labeling reviews on 141 submissions to CDRH last year. The OHIP also issued a guidance document last year on medical device patient labeling, including a suggested sequence and content, and principles on the appearance of text and graphics.

Guidance has also been issued about when a device manufacturer may report changes or modifications to the clinical protocol in a 5-day notice to the IRB as opposed to getting formal FDA approval. It clarifies the kind of protocol changes – i.e., modification of inclusion/exclusion criteria to better define the target patient population or increasing the frequency at which data are gathered – appropriate for the 5-day notice provision. Other types of changes, such as the indication or type of study control, require prior approval.

The FDA has also posted for comment a proposed regulatory change that would require sponsors and investigators to disclose to an IRB any prior IRB review of a proposed study. In the device world companies do IRB shopping since the IRB makes the determination if the device poses significant (SR) or nonsignificant risk (NSR).

Device manufacturers share with pharmaceutical companies the headache of complying with the Health Insurance Portability and Accountability Act (HIPAA). In terms of sponsor access to source data, there must be statement of when authorization expires, such as until the PMA is approved or when the product is on the market. There should be a description of how far back in time the patient's medical records will need to be searched. The consent process should also include a statement that treatment, payment, and insurance reimbursement are not conditioned on signing. The document should specifically indicate information that will not be disclosed to the sponsor. And there should be a statement of when, and if, study data will be made available to study subjects. Even though the sponsor pays for a lab test, it becomes part of the patient's medical record. Patients have a right to see it unless they sign away that right during the consent process.

Under HIPAA, doctors will no longer have the right to look at the medical records of referred patients, even those within the same practice group. Investigators will need to go to the IRB to ask for a "waiver of authorization." That will add another 2–3 months to the timeline. The IRB must also get educated.

The Review Speed Problem

Device manufacturers have been pressuring the FDA to accelerate the review and approval cycle time. The average useful life span of a medical device is 18 months. It is not a question of the patent expiring. Within 18 months, the product maybe obsolete. A competitor has a new bell or whistle that makes their product more desirable than yours.

In terms of review speed, FDAMA has clearly done more to benefit pharmaceutical companies than device firms. With breakthrough technology, the FDA has "a tendency to request information for 'educational purposes' that is not directly pertinent to determine the safety and effectiveness of the device in question," Weagraff explained. Timeliness and responsiveness could be improved.

A central problem at the FDA is a lack of resources and appropriately trained resources to review the mandatory, more complicated studies. "A growing number of premarket submissions are for medical technologies that pose novel review issues, like tissue-engineered products, hybrid technologies…and nanotechnology," according to the industry trade group AdvaMed.

Last year, the FDA received 70 PMA applications, the highest number in 10 years. The CDRH alone reviews some 17,000 device submissions and inspects 15,000 manufacturers a year. Though a proposed $10 million budget increase for the agency was awarded in 2003, none of these funds were earmarked for device review. "The FDA device program budget has remained essentially flat over the last 10 years, and has declined in real dollars after accounting for inflation," according to the AdvaMed report. "In addition, staffing levels have declined 8% since 1995." Limited resources have also prevented the FDA from offering up more device-specific guidance documents.

The FDA claims to be focusing on erasing holdups on PMA combination product reviews that often involve the expertise of "a drug person, a materials person and an engineer," according to one CDRH official. "The experts are all in-house, they're just not all in our center. And what's a priority for us is not necessarily a priority for anyone else." In the past, the FDA has taken as long as 13 months simply to decide which agency – CDRH, the Center for Drug Evaluation and Research, or the Center for Biologics Evaluation and Research – should perform the review. In February, the FDA also established a combination products program to help deal with the delays. Legislation is pending to create a formal combination products office to assign products to the appropriate component of the FDA.

Mark Kramer, director of the program housed in the FDA's Office of the Ombudsman, said, "Currently, we don't have an exact count on the number of combination products. And it's difficult to make a guess because a lot of these products don't require inter-center coordination and are reviewed entirely within one center that, over time, has developed certain expertise in that product area. Standard operating procedures are now under review by different centers within the FDA to make intra-agency reviews occur in a more organized and documented fashion."

"The regulatory clock on the request for a designation process used to determine which agency will review a combination product is 60 days," added Kramer. "But at

times submissions need to be supplemented with additional information, or companies request a meeting during the review period because they want to provide additional information. That can cause the total elapsed time to be over 60 days. However, we generally have an agreement with the sponsor to extend the review clock."

Some FDA critics, meanwhile, believe approval times have become too short since FDAMA, and they fear that some manufacturers exacerbate the problem by doing as little testing as possible or by "fudging" clinical data. A scathing July 29 article by *U.S. News & World Report* highlighted past regulatory violations of both Boston Scientific and Medtronic, including withholding important information and details on known adverse events from the FDA. It also pointed out dangers inherent in the 510(k) process and underfunding an overburdened safety-monitoring agency. The FDA's Office of the Inspector General found that, between 1994 and 1999, regulatory violations were far from rare. Device trials were twice as likely as trials for drugs and biologics to violate FDA rules, with such violations including but not limited to missing data, poor data collection, and falsification of data.

Several FDA information sheets have also been put out to offer a needed reminder to investigators and IRBs about the difference between "significant risk" (SR) and "nonsignificant risk" (NSR) device studies – i.e., extended wear contact lenses vs. daily wear lenses. NSR device studies have fewer regulatory controls and do not require submission of an IDE application to the FDA. "The IRB is supposed to make that [SR or NSR] determination," said Stark, "but they've been known to forget." FDA staff was given internal guidance in this area last fall.

Small device firms look for guidance and are respectful of clinical trial expertise once they find it. They are often idea-driven rather than market potential-driven. The entire organization may consist of an engineer, head of regulatory and clinical affairs, and a receptionist. Many folks in the medical device business are naïve and have little relevant experience.

Unless and until something is done to increase FDA resources, the number of required review days on some of the most medically important devices will likely continue to rise. Congress is reportedly looking at an FDA reform package that would give the agency more money to implement process improvements. A program similar to the Prescription Drug User Fee Act is now being implemented for medical devices.

Like pharmaceuticals, there are multiple steps involved in developing a new medical device. Because the product life cycle is much shorter for devices, the time lines for these steps need to be compressed.

The phases can be considered to include the following:

- Prototype design
- Vendor (to provide materials) selection and verification
- Biocompatibility and physical chemical evaluation
- Clinical evaluation
- Regulatory filing and approval

Through the networks of contractors (CROs) to support these steps are less extensive than that for pharmaceuticals, there are still a wide variety of available sources and management issues remain similar.

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Chapter 4
Functions and Types of CROs

The entire contract research/development and production industry has evolved into a major industry in its own right. The critical shortage of new drugs in the pipeline has forced a number of major pharmaceutical companies to form strategic partnerships with companies capable of bringing in resources not currently available in their own organizations, especially due to a lack of investment or downsizing. The dearth of new chemical entities and the pricing pressure from the managed care organizations and the state and federal governments has made every pharmaceutical company evaluate the costs of developing a new drug and its commercial manufacturing. Additionally, most new drugs arise from small organizations which have very limited (if any) internal development capabilities. At the same time, the limits of internal resources and increased regulatory requirements for bringing new products to market power the same needs for the medical device industry.

There are two fundamental drivers for outsourcing in the pharmaceutical and medical device industries. The first is the need for access to sources of information, essential for the long-term success of any company. This has resulted in pharmaceutical companies buying up small innovative drug delivery and biotech companies, as their own laboratories run out of new drug leads and molecules. There are a variety of reasons for the lack of innovative ideas in large pharmaceutical companies, but those are beyond the scope of this book. The second major driver for outsourcing is the imperative to reduce the excessive costs and time involved in development that have developed within these companies and not having to support the necessary resources except when they are needed. The push to reduce the costs and exploit the synergies that may come with partnerships has further led to an unprecedented rate of acquisitions and mergers within these industries since the early 1990s.

S.C. Gad and C.B. Spainhour, *Contract Research and Development Organizations: Their Role in Global Product Development*, DOI 10.1007/978-1-4614-0049-3_4,

Table 4.1 Types of CROs

	Appendix
Nonclinical biological testing	
Pharmacology	B
Biocompatibility	A
In vitro screening	A, B
Toxicology	A
Metabolism	A, B
Pharmacokinetic modeling	B
Chemistry	
Medicinal chemistry	D
Synthesis	D
Active pharmaceutical ingredient (API) manufacture	D
Radiolabeled synthesis	C
Analytical method development/analysis	C
Bioanalytical method development/analysis	D
Biological product manufacturers	D
Engineering	
Machine shops	B
Physical testing	B
Clinical	
Phase I centers	G
Clinical monitors	G
Statistical analysis	G
Site management organizations (SMOs)	G
Report writing services	G
Data management	G
Dosage forms	
Formulation development	E
Clinical test material (CTM) manufacturers	F
Labeling	F
Patient kit preparations	F
Pharmacy services	F
Contract sterilization	B
Regulatory	
IND preparation	H
NDA preparation	H
Annual update preparation	H
Regulatory advisors	H

Pharmaceutical companies have always supported a thriving service sector, partly due to the broad range of skills and technologies required to discover, develop, and manufacture a drug for the market. This has aided in the positioning of these outsourcing organizations in the role of strategic partners (Table 4.1).

Hole in the Virtual Model: General Contractor

The virtual companies that now predominate drug and device development have come to be as a way to reduce development costs. A major (perhaps the major) problem with the virtual company pharmaceutical development model is that the proper placement of monitoring and conduct along with the coordination of such efforts is complex and requires a level and range of skills which are rarely present in the virtual organization let alone in specific service providers. A single individual or organization is needed to be able to act as a "general contractor" for such activities. And such a service provider is all the better if they are experienced and able to provide some of the required key services on their own. As an example of the complexity of outsourcing operations, the task of contract formulation development should be considered.

The pharmaceutical industry is challenged by competitive pressures to shorten the new product development process. CROs have clearly demonstrated their ability to accelerate the pace of development in the clinical arena, where there are now myriad of companies offering services in statistical analysis, clinical trials management, report writing, project management, and bioanalytical testing (Parikh 2001).

There is a growing trend in the industry to outsource product development, including such processes as formulation development, stability testing, manufacture of clinical trial supplies, and the preparation of chemistry, manufacture, and controls (CMC documents).

Formulation development is a key area of product development patentability, lifecycle, and ultimately the success of a new product. Formulation development encompasses a very wide range of activities. Traditionally, formulation covers such functions as preformulation, including analytical assay development and characterization, excipient screening to stabilize or enhance the solubility of the product, and dosage form development, whether it involves a solid, liquid, topical aerosol, or other dosage form. Formulation development may also include assessing delivery options.

As advances in preclinical technology have generated a massive number of putative potential drug candidates, contract formulation development has become the only way for the industry to keep pace. There are essentially three reasons for companies of all sizes to choose to outsource their formulation development functions:

(a) To compress a timeline – i.e., reduce time to market
(b) To access a particular expertise, technology, facility, or skill
(c) To offset the true costs involved with the risks of product failure

The following issues must be considered in detail for the outsourcing of any activity in general and formulations development in particular.

1. Determination of specifically what needs to be outsourced
2. Defining and establishing the scope of the project
3. Identification and selection of an outsource partner
4. Protection of the intellectual property
5. Management of the project

Determining Outsourcing Needs

The need to consider outsourcing formulation development is driven by various and unique internal factors within each company. These could include lack of skilled staff, lack of access or timely access to suitable equipment, time constraints, and a general lack of technological know-how. In short, the sponsor must decide if outsourcing is being considered for tactical reasons (contracting the project out because of time or manpower constraints) or strategic reasons (the sponsor does not have the technical resources in-house and has no intention of making the investment and taking the time to build them in-house).

The former situation is quite common among major pharmaceutical companies, where the number of projects far exceeds the available suitably skilled and experienced manpower or the time allotted. The latter scenario tends to be found among virtual companies or small firms, where resources are at a distinct premium.

Nevertheless, the determination to outsource formulation development must be made with one clear understanding: the *initial* cost of going out-of-house will always be higher than doing the same project in-house. This fact always surprises companies when they consider outsourcing for the first time. This is understandable, for a number of companies because the true cost of developing the product is hidden by the complicated way the accounting department calculates the allocation of overhead costs.

Establishing the Scope of the Project

An integral part of formulation development is defining the ultimate clinical dosage form. In early development the dosage form is undefined. The decision often comes down to what is feasible, what is marketable, and what is cost-effective for a particular drug. Understanding the real goal of the project will define the selection criteria for identifying and selecting an outsourcing organization. Formulation development projects to be outsourced can span a wide range of needs. An outsourced project may range from preformulation studies to clinical supply manufacturing or it may comprise a very limited sub-set of the development project.

A clearly defined written list of essential activities and expectations must be unambiguously established. The outsource organization must receive such information and key objectives as a budget, a schedule of critical project milestones and deliverables in order to supply a Request For Proposal (RFP).

The scope of the project can be subdivided into preformulation development and formulation development. Normally, some of the preliminary information may be available with the originating company and can be shared with the outsourcing organization. In most cases, the preformulation and formulation development is outsourced as a single project.

The requirements for different dosage forms are obviously different and must be identified. Some of the considerations are listed in Tables 4.2 and 4.3.

Table 4.2 Preformulation development research

Active pharmaceutical ingredient (API) characterization
Stability indicating assay
Purity (IR)
Crystallization solvent
Melting point
% Volatiles
Probable decay products
Solubility profile, pK_a
Physical properties (i.e., LOD, dentistry, flow, particle-size distribution, shape, surface area, etc.)
Crystal properties and polymorphism
Log P determination
Identity (chromatographic)
Dissolution study, X-ray diffraction, IR analysis, thermal analysis, hot-stage microscopy
Porosity (BET, mercury, etc.)
Hygroscopicity
Intrinsic dissolution
Compatibility testing (i.e., excipients, components)
Dosage form types
API bulk stability
Preformulation summary report

Table 4.3 Formulation development scope

Preformulation development report and review
Chemical/physical stability
Dissolution profile (if applicable)
Bioavailability
Formulation optimization
Clinical evaluation

Selecting an Outsource Partner

As presented in Chap. 1, just as the pharmaceutical industry landscape is always changing with merging acquisitions and companies starting up or folding, so it is with the outsource service industry. The listings at the end of this book are certainly not globally complete, and will be out of date by the time they appear in print in this reference (as, by the way, even some magazine advertisements for such are!), but we hope to have provided an excellent starting place for the selection process.

After the first round of selection, one should contact the remaining organizations under consideration and conduct the following actions:

1. Initiate Confidentiality Disclosure Agreements (CDAs).
2. Study the printed literature and website of each outsourcer's literature.
3. Ask each outsource organization to fill out a "Pre-Visit Questionnaire" to gain a more complete understanding of the organization, its response time, and the

degree of understanding that it may have about the type of project the sponsor wants to undertake. Some of the information to request in a pre-visit questionnaire could include company name, location, facility description, equipment list, history, organizational chart, mission statement, financial report (for a public company), parent company information (if applicable), regulatory audit history, references, floorplan, total number of employees (broken down by department and educational level), whether the workforce is union or nonunion, industrial health and safety records, holding of any licenses (e.g., NRC), AALAC accreditation history (if applicable), complete listing of SOPs, description of project management system, description of any data capture system, description of the flow of communication, technical capabilities, and a list of the company officers clearly showing the flow of authority and ultimate responsibility.

4. Once the prescreening process is complete, a quality audit needs to be initiated to further observe all the capabilities and meet the people who will be managing the project. For the best possible outcome, this activity should be conducted by someone who is familiar with CROs and has a sound grasp of the project at hand. Find out what the workload on the formulation development staff is, how soon the project can be undertaken, and whether the company can provide a tentative schedule for completion of certain milestones. Answers to these questions will provide a good indication of the organization's technical and project management capabilities. A reputable organization will not be unwilling to put promises of adherence to timed milestones in writing and have their lack of achievement associated with financial penalties.
5. Discussing the reputation of the company with industry colleagues is another way of performing due diligence. These discussions can revolve around the quality of work, the meeting of promised deadlines, reaction and plan of action of the outsourcing organization when unexpected results were obtained, time between the completion of the project and the written reports, and the existence of any surprises in the final invoice for the services rendered. Make sure that the information garnered is specific, replete with adequate supporting detail, and objective. Keep in mind, the site or facility visit is the most important step in selecting an outsourcing company. If the scope of the project is beyond the formulation development, such as process development, clinical supplies, or manufacturing, it is advisable to include in the evaluation of the organization these additional anticipated outsourcing areas. If there is a remote possibility that you will need the outsource organization beyond the formulation development stage, you should consider the following:

   (a) Experience in pharmaceutical development and manufacturing
   (b) Financial stability and liquidity
   (c) Past performance in hitting deadlines
   (d) Production capacity at different levels
   (e) Current capacity utilization
   (f) How do they normally sign the commercial contracts? A normal commercial contract can be signed in several different ways:

- A "cost plus" contract could require the contract manufacturer to reveal all of the operating costs and profits (open book) to the sponsor (not too many contractors are willing to do this).
- Another type of contract could be based on the "spot price," which will mean that, when you want to manufacture your product, *if* the outsource organization has the time and capacity, they will entertain your business (this is not desirable if you want to have the assurance that the product will be available when you want it in the marketplace).
- The third type of contract is called "take or pay," which guarantees the outsource organization a certain level of yearly production volume and, in return, the sponsor reserves a specific level of capacity to make sure product will be available to sell. There may be other creative ways commercial contracts can be signed.

(g) How many commercial products are being manufactured at the current location?

6. Financial (price) and agreement reviews by the legal department for terms and conditions including the liabilities. It is advisable that you allow more than adequate time for the legal review, because it will always take considerably longer than both parties estimate.
7. Clear responsibilities of each organization must be spelled out in the services agreement. For example, if the preformulation work is done in your own or another organization's laboratory and the development report indicates that the excipients are compatible, the outsourcing organization will complete the formulation development project based on that information. If that formulation shows a stability problem related to the compatibilities of the ingredients, the outsourcing organization should not be held responsible for any delays. There are a number of similarly unforeseen issues that may come up during the life of the project; each organization should have enough confidence in each other's professionalism that they can be resolved without too much problem. You will never be able to put every unexpected event in a contract, because that is just how drug development works. You will waste valuable time trying to do this and only the attorneys will make money and you will lose valuable time. Rather it is important to do one's homework completely and thoroughly up front so that one knows that they are dealing with a sufficiently reputable and ethical organization and that one will be treated fairly when potential problems develop. Relationships are key in this business, so place your business where you know you will be treated well.

Protecting Intellectual Property

When you are considering outsourcing, protecting your proprietary information is critical. Signing of the secrecy agreement alone should not be considered sufficient protection. Unless you are going to license specific technology for your product from the outsourcing organization, your agreement should specifically

discuss who owns the outcome of the research especially if it involves some unique process or formulation technique, or the work yields unexpected positive results or product, etc.

Managing the Project

Managing the project requires clear, facile, timely, responsive, and open communication between the parties. Because formulation development is a relatively short-term project, the sponsor company can have a member of its staff, if possible, work alongside the outsourcing organization team at the critical juncture of the project.

Typically, detailed timelines and milestones are established early. The construction of a check list may be advisable with clear responsibilities delineated. The criteria for success are defined at the beginning of the project. This makes it easier to maintain focus and to control and monitor the activities at the outsourcing organization. Monitoring such a project will give the sponsor a good understanding of the outsourcing organization's capabilities, people, and business practices. This is a valuable assessment that will be beneficial down the line, if the sponsor company ever wants to consider the outsourcing organization for the next step in the project, such as process development or commercial manufacturing of the product and if the outsourcing organization has those capabilities.

Pharmaceutical companies are in need of a method to grow their product pipelines in order to accelerate drug development and reach revenue demands. Outsourcing formulation development can provide new technology not available in-house, besides compressing the time to market for a new drug. The processes of identifying the right outsourcing organization for a project may be streamlined by asking a series of questions internally, before seeking an outsourcing company.

A definitive project plan in terms of scope, timelines, and deliverables will help the outsource organization select a provider with appropriate cost estimates and time commitments. The proper level of due diligence after the selection of the organization must be carried out to avoid disappointments. Monitoring the project with clear milestones and proper supervision is of paramount importance for the success of the project.

Reference

Parikh D (2001) Formulation development. Contract Pharma Oct 2001:60–64

Chapter 5
Selection of CRDOs

The selection of service providers that outsourcing development activities require is a demanding activity. A successful development team will certainly include not just a single provider but rather a group of specialist companies, individuals, and organizations.

Despite the difficulties and new challenges this approach to R&D presents, data suggest that more and more companies – large and small – are implementing outsourcing programs as part of a strategy to accelerate the discovery process, control development costs, exploit profitable niche markets, and minimize time to market. Indeed for small and mid-sized companies, an adequate outsourcing strategy is of paramount importance from the beginning.

The Trend Towards Outsourcing

The "contracting out" or "outsourcing" of chemical scale-up and, more particularly, bulk manufacturing has always been an integral part of pharmaceutical industry activities, but the outsourcing of biology is a more recently developed phenomenon. This is because the more mature industrial chemical industry was already using contract providers, an approach that then became acceptable to the younger pharmaceutical industry entities. The expense of investing in and maintaining a chemical plant means that its capacity must be fully utilized in order to maintain profitability; its use by a number of clients has obvious cost-saving and revenue-producing elements. In the past, there existed neither the requirement nor the services necessary to consider outsourcing biological studies.

This changed in the early 1960s, when the tragedy of thalidomide revealed the importance of adverse findings in toxicology and transformed the public policy surrounding drug safety. It was furthered by the introduction in 1977 of Good Laboratory Practice (GLP). Since these two events, the pharmaceutical industry has adapted outsourcing of preclinical safety studies and their components as an integral and

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essential part of their overall strategy. This can be similarly applied to the clinical work that is performed to supply proof of safety and efficacy of new drugs, and has been the norm for medical devices since the 1990 Safe Medical Device Act.

Outsourcing is now an essential element in the strategy of pharmaceutical companies. Far from being solely the province of large company strategy, outsourcing is used intensively by small companies aiming to adopt modern techniques in a flexible, cost-sensitive, and competitive environment. Outsourcing can be taken to mean more than just contractual R&D, and can involve both academic and industrial collaborations. In the widest sense, outsourcing can range from contract R&D to acquisition, with a wide spectrum of joint ventures and collaborative research efforts in between. Arrangements between parties can stretch from preferred provider contractual relationships, through to equity investments interlaced with research collaboration. For the purpose of this chapter, we will narrow our definition of outsourcing to the contractual relationship between technology provider and client. This may involve a research or a development contract; however, the intellectual property in this definition remains with the sponsor, with payment based on completion of the sponsored work and not related to the ultimate success of the project.

Rapid Growth

In a recent report, outsourcing in the pharmaceutical industry was estimated at contributing to about 90% of overall R&D spending (50% for large pharmaceutical companies), and rising. Given that pharmaceutical R&D is estimated to run at more than $250 billion for the year 2008, this amounts to some $220 billion of expenditure annually. The overall outsourcing market is expected to continue to grow significantly over time, driven by the financial performance expectations of companies. In some areas such as outsourcing of chemistry-related functions, the figure has recently been rising at a compound annual rate of 40–50%. Given the huge amounts of money spent on outsourcing, it is perhaps surprising that more attention is not given to the process and procedures of selection.

This rather oligopolistic market representation should not disguise the fact that there is huge diversity amongst the smaller organizations that is not shown in the chart, and indeed, in the somewhat older manufacturing function, the split is much wider among a larger number of companies. In clinical and toxicological evaluation, many (though not all) of the tasks have similar skills requirements, and the generic nature of the processes involved tends to favor the agglomeration into larger business units. In chemical manufacture, there is a greater degree of specialization and a greater importance of specialized machinery and facilities required to execute different synthetic routes or manufacture different formulations. However, it is also true that this segment of the outsourcing market is less mature than chemical manufacturing; this may also be a factor in the number of companies represented.

The Buying of R&D

Management of outsourcing is a much more complex process than that of internal R&D. While the selling of R&D is a well-advanced process, the buying of it is not. Many companies incorrectly regard this as a normal extension of their in-house efforts with little training being given to those personnel who are expected to manage it. Frequently, they consider outsourcing as part of the purchasing function. The process of buying R&D can be divided into the following segments:

- The identification of potential providers
- Selection of preferred providers
- Negotiation of a contract
- Management of the work
- Receipt and utilization of the resulting product

Identification of potential partners is itself a complex process, with more than 2,300 companies in the business of offering contract pharmaceutical and medical device services. While there are "for hire" directories of such organizations published (DIA 2010; FDLI 2010; Contract Pharma 2010), only these volumes cover the entire span of available resources.

Reflecting the complexity involved, a few of the larger contract research organizations (CROs) are offering a wider menu of services, in an effort to capture "one-stop-shop" outsourcing. However, the risk for the buyer in choosing such offerings is that the quality, value for money, and coordination between groups are not always equally high. One is far better served by selecting different companies with expertise specific to the type of service sought.

Selecting, planning, and budgeting for the use of a CRO are critical to project success. CRO use continues to increase in the U.S. and Europe, and yet sponsors continue to encounter difficulties in these areas. Typical problems include:

- Insufficient knowledge of available providers
- Lack of understanding of CROs, their function, and how to select and deal with them
- Finding the time and resources for evaluating and selecting a high-quality, experienced CRO
- Unrealistic bid expectations
- Poor bid specification, leading to poor CRO performance
- Difficulty comparing competing bids
- An inability to specify rates and terms for any additional work on a basis comparable to the initial contract. This reflects the "scope creep" problem faced by both the client and the provider.

Sources of Information on CROs

Identifying Competent Laboratories

The first step is to obtain a list of laboratories engaged in the contract provider field such as toxicological testing. Although other opportunities exist for obtaining such services, for example, university laboratories, laboratories of a consortium member's company, and, in some cases, government laboratories, the vast majority of externally placed studies involve the contracting party (the "sponsor") placing a study in a "contract research organization's laboratory." Therefore, this situation will be used as the model for the rest of this chapter. The CRO (contract research organization) or CRDO (Contract Research Development Organization) industry has become truly international, as is reflected in the lists provided in this volume (Appendices A–I). Laboratories can be selected based on a range of factors, as we shall see.

Published Lists

Several lists of contract providers exist, but the most currently available list should be utilized. These lists are updated from time to time, since the contract laboratory industry is dynamic and the capabilities of an individual laboratory change over time. Also, it must be recognized that the contract research industry has become an international one, with services both provided and required by organizations in a large number of companies.

These compendia serve as basic sources of information for finding CROs capable of performing a specific task. More detailed information can be obtained by contacting (by phone, mail, or e-mail) the individual provider organizations and requesting literature or by visiting a Web site.

Information Available at Meetings

A great deal of information about CROs can be obtained at various scientific and industry meetings (e.g., Society of Toxicology, American College of Toxicology, Safety Pharmacology Society, American Association of Pharmaceutical Science, etc.). Brochures that explain the types of services a CRO is capable of providing, and descriptions of facilities, staff, and price ranges for standard activities are prominently displayed at such meetings by many contract service providers. Laboratory sales representatives (the current trend is to call these "BD" or business development personnel) attend these meetings frequently to discuss specific study needs with prospective sponsors. Sometimes actual working scientists attend these meetings and are available for discussion.

A second source of information available at meetings is the experience of professional colleagues, who may be able to provide advice on their personal preferences

as to where to have certain kinds of services provided, having had similar work done previously. Of particular importance is information about where their work was done, its perceived quality, the hitting of timelines, the handling of errors and how to avoid mistakes or misunderstandings in dealing with a particular contract laboratory.

This latter source of information needs to be taken with the proverbial "grain of salt." Almost anyone who has contracted R&D activities has had some problems; those who have contracted many projects have had at least one with a major problem; and probably every good contract provider has been inappropriately criticized for poor work at least once. A distorted evaluation is altogether possible if, for example, uncontrollable events (power shutdowns, shipping strikes, etc.) might have affected study results and the sponsor's overall impression of the provider. Remember the importance of effective and adequate communication in any work relationship. Keep in mind the essential nature of a quality business relationship. While mistakes and problems are not desired, they do occur because of human nature, and you will want to ultimately place your work at an organization or organizations where you ultimately have the confidence that you will be treated fairly and ethically. Relationships are key!

For highly specialized work, choices in providers may be very limited. The service and availability of phototoxicity testing, for example, is still a relative rarity. Reproductive and developmental toxicity evaluations, although offered by many laboratories, are tricky, demanding, and performed well by only a few. Inhalation toxicity testing is in similar circumstances. An even more complex situation involves tests requiring several kinds of relatively unusual expertise or equipment. A developmental toxicity study that requires inhalation exposure, for example, may limit laboratory selection to only a few facilities. Contract providers will usually provide information on the availability of services in specialized areas, if they are unable to provide such testing themselves. When looking at services, do not be misled by the availability of stunning new technology that a laboratory is trying to sell, in order to help pay for the investment. Rather the services sought should be well-based in regulatory requirements and/or solving a specific scientific problem that could be an issue in the drug development process at some time. Extra credit is not given by any agency for providing data using some new esoteric technique that may not even have adequate background of historical data. Including "extra" service studies always has the potential of causing problems downstream.

"Freedom of Information" Requests

Copies of reports of laboratory inspections conducted by federal agencies are available under the Freedom of Information (FOI) Act and online at the FDA Web site (http://www.fda.gov). These reports generally follow the format of the laboratory inspection guidance given to Food and Drug Administration (FDA) investigators and provide a great deal of information of varying utility. Since they are purged of references to proprietary activities, trademarks, specific sponsorship of studies, and much other information, it is sometimes difficult to understand the intent of the report.

In addition, they present the opinions of individual investigators concerning isolated activities and events and therefore may not be truly representative of a laboratory's usual practices. Although this information is at least theoretically intended to be objective in nature, sometimes it is not. Effort must be made to truly understand the nature, relevance, and importance of any citations. All points noted on an audit report are not equal in severity, and sometimes points are of no consequences at all. The analysis, interpretation, and advice of a good consultant can help a lot here.

On the other hand, since the laboratory inspection procedures used by a particular agency are usually consistent, the FOI reports permit some comparison among laboratories. This information, coupled with other inputs, is therefore valuable and should not be ignored.

FOI requests should be made to the specific agency that conducted the inspection. Since the FDA's inspection program has been in existence for some time, they are the logical first agency to call in seeking inspection reports on a particular laboratory.

Having developed a list of laboratories able to do the study in question, the most critical part of getting a good job done is in selecting *the* laboratory at which to place the study. The rest of this chapter will be spent reviewing selection criteria in detail.

This volume, of course is intended to meet several unmet needs. A number of organizations provide an interface between the provider and the client. These intermediaries provide a range of services, from information databases to consulting services, and in some cases even conducting studies themselves, acting as a sort of general contractor CRO.

Such companies can offer more extensive information on CROs than pharma or biopharma companies tend to have in-house, which allows a savings of time and contract costs by facilitating charge comparison and the negotiation of better CRO selection, thereby reducing the risk of selecting a poorly qualified CROs. Mistakes in selection can be very costly in terms of increased time to completion, project costs, and poor performance, particularly where there may come a need for additional studies to make up for poorly conducted contracts. Lost time is lost market opportunity. There are a number of independent consultants who also act as "one-stop" CROs, arranging and coordinating all required activities for development. These can each, however, usually handle only a few projects at a time (see http://www.toxconsultants.com or http://www.chemconsultants.com, for example).

DataEdge (http://www.dataedge.com) has collaborated with 30 larger pharmaceutical companies to define benchmarks and divide unit costs into 20 common budget categories, ranging from pretrial regulatory filing to manuscript preparation. They prepared a unified process for CRO selection, which the company claims makes the preparation and evaluation of requirements for proposal a much more facile and rapid task. The CRO responds to a proposal involving detailed tasks described in familiar terminology. This all-inclusive proposal reduces initial and add-on costs by eliminating double-charges. Preferred-provider rate can be readily compared to industry rates paid by other companies, and comparisons with other means of carrying out the work, such as using internal resources, can be made.

Similarly, Arachnova (http://www.arachnova.com) offers services in project leadership and outsourced project management, providing a database (the Technology Web)

with more than 1,000 companies specifically in the CRO industry. Limited searching of the database is freely available via the BioPortfolio web portal at http://www.bioportfolio.com, but a CD-ROM version is available at a commercial rate.

Technomark (http://www.technomark.com) has provided a register of CROs since its conception in 1988. Initially focused on toxicology and clinical outsourcing, an addendum has recently been published which identifies contract pharmaceutical manufacturers and chemical synthesis companies. The information provided by the Technomark registers has also recently been enhanced by an online version of the database. As well as basic contact information, there are details on the finances and the number of staff in an individual CRO. This information is not provided for all CROs, and is particularly lacking from the small, often private entities, which make up the bulk (in number) of the service providers. While it is often said that it is the smaller private provider that is more financially exposed, the recent failures of Oread and Azopharma exemplify the wide range of this business risk. It is interesting to compare the failed strategy of Oread which was to become a fully fledged multidisciplinary development service provider with that of Albany Molecular Research, which, while expanding its offerings, has nevertheless remained focused on chemical service provision.

A smaller version of the Technomark database is provided by InPharm (http://www.inpharm.com) in the FlexiPages part of the website. The information, which is given in more a directory format than a database, provides contact details for a wide range of agencies and suppliers serving the pharmaceutical and healthcare industries. The information is accessible for free on the Web, and can be searched by keyword or browsed by category. There is little information on many of the featured companies, but some have a profile with more information. Although the total number of companies is around 1,000, few are specifically in the contract pharmaceutical R&D field. From a business perspective, this data is funded by organizations paying for a profile to be included on the Web site. This has the advantage of being free to the user, but the disadvantages of being partial in scope and biased towards those that do pay for a profile. This is not the case with the information provided in the appendices of this volume.

The Middle Tier

As with the client pharmaceutical and medical device companies themselves, the merger trends of recent years in pharmaceutical outsourcing could be seen as suggesting a future with ever fewer, ever larger providers. While there has remained room for niche CROs, there is a trend to provide a wide range of pharmaceutical development resources to optimize the drug development services within a single organization. The real business challenge from such reorganization is to use this very large development resource to optimize the drug development process for the benefit of the pharmaceutical industry. As in any industry sector, integrating the activities of a large CRO organization, particularly one that has recently merged, has been a substantial internal challenge.

This trend has now been countered by the emergence of a new tier of company intercalating itself between the sponsor and the CRO, with the outsourced management of clinical trials through site management organizations (SMOs) as an example. SMOs provide CROs with physicians and coordinators to enable clinical research coordination and monitoring of Phases I, II, III, and IV clinical trials. The SMO often has a number of therapeutic specialties and access to a large and diverse patient population for inclusion in the proposed research. In addition, SMOs usually employ full-time certified clinical research personnel for trial documentation and case report form completion. SMOs are judged by their ability to enroll patients in studies and start and complete a clinical drug trial in a timely manner. In essence, therefore, SMOs aim to streamline the functions of CROs and operate between the CRO and the investigator.

Unless and until the cost savings and efficiencies promised by the continuing round of CRO mergers can be realized, there will remain room for such intermediate-sized organizations, which can operate in a highly flexible sense to add value to the outsourcing process in pharmaceutical R&D.

The CRO business is highly competitive and in this respect it is similar to the product-based industry it serves. However, there is a major difference in the way the two industries compete for business. The pharmaceutical industry can hope to very clearly differentiate its products based on hard data obtained from efficacy, safety and pharmacoeconomic studies. Even in today's new healthcare environment, the market place is less price sensitive when clear clinical evidence for product advantage can be shown. This is in marked contrast to the CRO industry, which has an ever-shrinking number of large well-founded mature customers and a vast and expanding pool of young and small and venture capital–hungry customers. Differentiating and selling technical services to senior R&D management is very different from marketing products to doctors and healthcare providers. Claims that work can be completed faster, error free, and reported to agreed timelines are simply generally not credible to customers, because all CROs make these claims. A highly placed big pharma executive once said "…all CROs are the same; they promise you the world and then fail to deliver. One does not truly find out what he or she has until something goes wrong. The way that the situation is handled and the client is treated is the key to success." This is also the key to the development of business relationships. As stated previously, relationships are key and work should be placed with organizations, management, and study directors that one can trust.

The real added value that an individual company might bring in its service offerings needs to be more carefully considered. Given that the facilities, GLP/GMP/GCP status and technical competence and the like are mostly undifferentiating for the successful CRO, the simple answer has to be the knowledge and experience that an organization has, that is of the technical and scientific complexity of the pharmaceutical and medical device development process. CROs that can capture this knowledge by employing professionally experienced leaders who can then cultivate the scientific culture of pharmaceutical development into their organization will be the winners of the fight to capture increased market share in a generally mature or shrinking market. Such people-based elements last only as long as these individuals

are employed by the organization. Knowing the good and bad elements comes from experience of working relationships; expertise in one area does not imply equal or similar talent in all areas. In some cases, specific technologies might add a further element of uniqueness, for example inhalation technology, continuous infusion technology, telemetry, and transgenics.

There is increasing recognition that specialist companies can add value to the outsourcing process, and many now see the role of an intermediary organization as beneficial to serving the research-based pharmaceutical sector. Indeed we should not be surprised. The word "entrepreneur" literally means "to take between": in all industries, as they mature and become more integrated, companies often become more specialist in their offerings, and opportunities can open up for new commercial intermediaries. A useful comparator here is the computer manufacturing industry, which is highly fragmented and based on outsourced networks. A final validation of this concept comes from the large CROs themselves, which, in order to offer the one-stop shop from which they can benefit substantially as a provider, often resort themselves to subcontracting. It will be interesting to see how this trend develops in the next few years, in an age when the business of pharmaceutical development is still growing, becoming ever more international in scope, more competitive, and more complex.

Outsourcing is no doubt a trend that will continue to expand, and in order to improve its efficiency, the ways in which it is approached and managed are likely to see dramatic evolution.

Key Considerations in Selecting a Lab

Dependability: Far and away of greatest importance should be confidence that the contractor will perform as agreed to (on time, on budget, honestly, and delivering the agreed product in the quality anticipated) and will inform the client or their agent of any problems and issues as they arise in a timely fashion. For longer projects, such unexpected occurrences will occur and are most likely and easily solved or addressed if attended to early.

Experience (activity or study type specific): Unless a study or activity is very unusual, any CRO selected to perform it should be able to demonstrate having previously performed the desired type of work in a successful manner. If the lab has not performed the work previously, keep in mind that everybody at some time has to be the first. To that end, fair and due consideration should be given to an organization that presents a plan that provides a detailed description of the important aspects of the study in such a fashion as to provide sufficient confidence in the proper execution of the project. It is not whether or not one is the 1st or the 99th, but rather whether the organization is adequately prepared with sufficient resources to perform the work. If the desired work is unique or of an unusual nature, the CROs wishing to provide the service should provide a plan for "refresher" training or performing a "pilot study" (at no charge to the client) so as to maximize the chances of success.

Does the laboratory employ personnel trained in the needed specialty? What about ancillary expertise (clinical pathology, special services, ophthalmology, cardiology, pathology, statistics, pharmacokinetics)? If not directly employed by the laboratory, are trained specialists available on a consulting basis? For example, if the major emphasis of a study is the determination of the inhalation toxicity of a test agent, but a minor component concerns teratogenic effects, the selected laboratory should require the presence of skilled, experienced inhalation toxicologists on staff. The laboratory does not necessarily have to employ its own teratologists, however, since coverage of these evaluations may reasonably be conducted by consultants in this specialty.

A skilled, competent staff will be necessary to the conduct of the work. Prospective laboratories' personnel environments should be scrutinized for signs of frequent or rapid staff turnover, difficulties in recruiting and retaining new staff, lack of career pathways for staff currently employed, and good wholesome interaction between employees. When visiting a laboratory, observe how the employees interact. Do they work well together? If they work well together, they can probably work with you.

Many laboratories rely on independent organization certification to demonstrate a standard of achievement and competence on the part of their technical and scientific staff. For example, both the American Board of Toxicology and the American College of Toxicology have certification programs for toxicologists. Likewise, the American Association of Laboratory Animal Sciences (AALAS) has three stages for certification of laboratory animal technical staff (ALAT, LAT, LATG). Other specialties have similar certification programs based on some combination of experience and achievement demonstrated by written and practical testing (e.g., Quality Assurance, Pathology, Laboratory Animal Medicine).

Hand in hand with personnel availability is the selection criterion of technical expertise. Many different specialties are brought to bear on a particular study. The more complex the study, the greater the difficulty in finding a contract laboratory with all the necessary expertise.

In attempting to evaluate the qualifications of contract laboratory staff, organizational charts, training records, job descriptions, and *curricula vitae* should be obtained. These documents are standard tools, which are used by contract laboratories as marketing aids. FDA's GLP regulations require laboratories to maintain documentation of the training, experience, and job descriptions of personnel. This is usually done by means of compilations of curricula vitae.

Another important point in evaluating staff capabilities is the number of people employed by the laboratory. The proposed study staff should be sufficient to perform all the work required. Attention should be directed to the laboratory's overall workload relative to available staff. While this is difficult to specifically assess, an open and frank discussion between the CRO and the client should take place. DO not fall into the trap of calculating various ratios, which will not be applicable in a cost-effective organization where there is a substantial degree of cross-training and cross-departmental sharing of technical resources based upon work load.

Equipment: Are all of the required instruments, tools, supplies, reagents, computers and such in place, operational, properly maintained, calibrated, validated (if necessary),

and labeled (check records)? Are the knowledge and skills of senior scientific staff suitable to the required works? Do they have prior experience performing such works? Are the actual technicians who will be performing the day-to-day works suitable? What is the turnover rate for the staff at the facility?

Cost: As a general rule, all contract research and development should be put out for bid by several CROs (but not too many because such bids take work and time to prepare, and it is unfair to ask for such a proposal if there is not a good chance that a contract will be awarded). Three or possibly four bids are common, but requests in excess of a half-dozen are unprofessional. Care should be exercised to provide sufficient information and detail to the potential bidders to ensure that all participants end up rendering bids on the same scope of work.

Facilities: Are the facilities (buildings, rooms, and environmental support services such as water, heat, air and power) sound, well maintained, suitably monitored, sufficient for the tasks, and clean? Particularly if living organisms are involved, it is essential that provisions for any power failures (i.e., backup generators) be present.

Laboratory animal care facilities may be accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). This is a voluntary organization that accredits laboratories based on its own standards as supplemented and reinforced by those of other organizations (academic and industrial). Accreditation is based on elements of several major activities, programs, or capabilities of the individual laboratory, such as veterinary resources, physical resources, administrative matters, pain management policy, animal enrichment program, and the presence and activity of an effective animal care and use (animal welfare) committee. AAALAC accreditation is frequently the only objective symbol of the general compliance of the laboratory with standards of good practice in animal use and care, veterinary, physical plant, and administrative areas. Although this provides no guarantee that the laboratory does good testing, AAALAC accreditation represents a worthwhile first step toward excellence in the care, handling, and management of animals and a sound level of assurance that one's study will not be featured on the 6 o'clock news for violations of animal welfare.

Regulatory History: Regulatory agencies remember both good and bad performances by regulated contractors. They regularly audit such, and the results of such audits are public records which should be provided upon request by the contractor and which are available online from FDA.

A large portion of the initial visit to prospective contract laboratories can usefully be spent in reviewing standard operating procedures (SOPs). These should be written for all routinely performed activities.

GLPs require that SOPs be established in the following general areas: animal room preparation, animal care pain management, test and control substance management, test system (animal) observations, laboratory tests, management of on-study dead or moribund animals, necropsy, specimen collection and identification, histopathology, data management, equipment maintenance and calibration, identification of animals, the IACUC, and quality assurance. Although not specifically required by GLP regulations, the laboratory should also have SOPs for archiving activities.

In each of these areas, numerous individual SOPs should be in place. For example, in the area of histopathology, SOPs should be available to describe tissue selection, preparation, processing, staining, and coverslipping; slide labeling and packaging; and storage and retention of wet tissues, blocks, and slides. Similarly, SOPs should be available for maintenance and calibration of all equipment and instrumentation that requires these activities.

The laboratory's SOPs should be clear, understandable, and sufficiently detailed to permit a technically experienced person to perform them. They should be up to date, and the method for keeping them current should be described. They should have the sanction of facility management, usually provided by signature of the person responsible for the pertinent laboratory activity. The SOPs should be simply written and in a level of detail that provides confidence in the task being done repeatedly well, but not so much detail that it is impossible to be in compliance with the SOP. SOPs should be written by the people performing the work and not by management, so look closely at the signatures on each SOP.

To be effective, SOPs should be readily available to those who need them. For example, animal care SOPs should be available to vivarium workers, as analytical and clinical chemistry SOPs should be available in these laboratories. Compendia of SOPs which sit pristinely on shelves in offices may not reflect what is actually occurring in the laboratories and animal quarters. Likewise, SOPs which have not been reviewed or revised in several years should be viewed with suspicion. Improvements in actual methods occur frequently, and should be reflected in the written procedures.

If the laboratory has contracts with other laboratories, SOPs should be available for the secondary laboratories as well. Both the SOPs and these contracts should be reviewed in the same way. Subcontractors used by the CRO should be audited on a regulator basis.

Computerization: The days when all but a minority of data and records were recorded, captured, and manipulated by hand are gone. The degree and quality of automation and computer resources of a potential contractor must be assessed as should the overall integration of such systems and plans and progress towards Section II GLP compliance.

Financial Soundness: In Chap. 1 a listing of extinct laboratories was provided. Several of these ceased operations with studies in progress and without notifying sponsors in advance due to financial failure. To avoid this, one needs to assess the financial ability of a contract organization to continue operations and complete works. For many contractors, Dunn and Bradstreet can provide such information. However, such information is difficult to secure from privately held companies. However, in these cases, do not be afraid to sit down and talk with the president of the company and/or its owner about financial performance.

Location: Much is sometimes made (frequently by competitors in a negative way) of the importance of location of facilities. While there are some factors which are related to location which should be considered (ease of trend and perhaps trend cost, stability, and availability of technical staff and security come to mind), the author's belief is that this is near the bottom of the list in terms of priority.

A consideration in selection of contract laboratories is the sponsor's ease of monitoring the study, which is largely a function of distance between the sponsor and the laboratory. In some studies, this may be a major consideration; in others, not worthy of mention. If the study is complex and requires frequent oversight, a trade-off may need to be made between the best laboratory relative to the previously mentioned selection criteria and monitoring ease.

On the other hand, sponsors do not plan complex studies unless they anticipate substantial product safety evaluation concerns, and therefore, considerable potential profit. If this is the case, the relatively small additional sum spent in the increased cost of frequent or distant monitoring may be minuscule in the eyes of those selecting the laboratory.

Site Visits of Prospective Contract Laboratories

In scheduling site visits with contract laboratories, the objectives should be clearly defined up front. Meeting those people who will be directing and contributing importantly to the study provides an opportunity to evaluate their understanding of the nature of the questions or problems which may arise. Ancillary contributors (pathologists, statisticians) should be interviewed carefully as well, since their contributions can be of fundamental significance to the quality and outcome of the study.

The facilities should be toured, looking for appropriate size, construction, spacing and design. GLP regulations as promulgated under the Food, Drug and Cosmetic Act, the Toxic Substances Control Act, or the Federal Insecticide, Fungicide, and Rodenticide Act provide guidance as to the general facility, equipment, and operational requirements of laboratories.

Storage areas for extra racks and cages, feed and bedding, and so forth are frequently inadequate in laboratories (cost issue), but these facilities should be inspected and evaluated anyway. One's evaluation of a facility should be against a reasonable standard of functionality and not against some prior experience with a multibillion dollar year operation that had no limits to spending.

The FDA provides their field investigators who conduct laboratory inspections for compliance with GLPs with "Compliance Guidance Manuals." These are comprehensive documents which use a checklist approach to inspecting a laboratory for adherence to all the elements of GLP regulations. They can be obtained from the agencies, and can be used as guidance for study sponsors in evaluating prospective laboratories. An advantage of using this approach is that the sponsor will not omit an important element in inspecting a prospective laboratory. However, the sponsor should not get so bogged down in reviewing checklist items that actual observation of the laboratory is abbreviated.

Once an initial review of potential service providers has been conducted, some organizations will be eliminated from consideration, but those that remain in consideration (no more than three is a suggested limit) should be visited for on-site qualification. Table 5.1 (with CV's provided) provides a sample agenda for such a visit.

Table 5.1 Sample agenda for a qualification visit to a contract research organization (CRO)

Global presentation by the CRO/vendor
Range of services offered
Company history
Organizational chart of the company
Presentation of potential study team
Previous experience and references
Number and type of ongoing/future projects
Previous audits
Presentation by and specific to the business of the company placing the work
Tour of the facility
Project management
Discuss interfaces/coordination with CRO and sponsor, project team structure, and reporting processes (including review of staffing estimate, CVs, training plan/records, job descriptions)
Discuss logistics/process review and project team coordination (including data flow, data transmission capabilities, reconciliation with other databases, management of committees, samples of timelines, quality controls, problem identification and resolution processes)
Data management
Demonstration of the data management system (data entry, data query system, tracking of CRFs, tracking of queries, process flow chart, standard metrics – e.g., time from last subject out to database lock)
Demonstration of the central randomization system
Review drug distribution capabilities and interface with the central randomization system
Review data management and central randomization system validation documentation
Review procedures for reconciliation with other databases
Review manual vs. automated processes and validations
Discuss ability to use sponsor coding dictionaries
Quality assurance
Review CRO organizational structure (organizational charts, mission/quality statement, training records, training policy)
Review QA department activities, reporting relationships, quality manual, quality records, and QA standard operating procedures (SOPs)/standards
Review reference files management (regulatory documentation/guidelines)
Review SOPs
Review quality controls and audits
Review equipment inventory
Wrap-up/summary of findings (sponsor)
Present and discuss any finding from SOPs or other departmental review
Determine need for additional qualification data or visits by additional sponsor personnel
Establish plan for CRO to provide any missing data identified during visit
Schedule a mutually acceptable time for presentation of the formal report of the sponsor's findings. During this meeting the CRO should be ready to create a plan to address any "deficiencies" found during the visit
The written audit report should in NO way be a surprise to the CRO and should be entirely consistent with discussions held during the exit interview

Cost

A key factor in the selection of a laboratory for most sponsors is the cost of the study. This single element can largely affect the quality of a study. "Caveat emptor" applies equally to the toxicologist as to the home consumer. Many of the negotiable elements of a carefully defined study will not be performed in a similarly titled study at a different laboratory for a lower cost. Conversely, some of the extras offered for a higher priced study should not be included for extra cost if they are neither scientifically or regulatorily necessary nor desirable. The objective in considering the cost of a study is to select the laboratory which offers all of the same essential study elements at the lowest cost consistent with good quality. Good quality in turn relies on the other criteria previously discussed. When a laboratory is found which can perform all desired elements of the study, does high-quality work, and offers a lower price for the study than its competitors or highly competitive price with its competitors, then this is probably the laboratory to choose to perform the study. Pricing of studies from competitors should be clustered together (within 10% of each other). Organizations providing extremely high prices (fliers) or low prices (sinkers) should be eliminated from consideration, unless a rebid process is desirable for some reason due to bid requirements confusion. The former typically tells you that the laboratory is full and they are only willing to perform the work at an extremely high margin. Similarly, an extremely low price tells you that the laboratory is hurting for business.

It is so very important to compare bids carefully to make sure that the prices are for the same work. Unfortunately, it is not an uncommon event to see prices for studies quoted at a very low amount, because some essential study components have not been included (ECG, ECG analysis, ophthalmic exams, limited histopathology, etc.). The strategy in this case is to provide a very low bid to secure the business and once the business is secured, to raise the study price with all the "necessary" additions. In the end, the actual true price tends to be very similar to that of others. The strategy usually works as clients tend for a variety of reasons to not walk away, as they should.

Remember the golden triangle: quality, cost, and timing. You can only get two of the three parameters at any one time. So for example, if one wants it fast, the cost will not be cheap and the quality may be marginal. Similarly if one wants very high-quality work with a lot of detail, the price will not be cheap and it will take longer to execute.

In discussing costs, the sponsor should attempt to determine whether the laboratory will be able to add elements to the study if this appears desirable as the study progresses. The laboratory should have the capability to expand the original study design. Sponsor and laboratory should attempt to foresee how the cost of such additions would be determined.

Reputation

The reputation held by particular contract laboratories is clearly a guide in laboratory selection. Although it is not an absolutely reliable indicator of the worth of a contract

laboratory's efforts, by and large laboratories earn their reputations over a long period of time. Again, beware of laboratories which submit extremely low bids for studies and either cut corners to stay within their quoted cost or include add-ons, at the sponsor's expense, through the course of the study. Study additions can significantly increase the actual cost if the contract requires the sponsor to pay for them.

Other laboratories try to foresee likely additional aspects of the study, which may increase the quoted cost but yield a much better product. A good CRO will at least discuss with a potential client possible future extensions of cost. Producing the study at the price quoted is only one part of a contract laboratory's reputation. Quality, professional qualifications of staff, activity in scientific professional societies, accreditation, regulatory performance, and many other issues are important as well.

Protection of Client Confidentiality

Most contract laboratories expend considerable effort in trying to maintain confidentiality on behalf of their clients. In walking through a laboratory, clients should not be able to see proprietary labels on test material containers, or cage labels that state company names. A contract laboratory concerned about client confidentiality will be careful not to allow visible evidence to be seen by other potential clients. Confidentiality is usually of significant concern and should be discussed with laboratory management. The laboratory's master schedule should maintain client confidentiality as well.

Prior Experience

Prior experience with specific contract laboratories highly simplifies the task of selecting a laboratory. Establishing a continuing relationship with one or several laboratories in the case of routine testing provides an opportunity to fine-tune study protocols. This will be discussed in greater detail in section "The Study Protocol" below.

Scheduling

Undoubtedly, starting the study as soon as possible is important. The ability of the laboratory to begin the study soon may well determine where the study is performed. Most of the larger contract houses can start all but very large studies within 4–6 weeks. Some studies may be able to be initiated on even shorter notice. Certainly for shorter studies, less complicated protocols are needed and generally less lead time is required to begin the study. The converse is equally true, so if the study is large, long-term, or complicated, a fairly long time before study initiation will be needed to get the details of the study worked out with the laboratory. As a result, a laboratory that is willing to start a lengthy or complex study before the details have been

settled should generally be avoided. Again, most CROs can start studies relatively quickly, unless they are very complicated. However, the biggest delays in getting studies started are the supply of the test article, adequate formulation for the test article, availability of an adequate bioanalytical method, and a signed protocol.

Special Capabilities

As the science of toxicology and the questions society, regulatory agencies and companies seek to answer become more complex, technical skills and equipment which are not widely available become more in demand. Such special capabilities are frequently resident in smaller or university laboratories where procedures, documentation, and adherence to regulatory standards may not be as rigorous as either one's own corporation or larger contract laboratories. One may even have to help investigators develop protocols, SOPs, and record-keeping systems.

Evaluating technical competency for specialized procedures is obviously difficult, as one is usually dependent on others to initially identify such specialists and they may have to also get outside help to evaluate the appropriateness and quality of the results. A not uncommon case of special capabilities is when human testing (such as repeat insult patch testing or RIPT, must be performed). Here one must understand the special regulatory, legal, and ethical constraints on work with human subjects, and generally deal with an IRB (institutional review board) which must review, approve, and oversee any such human studies from the perspective of subject protection and ethics.

The Contract

General terms of the contract should address such aspects as timeliness, proprietary rights, confidentiality, adherence to regulatory requirements (in the research effort and in the laboratory's practices in waste disposal, workers' protection, and safety, etc.), type and frequency of reports, communications between parties, conditions under which the study may be aborted and restarted, timing and method of payment, insurance, and the like. Such a contract "…should be negotiated by a team of lawyers and scientists who have a thorough understanding of the problems to be investigated, including both the scientific issues and the potential business implications. Armed with this understanding, the lawyers can then proceed to develop a contract that is appropriate to the situation. Much of the language will be routine or 'boiler plate', the type commonly found in agreements of various kinds."

The contract should specify who does what in the furtherance of the study. For example, if analysis is necessary, the sponsor may wish to retain the responsibility to analyze the test material as a means of keeping its identify confidential. The derivative concern about documentation of the analysis is presumably also retained by the sponsor, but the contract should be clear on the responsibilities of both parties.

When discussing study personnel, various degrees of authority are vested in contract laboratory study staff by the sponsor. The study contract should define as clearly as possible the degree of authority vested in the contract laboratory staff and at what point the sponsor would be consulted for a decision when unforeseen situations arise. In general terms, then, the contract should define the rights and responsibilities of both parties.

The contract should also address financial matters, such as the cost of the study and the method and timing of payment. Certain unanticipated activities not directly related to the study may increase the cost to the laboratory; the contract should attempt to anticipate these events and establish reasonable incremental costs to the sponsor to deal with them. For example, study-specific inspections by agencies authorized to review a study (FDA or EPA) may add to the cost to the laboratory for additional staff time to accompany inspectors, copy documents, and otherwise field the inspections. If the sponsor wishes to be present at such inspections, additional direct costs will be incurred. Although many readers would view this simply as part of the laboratory's cost of doing business, the contract should anticipate how each party is expected to respond financially if the inspection becomes very time-consuming or onerous.

Likewise, poststudy activities and responsibilities should be defined in the contract. Who will archive tissue and other samples and specimens? For how long? If statistical analysis is to be performed, of what does it consist? Who decides? If further analysis appears desirable after evaluation of the data, will the sponsor incur extra costs? If a failure should occur, the details of how this is to be handled with regard to timing and cost responsibility needs to be addressed in the contract.

The Study Protocol

The study protocol is not the contract, and items that are to be placed in the contract have no basis to be in a scientific document such as a study protocol. The most important part of site visits to laboratories will be the discussion of the specifics of the study and establishment of the protocol. Extensive prior experience of the sponsor in conducting the contemplated study is very helpful although many elements may still have to be negotiated. If the sponsor has limited experience, the importance of the protocol increases, since it contains the specific language of the scientific and regulatory contract between sponsor and laboratory which governs the conduct of the study.

To write a protocol with little flexibility may preclude the study director's judgment and may actually compromise the quality of the study. Each party must feel comfortable that the study protocol provides sufficient detail to specify what is to be done, when it is to be done, and under what conditions it is to be done. However, the protocol must not be so rigid that the study director is hampered in responding to changing conditions and events as they occur during the course of the conduct of the study. Since unanticipated events almost always occur, the objective is to provide a protocol which permits the study to be conducted as closely as possible to the original

study plan, to answer all the important study questions and provide sufficient flexibility for the study director to adequately manage the study and not create a quality assurance and regulatory nightmare.

Other Terms

Authorship

The question of authorship of publications resulting from the proposed study should be covered in the contract and not the study protocol. Not all work is worthy of publication nor do contract laboratory staff often get an opportunity to author papers. But if the laboratory has contributed significantly to the work, and a publication is contemplated, help in writing portions of the manuscript should be solicited from members of the study staff, for which coauthorship is a deserved award.

Reports

The contract again and not the study protocol should specify the nature and frequency of reports which the laboratory will make to the sponsor. For example, a short-term study (2 weeks or less) may require only telephone confirmation of study start, status of the animals at the halfway point, confirmation of termination, and the usual draft and final report.

For a longer study, the sponsor may request written status reports at regular intervals. In the case of chronic studies the sponsor may wish to have formal interim reports prepared by the laboratory. The contract should clearly specify the expectations of both parties concerning reports.

Inspections by the Sponsor

Most contract laboratories do not like the thought of unscheduled site visits by study sponsors, for understandable reasons. Under ordinary circumstances, a large amount of staff time is spent escorting visitors through the laboratory. Unscheduled visitors therefore place an additional burden on already stretched resources.

Nevertheless, the right to monitor a study's progress at any reasonable time should be explicitly affirmed in the contract. This right, although perhaps never exercised by the sponsor, should not be relinquished. As a practical matter, unscheduled monitoring visits almost never occur, since the sponsor must recognize that the study staff may be unavailable at the time of the visit, making the trip a wasted one.

Likewise, the contract should explicitly grant the sponsor access to the laboratory's quality assurance (QA) inspection reports of the study. These reports are ordinarily

not available to government investigators, and some contract laboratories prefer not to share them. However, a sponsor should ensure that the contract grants access to the QA reports.

References

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FDLI (2010) Directory of Lawyers and Consultants. FDLI, Washington, DC

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Chapter 6
CROs in China, India, and Elsewhere in the Broader World: Outsourcing Science Gone Global

At the time of the preparation of the previous edition of this book, contract research organization (CROs) that supported the development of new drugs and medical devices were located in a limited range of countries: the US, Canada, Japan, Western Europe, and Israel. For any of a number of reasons, this is no longer the case.

There was previously (going back to the 1970s) a frequent desire to perform much first in human testing in Europe, largely driven by the fact that it was possible to get into human trials outside the US. Thus, there were a number of Phase 1 trial CROs operating to offer this possibility. However, in recent years (since the implementation of the EU Clinical Trial Directive), the speed to human advantage for Europe has disappeared.

Starting in the second half of the first decade of the twenty-first century, CROs have been appearing world wide. These organizations operate in almost all the areas of development support, with (currently) varying degrees of success. The major areas of operation include the following:

- API (Active Pharmaceutical Ingredient) Synthesis
- Toxicology
- Nonclinical Pharmacokinetics
- Formulation Production
- Phase 1 Clinical Studies
- Phase 2 Clinical Studies
- Phase 3 Clinical Studies

The development of these CROs reflects (1) improved technology, infrastructure, and capabilities in the various countries, (2) a desire to enter the health care R&D business sector, (3) a response to demand for both lower costs and (in the case of clinical trials) decreased costs and a larger pool of patients and (4) economic and financial opportunity.

S.C. Gad and C.B. Spainhour, *Contract Research and Development Organizations: Their Role in Global Product Development*, DOI 10.1007/978-1-4614-0049-3_6,

For US and European companies, the factors behind going to CROs in these new countries have been somewhat different (Berens and McCoy 2005).

- Lower pricing
- For nonclinical animal work, fewer animal rights complications
- To provide leverage to capture work in host countries that are also large economies (particularly China and India)
- Access to larger or new pools of patients or subjects for clinical trials with these

Potential advantages, however, have exposed a number of real or perceived problems

- Security/protection of intellectual property
- Regulatory (GLP, GMP, GCP) compliance
- Quality of work
- Logistics of monitoring work (level required, costs, etc.)
- Documentation of work and data
- Uneven levels of technical capabilities
- For clinical studies, unclear adherence to patient protection procedures

China

Accelerating investment and growth of CROs in China builds in momentum as multinational clients look to sell more medicines in the world's most populous country and at the same time cut development costs. Most of the world's largest drugmakers, and some of the smaller ones, have turned to local Chinese drug contractors with niche specialties and a cheaper pool of scientists to deliver less costly drug trials and to gain access to China's large pool of patients. CROs in China that specialize in late stages of research, including clinical trials, have an annual revenue of about $1.45 million, or less than 2% of the global CRO market. They are expected to expand at a rate of approximately 18% annually, with forecasts predicting an amount of $240 million by 2012. Hence, multinational CROs, including US-based Covance Inc. (CVD.N) and Charles River Laboratories International Inc (CRL.N) are aiming to be far bigger players in this country. China, India, and other emerging markets are expected to help offset tepid CRO growth in other parts of the world. However, Brazil is now seen as another emerging potent market.

China's CROs largely came into being after the country joined the World Trade Organization in 2001 and developed a drug regulation system under China's State Food and Drug Administration (SFDA). This increasingly competitive sector has at a minimum 138 CROs.

Beyond Chemistry to Toxicology

Over the years, Chinese CROs have focused on relatively inexpensive areas such as biology and chemistry – including screenings of chemicals to identify single entities

and combinations with potential as medicines. They have also performed a significant amount of work in the manufacturing API for generic drugs. Experts said an increasing number of CROs in China, local and foreign-based, are moving into more lucrative stages of the drug development chain. They include preclinical studies, such as toxicology and other animal research, as well as human studies (Anon 2010). James Foster, chief executive of Charles River, estimated that toxicology demand would surge "significantly" in 2010. "We would anticipate all the businesses we do in the U.S. and Europe we will eventually do in China," Foster said in an interview. His company built a new preclinical facility in Shanghai in January and was planning to build a second site in China. China's annual market for toxicology – studies that typically use animals and are designed to root out serious side effects of drugs early in the game – is worth about $20 million. But it may jump to $200 million in 5–7 years, said Joe Herring, chief executive of Covance. Covance's CRO business in China should be profitable this year, with revenue doubling in 2010, he said. With an abundant supply of nonhuman primates, and little animal-rights advocacy, China has become a favorable destination for animal testing. To sell existing drugs to China, multinational drugmakers are required to conduct additional testing to obtain local approvals (Ng 2009; Snyder 2010).

Why NOT Use a Chinese CRO? The #1 Response

"We think utilizing a Chinese CRO will put our program/project/compound at too big a risk." This is the Number One reason that Western companies cite for reluctance in leveraging resources in China for their Good Laboratory Practice (GLP) toxicology work. Most often, the concern is that the FDA or EMEA will reject a GLP toxicology study from China because it does not meet global regulatory expectations, thus forcing a repeat of the study at additional direct costs and significant delays. While this presumed risk seems to be reasonable, there is absolutely no critical mass of evidence that it exists. In fact, using a *top-quality Chinese CRO* to perform a GLP toxicology study puts a program at no more significant risk than using a Western CRO, and there are cost-effective ways to reduce that risk to a point where it is actually lower than that experienced in utilizing a Western CRO. What evidence supports that contention? (Bush 2010).

Track Record

- GLP toxicology data from Chinese CROs have been used to support more than 30 US INDs and a few NDAs since 2006. CPMS (China Preclinical Management Services) has monitored/conducted over 20 GLP studies at Chinese CROs, and data from these studies have been used to support 3 US INDs. Each of these INDs has been opened with no questions to date regarding the quality/validity of the GLP studies.

Audits in China

- Last summer, staff from the US FDA (which has now opened permanent offices in China) audited all the CROs that have submitted GLP toxicology studies in

support of INDs and NDAs. These were audits of specific GLP studies and of facilities. No studies in any of the audits were disqualified for any reason, including compliance, and only minor findings were reported in the 483s issued (some facilities did not have a single 483 issued).

Chinese vs. Western Technicians

- How do Chinese technicians rank in comparison with their Western counterparts? CPMS has been monitoring, conducting, and training Chinese CROs since 2006, and we believe Chinese animal technicians at the major CROs are top quality; they are unusually well educated, highly trained, and very committed to their jobs. To us they represent a major strength of the Chinese CRO system.

Keep in mind that there is a high degree of physiological and biological similarity across various mammalian species. The key goal of preclinical safety evaluation is the assessment of potential toxicity from exposure and reversibility of any lesions, and it is often possible to assess with reasonable certainty whether animal toxicity findings are relevant to humans. Reproductive toxicity and carcinogenicity studies in animals provide vital information. However, remember animal tests are not the ideal nor perfect predictors of the human hazard of new drugs. The problem of extrapolating the results of animal tests to humans is complicated by the subjective nature and substantial inherent biological variability associated with many animal tests. Many drugs react differently in humans than they do in animals. Aspirin causes birth defects in rats, mice, cats, dogs, guinea pigs, and monkeys but is considered safe for pregnant women. The arthritis drug, fenclozic acid, causes liver toxicity in humans but not in rats, mice, dogs, monkeys, rabbits, guinea pigs, ferrets, cats, pigs, and horses. Thalidomide produces birth defects in humans but not in mice, whilst cortisone works the other way around; penicillin is highly poisonous to guinea pigs and hamsters; insulin causes birth defects in animals but not in diabetic patients. There is only a 66% correlation between rat and mouse carcinogenicity tests. So to be fair, keep in mind the fact that study-to-study differences can be a consequence of biological variation or technical performance variation or both.

Good Laboratory Practice

In drug development, GLP provides the framework within which laboratory (regardless of location) studies are planned, performed, monitored, recorded, reported, and archived. In 1981, the Organization for Economic Co-operation and Development (OECD) finalized its Principles of GLP. The OECD and EC (EC Directive 1999) require the establishment of national compliance monitoring programs based on laboratory inspections and study audits and recommends the use of the OECD Guides for Compliance Monitoring Procedures for GLP and the Guidance for the Conduct of Laboratory Inspections and Study Audits. The harmonized ICH safety guidelines define the circumstances, duration, and types of toxicity studies on new medicinal products. These recommendations take into account the known risk factors

as well as the intended indications and duration of exposure. An organization is either GLP (International) compliant or not, there is no in-between. International GLP compliance and a history of it should provide at least some confidence in the organization performing the work, regardless of location.

GLP in India

India has recently joined the OECD GLP Committee as an observer and has set up a national GLP compliance authority under DST (The Department of Science and Technology). India should move to full membership of the OECD GLP and ICH and amend its law to require GLP compliance and inspection of its testing laboratories as a condition of approvals of all medicinal products. Many Indian laboratories have obtained certification and inspection by the Indian National Accreditation Board for Laboratories (NABL), which provides a certificate valid for 3 years after inspection.

India

The 2004 amendment to the law allowing toxicology testing with NCE/NME discovered abroad and the importation of standard animal models has served to attract ethical companies to contract out animal studies and cast favor of investment in toxicology labs working to attain international GLP standards (Kumaravel and Murugan 2009).

Most of the Indian toxicology laboratories seem to follow the OECD protocol, which is available from the public domain. However, there are toxicology laboratories in India, which can meet the GLP requirements of FDA/EMEA in the performance of toxicology studies of new drugs. Indeed, there is one good laboratory dealing mainly with agrochemicals, which claims to have performed over 80 studies for foreign clients and passed GLP inspection from some European agrochemical and environmental regulatory authorities, but does lack experience in dealing with the ascertainment of drug toxicities.

There is a lack of trained and experienced animal histopathologists to detect early signs of drug-induced toxicity like cardiotoxicity, nephrotoxicity, hepatotoxicity, neurotoxicity, and immunotoxicity. The growth of quality clinical pathology laboratories in India, approved by USA based College of Pathologists is limited but growing. The costs of some Indian laboratories are relatively (compared to Chinese labs) high for rodent studies, and the work may be considered GLP in India but is essentially non-GLP when compared to the international standard.

There is a tendency to issue clean reports for local registration, by excluding diseased, dead, and out-of-range animals, leading to overestimation of safety and underestimation of toxicity. The upgrading of facilities for animal housing, feeding, and care will require major long-term investment, continuous training of personnel, and very high standards of animal care and cleanliness.

Guidelines and rules by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) in 1998 and revised in 2000 require a central approval by CPCSEA for all experiments on large animals (dogs, monkeys, pigs). Indian laboratories need to implement a comprehensive health program with regular and routine monitoring of experimental animals for the presence of common pathogens including bacteriology, virology, parasitology, and gross pathology to detect any breaches in health or genetic integrity of animals (Maggon 2004).

The toxicology laboratories in India should pay close attention to the bioanalytical and drug assays needed to meet GLP standards. The analytical methods development for drugs in animal biological fluids and tissues and their validation is a long complex process, which requires trained and qualified staff and sophisticated instrumentation like a mass spectrometer. Most bioanalytical methods requiring the use of LC-MS/MS, IT-MS and SPE take considerable time even for a highly trained scientist to develop and validate. Solid phase extraction of drugs where the concentration in biological fluids is in the low nanogram per milliliter range is a highly demanding task, and there are cases where the samples from the same animal are repeated to save on the cost of solid phase extraction cartridges.

The repeated use of items intended to be single use is still very common in India. Several analytical laboratories doing toxicology studies lack trained and experienced staff, invariably produce positive results and assay validation as routine work within a record time and may not pass an international analytical audit. Strict certification, audit, control, and regular annual inspections of all toxicological, pharmacology, drug metabolism, and animal PK laboratories using animals for research are required.

Until recently, Indian law made it illegal for any Indian toxicology laboratory to test NCE/NME discovered abroad. However toxicology studies have been and are still being performed for foreign sponsors.

Other New Entrants

The countries that newly host GLP toxicology laboratories continue to grow, as a simple inspection of the entries in Appendix I will show.

While Brazil, Korea, Singapore, and Australia are on the list, eastern and central European countries are almost all now represented. Of the estimated 1,100+ CROs (nonclinical and clinical – about 70% clinical) worldwide, only a few are yet existent in any of these other countries.

Problems and Solutions

As pointed out earlier, a number of problems are attributed to work performed by newly opened labs in various countries.

A number of these problems are common with new labs, pigmented by cultural differences between existing labs (and first world regulatory agencies) and new entrants to the CRO field.

The best solutions are of course to

1. Only deal with labs which have some track record of performing studies and submitting reports to the FDA and EMA
2. Perform extensive and thorough qualification audits
3. Secure references for previous work if possible
4. Pay careful attention to the structure of protocols and SOPs
5. Look closely at the training program
6. Scrutinize project management techniques
7. Evaluate the potential for good, effective, solid, and timely communication. So many problems and disappointments occur because expectations have not been adequately communicated on both sides
8. Have long-term on-site oversight (monitoring) of phases of studies conducted at such facilities

Opportunities exist if the opportunity is managed properly. Take for example the United States, which has been performing GLP studies for nearly 40 years. A study of public records indicates that organizations in the United States still are not perfect in GLP. So why should one expect an entity with less experience to not require guidance and time to get up to standard?

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Chapter 7
Contracting, Pricing, and Cost of Works Performed by CROs

Once a source is selected to perform a body of work under contract, a great deal of effort still remains for the sponsor or sponsor's agent before work can be actually initiated, and more still before the desired product is in hand. At the front of this process is the development of a contract that ensures that the desired work will be done and that the final product will meet your needs and expectations.

As a starting place, consider a few "rules" that any contractor should adhere to. A vendor or consultant should:

1. Provide open, detailed, realistic costs, dates, and number estimates to the client or potential client.
2. Do whatever is possible to establish and maintain a positive, open, and honest relationship with each client.
3. Be proactive about providing information and suggestions to help a client enhance the quality or speed of their work.
4. Appoint a primary contact person to interact with each client. This needs to be a single person and not a group or multiple individuals.
5. Do whatever is necessary to meet one's time and cost commitments.
6. Provide the highest quality product possible given the time and cost constraints.
7. Provide all services required and be willing to go beyond the strict limits of the contract to ensure that the client is pleased with the services and expectations are met.

At the same time, both parties must be particularly vigilant for scope creep – either the addition of expected work to a project with no explicit agreement to pay for some, or the addition of costs and billing to a project without the client clearly being advised as to the fact and of totally new cost expectations.

With all this fresh in mind, careful consideration can now be given to key areas.

S.C. Gad and C.B. Spainhour, *Contract Research and Development Organizations: Their Role in Global Product Development*, DOI 10.1007/978-1-4614-0049-3_7,

Costing/Pricing

Probably the first component of a contract to be addressed is the cost of the work. Indeed (as presented in Chap. 5), this is almost always a part of one's consideration in the process of vendor selection. But the need to be clear and precise in what is expected from a contractor does not end with the selection of the same in the bidding process. From this point, an agreement and/or contract must be developed. If a protocol is involved, it should also be considered as a significant part of the specifications of the work.

We live in a time when social concerns over the growing impact of technology on our environment and our ultimate well-being erupted into positive political action leading to a new array of laws and regulations. This of course is a bonanza for attorneys, who, in customary unbeloved fashion, have proceeded to establish themselves as indispensable participants in defining and resolving new fields of conflict, fields about which their knowledge and experience is significantly lacking. Quite obviously, it is also a bonanza for bureaucrats, who have inherited a Solomon's mine of new power and jurisdiction from which they have already produced considerable gold-plated gobbledygook along with a veritable waste dump of semantic sludge.

But lawyers and bureaucrats have not been the only ones to find prosperity in these new laws. They have served to increase demand for well-educated toxicologists and other scientific professionals, to whom we must all look for answers to so many questions and whose services are therefore in such marked demand. The current (late 2010) economic situation aside, this will undoubtedly continue for the foreseeable future.

Some people continue to battle what they regard as the "nonproductive nature of all this activity and expense," even while reluctantly accepting it as a fact of contemporary business life. Certainly the impact of the environmental era is making it harder for some businesses to make money, at least in the short term. Certainly the additional costs of regulatory requirements ultimately add to the cost of goods and are aggravating our vexatious inflation problems. Certainly the social cost is compounded by the huge new bureaucracies that this movement has fostered. But a purely materialistic balance-sheet concept of productivity seems far too narrow. If productivity is defined more generously to include the objective improvement of everyone's health and safety, then the great surge of concern over health and the potential hazards of drugs are very productive indeed.

In all events, it is clear that lawyers, investors, managers, and scientists must learn to deal productively with each other if the problems of the environmental era are to be resolved in a positive fashion for everyone involved. This means that they must communicate effectively and resultingly completely understand each other. In the interest of such understanding, and before passing to a discussion of some practical legal issues, it will be useful to mention one dichotomy that frequently gives rise to confusion, failure of communication, and sometimes outright antagonism between lawyers and scientists. We are referring to the difference between "scientific fact" and "legal fact."

This dichotomy arises from the different basic objectives of the two disciplines. The objective of science is the pursuit of knowledge about the physical world in all its attributes. The objective of law, however, is the minimization and resolution of disputes. To the scientist, a "fact" is a particular aspect of objective reality; to the lawyer, a "fact" is simply a state of knowledge that is adequate to support the interest of the client in a particular dispute. For example, toxicologists are typically extremely interested in the mechanism of genetic mutation as an element in understanding the biochemistry and molecular biology of carcinogenesis. They want to know objectively whether a single dose or a few doses of a new drug can induce a cancer or whether the mechanism requires some threshold of concentration or duration of exposure. The question has enormous practical consequences, but scientists are fundamentally interested in finding out the truth, regardless of the consequences. The lawyer is also interested in scientific truth, but will seldom be objective about it. For example, in the case of a pharmaceutical manufacturer whose business would be wiped out by a "zero tolerance" rule, the lawyer's take on things will be to try to persuade the court or agency that there is in fact a "no-effect" level within which the client should be allowed to operate. If representing a "class" of possible injured patients who would like to see a specific drug or class of drugs taken off the market, the lawyer will now argue that the single-molecule concept is in fact correct and not a threshold or level. If doubt must be conceded, the lawyer will still argue that the theory most congenial to his of her client's interest is the more likely. In short, there would be no hesitation to build arguments in support of the client's desired conclusion and to ignore or explain away any contrary views, which is the very opposite of the scientific method. Furthermore, if the trend of objective scientific research seems to be running against the argument, the lawyer will often mount a rearguard action to postpone as long as possible the legal recognition and acceptance of this adverse scientific reality. To attorneys, the law and fact is what and how they can twist and contort it to leverage their own position. To scientists, laws and facts are what they are, proven experimentally and only changing when errors are discovered.

Of course, this is possibly an unfair oversimplification of the lawyer's role. In practice there are ethical constraints on the lengths to which counsel may go in advocating the client's cause, and sophisticated clients will seldom want their lawyers to fight to the bitter end at the cost of adverse publicity and a poor public image. Nevertheless, the lawyer dealing with a scientific issue will frequently dispute the fact which a scientist regards as settled. Attorneys also will attempt to eradicate the value of a scientific fact with some trivial ancillary distraction that really bears no actual weight on the issue at hand. Attorneys and scientists should understand that their choices in career paths dictate differing roles may which compel differing views of reality, at least over the short run.

So much for philosophy and generalities on this topic. Let us pass now to some more important specific legal issues that toxicologists are likely to encounter in their work, first in relation to research contracts and second in relation to their regulatory responsibilities.

The Contract

The enormously increased demand for contract research and development has produced a corresponding increase in research contracts. Companies of small and medium size generally do not have the technical or financial resources to conduct in-house development efforts such as preclinical safety studies, while even the larger companies often elect to farm out at least a part of this work. By their nature such arrangements are likely to involve highly sensitive issues, which may have economic implications far beyond the cost of the research itself. Contracts of this kind should be negotiated by a team of lawyers and scientists who have a thorough understanding of the problems to be investigated, including both the scientific issues and the potential business implications. If the research is to pursue a specific, predefined problem, such as evaluating carcinogenicity, as distinguished from a general screening program, such an understanding is particularly important.

Contracts are promises that the law will enforce. The law provides remedies if a promise is breached or recognizes the performance of a promise as a duty. Conflicts arise when a duty does or may come into existence because of a promise made by one of the parties. To be legally binding as a contract, a promise must be exchanged for adequate consideration. Adequate consideration is a benefit or detriment that a party receives that reasonably and fairly induces that party to make the promise/contract.

A point worth mentioning here is that for many people, contracts are binding instruments of understanding governing behavior and conduct involved in a specific area of concern. However, there is a not insignificant number of individuals out there who view contracts merely as necessary hurdles to clear in the course of doing business. These special people have no intention of complying with any contract that they sign and will do what they will. Their attitude is that contracts are nothing more than feed or slop for the attorneys to banter over. Although not recommended, contracts are not truly necessary if dealing with completely and totally honest people. Contracts can be truly valuable instruments to document expectations of both sides. In the course of contract negotiation, try to assess the level of commitment of the "alternate" party and if a sense of lack of long-term honoring of the agreement is not there, perhaps it is better to take a different approach to a solution.

Contracts are mainly governed by state statutory and common (judge-made) law and private law. Private law principally includes the terms of the agreement between the parties who are exchanging promises. This private law may override many of the rules otherwise established by state law. Statutory law may require some contracts be put in writing and executed with particular formalities. Otherwise, the parties may enter into a binding agreement without signing a formal written document.

In our experience, good contracting is a result of three components: legal expertise, subject matter expertise, and common sense. Assuming a modicum of common sense and a substantial understanding of the subject area of the contract, presumably contract law is the only area for which the RA (regulatory affairs) professional needs knowledgeable guidance. Most of the principles of the common law of contracts

are outlined in a compilation entitled *Restatement Second of the Law of Contracts* published by the American Law Institute. The restatements are an attempt to organize (restate) common law rules in selected broad areas (e.g., agency, contracts, conflicts of law, etc.). Restatements do not reflect statutes, which can alter common law rules and principles. Restatements are secondary authority, not law, but they are drafted by respected scholars, attorneys, and jurists. They are useful as research tools and study aids.

Of greater importance is the Uniform Commercial Code (UCC), whose original articles have been adopted in nearly every US state. The UCC represents a body of statutory law that governs important categories of contracts, so it should be consulted whenever an issue arises. The UCC, Article 2 regulates every phase of a transaction for the sale of goods and provides remedies for problems that may arise. It provides for implied warranties of merchantability and fitness. There is also a duty of good faith in the UCC that is applicable to all the sections.

The RA (regulatory affairs) and product safety professionals routinely enter into the contracts themselves as well as their negotiation, or review draft contract proposals, related to a wide range of goods and services necessary to develop and commercialize a regulated product. These include confidentiality agreements, and service agreements (e.g., contract manufacturing, raw material purchases, consulting agreements, clinical research organizations, clinical investigator agreements). It is essential that the RA and toxicology professionals understand the essential elements of contract law (offer, acceptance, consideration, breach, remedies, etc.) as they relate to the technical aspects of their particular industry and the specific scope of the contract. The effort these professionals should invest in properly drafting or reviewing a contract is directly proportional to the criticality of the product or service to be provided. Like regulatory submissions, poorly drafted contracts can significantly affect the regulatory timetable and delay product commercialization, resulting in lost market opportunity. In particular, pay close attention when specifying the goods or services expected from the vendor. Whenever possible, tie deliverables to well-recognized and ascertainable standards (GLP compliance, cGMP compliance, GCP compliance, etc.). Vague, unspecified or imprecisely defined standards often result in a legally binding agreement that is hard to enforce and totally unsatisfactory deliverables.

Part of the job is to educate the lawyer about the nature of the work, including its limitations. The lawyer needs to know, for example, the extent to which test instruments and procedures are reliable and must have a grasp of the statistical presumptions and methods so that the contract can be approached with these parameters in mind. Do not assume that your attorneys are incapable of assimilating a good knowledge and understanding of the scientific issues. Their job requires them to become experts *pro tem* in such matters whenever they have legal relevance. Any competent lawyer should be able to understand and talk the language of toxicology and research with appropriate instruction. Many companies have sought out lawyers with appropriate technical backgrounds to make this process easier and more dependable.

Armed with this technical understanding, the attorneys can then proceed to develop a contract that is relevant to the situation. For a low-risk, uncomplicated job, they may suggest a relatively simple letter agreement with a minimum of verbiage.

They might even be willing to go along with an oral understanding if the issues are very simple, but this will be rare and depends upon the parties involved. For a more extensive project on which substantial economic interests are riding, they will undoubtedly propose a very thorough and definitive agreement. Much of the language will be routine or "boiler plate," the type commonly found in agreements of various kinds. Other clauses may be addressed specifically to the special situations of research contracts. What are some of these special problems?

Purpose and Description of Work

The basic purpose and end goals of the project should be described carefully in the contract with sufficient breadth and detail as to ensure that the researchers do not overlook something because of an inadequate understanding of the context. While some contracts may call for "pure research" and be concerned only with the objective development of new data or information, most projects, particularly from the private sector, will have one or more very pragmatic objectives that are specific to the business purposes of the sponsor. These purposes may well affect the design and scope of the research project. For example, a pharmaceutical company may be looking for a more effective antiviral agent for use in the HIV therapeutic market. By this the company may mean that the new agent must be biologically effective for a broader range of patients, be effective in a smaller dose than the current agent, have a longer shelf life when combined with the other ingredients of the product, or have a lower incidence of side effects. Any one of these factors might justify the use of a new antiviral and could be the objective of contracted research, but it is obvious that an antiviral with more than one of these qualities would be even better. Researchers should know about these advantages so that their work can be designed for maximum usefulness and synergy with other research on the same general problem.

Of course, the sponsor may be concerned about confidentiality and may therefore want to limit the extent of the research's knowledge and involvement. A producer might be aware of some emerging side-effect problem with the drugs currently on the market. Obviously, this kind of balancing is for the sponsors to decide, but they should remember that researchers working with blinders on may overlook some collateral problems and opportunities if their efforts are too constrained.

In addition to identifying the purpose, the contract should also identify the research methods that are to be employed. In some cases the method itself may be a subject for research, but in most situations there will be at least a general understanding of the work to be done. This should be spelled out, along with any limitations or variations from normal practice. Specific research protocols found in the literature may be adopted by reference, or the sponsor and the researcher may jointly work out a protocol of their own. There must be absolutely no ambiguity about what the researcher is called on to do as well as the anticipated results.

Time Frame

Much development research is mandated by various regulatory agencies such as the FDA, and marketing of a product or reaching a milestone associated with payments from partners or investors may have to await the results. Thus, companies will frequently insist that time is of the essence, that the researcher must meet the stipulated timetable or be liable for damages or forfeiture of fees. Faced with such a clause, the researcher will want to be sure that he or she can in fact meet the deadlines.

Regulatory and Judicial Proceedings

Toxicological research data and results will often be of key importance as evidence in regulatory proceedings or in lawsuits. Hence, it is important that the work product, or at least key parts of it, be reflected in documents and records (written and/or electronic), which will be useful for this purpose. A brief overview of the applicable rules of evidence may help one understand this. These are procedural rules that are applied quite strictly in the courtroom and somewhat less strictly in administrative hearings. Basically, a document that purports to contain information that is relevant to the issue at hand cannot be admitted as evidence without first being authenticated. This means that a live witness must testify from personal knowledge that the document is genuine and that the information is in fact what it purports to be. The live witness might be the research scientist who actually produced the report or it might be a higher-echelon person under whose supervision the work was done. Whoever he or she is, the live witness can expect to be the subject of intensive cross-examination, first in an attempt to show that the document is not admissible as evidence and then, if this fails, in an attempt to discredit the methods, the results, the conclusions, and indeed the competence of the researcher.

Needless to say, this can be a very stressful and unpleasant business, particularly if the document is ambiguous or incomplete or if the witness has not done the necessary homework. It can also be very time-consuming. Hence, the research contract should spell out the understanding with regard to the use of researchers as potential witnesses. Typically, the contract will require the research institution to supply an appropriate person or persons to testify for the purpose of authenticating and defending documents reflecting the work done. Such appearances are usually made at the expense of the interested party, including a reasonable *per diem* or other fee and the reimbursement of expenses. If special preparation for the appearance is anticipated, the contract should indicate whether this time is subject to special reimbursement.

Incidentally, the courts and agencies are not limited to final reports to the client in their search for relevant documentary information. It is entirely possible that research notebooks, reports of internal meetings, diaries, e-mails (personal and company), and even informal scratch notes may be requested and scrutinized. CROs, like business corporations, should therefore develop carefully designed record management

programs to control the creation and maintenance of formal and informal paperwork. The destruction of relevant documentation for the purpose of keeping it out of court can be a criminal offense (ask ENRON or Arthur D. Anderson). Consequently, it is important to limit the information that becomes part of the written record and to establish and observe a general record retention and destruction policy and schedule that will justify the routine weeding out of nonessential records.

For similar though not identical reasons, the contract will usually require the researcher to retain samples of testing materials, feed samples, histological specimens, and the like. These do not usually find their way into the courtroom, but may be critically important in confirming the accuracy of challenged data, rebutting allegations of misfeasance or faulty diagnosis, or accomplishing similarly constructive purposes.

As to retention period, it is almost impossible to be too conservative. The longer the better, not only to satisfy regulatory agencies and requirements but also to help establish a solid defense against future damage claims. Unfortunately for manufacturers, the statutes of limitation on claims for breach of warranty and negligence often do not begin to run until the damage or injury occurs. Thus, companies have been held liable for asserted defects in drug taken to market decades before the damage or injury is discovered. Since both drugs and devices are an easy target of such claims, proof of adequate toxicological research can be of great defensive importance. Generally, the sponsor of a project should want samples retained for a substantial time (10 years or more), and researchers will generally share this desire in order to minimize their own potential exposure.

The long-term retention of documents and samples creates obvious storage problems and their associated costs. Document retention can be minimized by the disciplined use of microfilming or PDF techniques. For almost all legal purposes, a properly made and authenticated microfilm copy is equivalent to a paper original. Sample storage is a more difficult matter. The main legal problem is to be absolutely sure that each sample can be properly identified and authenticated for possible future use. Procedures for cataloging and retaining samples should be carefully worked out and scrupulously followed. This is not a mere clerical or managerial responsibility; it calls for careful and continuing management attention. Storage conditions (environmental) themselves cannot be ignored as well as security.

Reports

Depending on the nature and extent of the research, the contract will include provisions for reports of various kinds. Progress reports will usually be appropriate if the work is complex and extended, and a final report is routine. The parties may or may not wish such reports to include editorial matter or commentary on the results.

This raises a very difficult and potentially sensitive problem area, namely the extent to which the sponsor should be entitled to review, comment on, and edit proposed reports before they are issued. Sponsors will generally require a review of a

draft report, and will often react with questions, comments, and suggestions for change. They may also want the opportunity for informal discussion of the draft report and the data and results on which it is based. There is nothing inherently wrong with this, but if the work relates to product safety and is being performed in the context of present or anticipated regulatory involvement, the parties should be extremely careful to preserve the fundamental integrity of the final report. The right to review and offer comments should never be constructed as a right to censor or suppress. This has become quite the area of concern with the FDA of late. It appears that the FDA's position is that subcontractor reports (veterinary cardiologist, veterinary ophthalmologist, bioanalytical, etc.) are to be finalized with no input from the sponsor or the study director. The study director then writes the final report with all of this information with no input from the sponsor. This is foolish, because the true expert in any research or development project is the sponsor. So with this approach, good science is the true loser. Until this matter is completely resolved, one needs to make sure that EACH AND EVERY step along the way to the production of the final report is heavily documented showing changes made, when they were made, by whom they were made, and for what reason they were made to demonstrate to the agency that no collusion or misrepresentation of facts has occurred.

It is easy to believe and affirm that no ethical businessman, attorney, or scientist would tolerate or encourage the suppression or distortion of research results. It is less easy to apply this faith in a specific situation, which may involve large gray areas concerning the reliability of test methods, the adequacy of samples, the significance of an occasional anomalous result, and the subjective assessment of results as a whole, not to mention the semantic nuances that can arise in the process of articulating all these issues. Because we are human, we tend to see what we want to see and to find what we want to find, if there is any room at all for doubt or more favorable alternate interpretation. The legal danger lurks in the possibility that editorial changes in a research report may be influenced, at least subliminally, by considerations of self-interest.

There are several ways to minimize this problem. First, and perhaps most obvious, the contract may simply provide that the sponsor shall have no right of prior review. Unhappily, this deprives both parties of the opportunity for legitimate synergy and may simply be unacceptable to the sponsor. Second, the contract might provide expressly for review and comment by the sponsor but affirm the researcher's right to control the form and content of the report. This is a good approach, provided the parties do in fact observe the contract.

A third technique is to apply what might be called the "future appearance" test to the editorial process and its end result. The test can be posed as two questions:

1. Do any of the editorial changes involve a matter that, with the benefit of future hindsight, could be viewed as having material significance in the context of any presently applicable health or safety law or regulation or reasonably foreseeable health or safety problem?
2. If so, do the changes tend to lean toward avoiding or obscuring a potentially adverse condition?

If the answers to both questions are "yes," the changes that produced these answers are vulnerable to future criticism and should probably be omitted or modified.

Note that the first question calls for a deliberate effort to view present events from a future perspective, because that is the way our present judgments are being judged in the context of health and safety regulation.

An example may help to clarify this concept. Suppose you are engaged in some rabbit-feeding studies to determine the oral toxicity of a submitted compound. At a certain point in the studies, several test animals die. Autopsy discloses gross liver damage, which is not encountered in the remaining test animals, all of which live considerably longer. You discover that an inexperienced technician may have inadvertently contaminated some of the feedstock given to the animal that died early, but you cannot prove this. There is no other obvious explanation for the early deaths. The size of the study is such that the anomalous deaths are of minimal statistical importance. Nevertheless, you decide to mention the early deaths and the liver damage in your final draft report and to include the deaths in the statistical data base. Your sponsor then suggests that since the early deaths are clearly anomalous and do not affect the general conclusions of the study, it would be preferable that they be omitted from the report.

Applying the future appearances test, it seems clear that if other studies were later to confirm that liver damage is a potential side effect of the ingestion of this compound (perhaps in animals other than rabbits), it might be said, with benefit of hindsight, that your anomalous results were in fact significant. It is also clear that the requested deletion of these results would tend to minimize or discount their importance. Hence, both questions are answered affirmatively. One should reject the proposed deletion. The anomalous results should be included for what they may be worth.

If, on the other hand, the sponsor had simply requested the addition of a footnote explaining your suspicions concerning contaminated feed, this would not tend to avoid or obscure a potentially adverse conclusion. Hence, your answer to the second question would be "no," and the requested addition would be acceptable.

Innocent Mistakes and Culpable Tampering

A related issue, though not strictly a contract matter, is what to do when it is discovered that someone has made a significant mistake in the course of the study or has perhaps even fabricated or tampered with the results. If the work is not yet public and is not part of a submitted or approved regulatory program, it may be possible to make corrections without announcement or publicity, provided a complete record of the situation is maintained. However, if the study is part of a submitted record or an established compliance program, the best course will be to "fess up" promptly and completely candidly, with an offer of full collaboration in any resultant investigation or necessary follow-up. This is embarrassing and could have serious legal consequences, but delay and/or cover-up can only make things worse. Remember, one typically in such situations has only one chance at saving one's integrity and credibility, so behave accordingly.

Communications

One of the most important problems to be addressed in a research contract is communications. No matter how competent and sophisticated the work, its value will be reduced or even lost if its significance is not properly communicated to and understood by the sponsor. This is particularly true with projects whose shape and direction involve some subjective judgment or "art" on the part of the researcher. If the implications of a judgmental decision are not made known, the sponsor may be deprived of important information for the evaluation and utilization of the results.

Therefore, the contract should specify the frequency, method or methods of communication, the timing (if there are to be interim reports), the circumstances, if any, in which a special report may be appropriate, and the channels through which communications are to be made. Specific contact points should be well defined. Each project will have its own specific needs, but generally speaking, the broader or more loosely defined the methods and objectives, the greater the need for ongoing close communication between the parties.

Since scientific issues and judgments will invariably be involved, the sponsor should designate specific scientific personnel in its organization as the initial recipients of reports. It is not uncommon to designate a manager for each project, with responsibility to receive all reports, communicate as appropriate with the researcher, and distribute the reports within an organization.

The communication of new information can have important legal implications for both parties. The researcher will have a duty to report any significant adverse results or effects as promptly as possible, because actual knowledge of such things may trigger a reporting responsibility on the part of the sponsor, either under FDA or under some other regulatory body's requirements on a common-law duty. For this reason, it is critically important to maintain a good record of all communications on ALL matters and especially those of potential significance. In addition to copies of written reports, it may be appropriate to maintain copies of all e-mails, a log of telephone or other oral communications, and a record of any meetings between the parties. The phone log can simply be a record of calls made, giving date, time, and names of the communicants or participants. If the project is likely to produce sensitive interim information, it may be wise to go further and include a brief synopsis of the conversation. The same options apply to meeting records.

This raises a difficult policy question for both parties. If they elect to keep separate records, there is always the chance that the two records may be inconsistent in some important respect. This could produce embarrassment in the future. One needs to work in such a way as to think of oneself being in court at some point and use that perspective to decide how to handle a given situation. On the other hand, if the parties decide to maintain a single record of their communications, the editorial dangers discussed earlier will obviously be raised.

Whatever the record-keeping protocol, it is a good idea to be consistent when following the agreed procedure. Variations from a customary pattern are favorite clues for hostile lawyers to find evidence of malfeasance, nonfeasance, or cover-up. Nothing is more intriguing and suspicious than a hole in a file at some critically important time.

The problem of communication also embraces some very difficult judgmental questions for the researcher whose work uncovers some new and perhaps significant information. What constitutes a reportable event, and when should it be reported? The basic standard is one of reasonableness and good faith. For our purpose, reasonableness will be judged in relation to your scientific expertise and sophistication or the "reasonable scientist" test. If it would be reasonable for a competent scientist to believe that the development is materially significant in relation to the regulatory purpose or some other legal issue, it should be reported to the sponsor, even though you yourself might not share this belief. If, in good faith, that scientist does not believe that the development is significant in this sense, it need not be reported immediately, although it may become a part of some later routine report. However, relationships are best maintained if full disclosure is maintained on a timely basis.

Proprietary Rights

If the research is of such nature that original methods, techniques, or equipment may have to be developed, the contract should deal with the problem of ownership and right of use. Generally, parties who pay for the research will want to own any resultant inventions, although they may be willing to give shop rights to the researcher for applications that are not adverse to their particular interests. A research company may be reluctant to surrender the right to further use of its own inventions. Obviously, these situations should be addressed in the contract. The final result will depend on the negotiation itself. Even with a well-drawn contract, difficult problems can sometimes arise in the problem area.

Confidentiality

Every research contract should include a clause dealing with the use and disclosure of proprietary information. The first, often difficult step is to define what is meant by proprietary information. Although many judicial decisions attempt to define this term, the peculiar nature of research will often justify a carefully drafted contractual definition based on the specific situation. The clause should cover both information supplied to the researchers by the sponsoring party and information developed by the researchers in the course of their work. The party supplying data will want the broadest possible definition, usually one that attempts to cover all submitted information regardless of whether it is actually proprietary or a trade secret. Researchers, on the other hand, should be careful not to accept an excessively broad clause that might seriously hamper their legal or ethical responsibilities.

A very common traditional approach is to restrict the use and disclosure of all submitted information except in three specific categories: (1) information known to disclose prior to disclosure, (2) information properly available to disclose from another source and without restriction, and (3) information in the public domain.

Despite its popularity, this approach can pose problems for parties involved in research because the traditional language does not adequately protect a party's rights with respect to the future fruits of ongoing or incipient projects. For example, if a research organization has begun a line of inquiry that may lead to valuable new information or methodology, the receipt of related data from another party under conditions that restrict its use may restrict the freedom of researchers to pursue their preexisting inquiry along its logical path. For this reason, each party to a proposed research agreement should carefully review his or her then-current activities to determine whether the confidential receipt of information would be likely to cause any problems with other projects. If a problem is foreseen, the lawyer may be able to draft contract language to reduce or avoid the difficulty. The confidentiality clause should also cover such questions as mandatory disclosure to government agencies, limitations on the persons within the contracting organizations who will be allowed access (frequently limited to those who have a "need to know"), and limitations on publication rights, if any. If there are to be subcontracts, the confidentiality clause should be extended to cover the subcontractors.

In conclusion, it should be clear that there is almost no such thing as a routine research contract and that an adequate contract demands close cooperation and mutual understanding between the attorneys and the scientists involved and any other ancillary personnel (e.g., management, marketing, etc.). The contract may end up looking simple and commonplace, but its underlying homework should always be thorough.

Ethical and Legal Problems of Regulatory Disclosure

It should be obvious by now that many scientists involved in research may need help in understanding the legal aspects of their position. There is nothing wrong with using a company's law department or legal counsel as a first recourse, but bear in mind that they represent the employer, not the individual researcher. While such an option is possibly financially attractive, it may not provide the best outcome. These points remain, ultimately, personal ethical issues to resolve.

Chapter 8
Monitoring Ongoing Studies and Work

The General Rule

Always remember that working with a CRO (and indeed the CRO staff) is not a statis relationship. CROs are constantly growing and evolving to respond to the priorities and demands of research and the concomitant fundings (Vora 2006) that shift and change over time (Underwood 2001). CROs should and need to be audited by clients on a regular basis. Annual qualification visits are preferred, but typically most CROs can expect client visits once every 2–3 years. Additionally, many sponsors opt to schedule visits that coincide with important study milestones.

During these visits, expectations can be reviewed, modified if necessary and CRO records evaluated. Sponsor veterinarians, research directors, quality assurance personnel, management, and regulatory affairs professionals are typically involved with making ongoing assessments of the performance of a CRO. Specific subjects to address during these visits and assessment include any significant changes to the CRO staff, the quality of data and communication, as well as regulatory or accreditation compliance issues:

- Review any significant changes in organizational structure. Review personnel training records. Specifically, have individuals directly involved in contracted studies been appropriately trained? Is there significant turnover in the technical, veterinary, and/or scientific staff? Are the training records comprehensive, containing the appropriate information, and indicative of a rigorous training program?
- Review the quality of the data and status of the generation of the data. Are the raw data from current or finished products complete and of the appropriate quality? In addition, do they comply with applicable regulatory requirements, and do they accurately reflect information shared with the sponsor when compared to previous reports and correspondence?

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- Review of incident reporting and communication. If any adverse incidents arose during study conduct, determine if they were appropriately handled and reported to the sponsor in a timely manner.
- Review adherence to regulatory mandates and AAALAC accreditation. Determine if there have been any changes in the CRO's AAALAC accreditation status. In addition, request to review any reports that were based on inspections by regulatory agencies (e.g., USDA, FDA, EPA) while sponsor work was being performed.

Study-Specific Monitoring

Once work is initiated at a vendor, steps must be taken to ensure the progress, quality and conformance with the protocol, and the regulatory requirements of the work performed. This is achieved by an active program of monitoring of the ongoing work. Such monitoring can be performed either by client employees or by contract monitors, but those conducting such audits must have the suitable skills, experience, and knowledge to successfully serve this purpose. The earliest text on the subject that we are aware of (Gralla 1981) is still valuable though now significantly dated.

Such a monitoring program should be viewed as important and priority and be planned and scheduled in advance, and as such must be considered an integral part of the project and its success. While for purposes of example the case of a toxicology study operating under good laboratory practices (GLPs), the general principles are operative for GMP and GCP situations, and references are provided for these.

In-Progress Monitoring

As mentioned before, "Compliance Inspection Manuals" which are used by inspectors in their agency laboratory inspection programs are available from FDA (1984). The manuals offer a systematic and thorough means of reviewing elements of GLP compliance and can serve as guides regarding standardized aspects of laboratories and studies. The reader is also referred to the audit checklist provided in Appendix I. The results of prior regulatory inspections may also be accessed online (FDA 2002).

Having carefully evaluated the laboratory before contracting the study, the focus of in-progress monitoring changes from the general to the specific. Whereas initially the animal feed room was inspected for cleanliness, good housekeeping and a rodent-free environment, now the feed should be inspected to see if it is segregated in an isolated area, stored properly, stamped or labeled with expiration dates, accompanied with appropriate feed analysis data, and logged out at suitable times and in amounts proportional to specific study needs. In the cases of nonhuman primates, inspect the quality, nature, and frequency of "treats" that animals should be receiving.

Likewise, much of the other in-progress monitoring will focus on data which have already been gathered. In performing this review, notes should be made and a list of items prepared for discussion with facility and study management at an exit

conference. In-progress monitoring should also include a review of vivarium conditions (temperature, humidity) and animal husbandry records. Although not the most fascinating data to review, the conditions under which the animals are housed can seriously influence the study's outcome, both from a biological point of view as well as relative to the study's acceptability by regulatory agencies.

All data pertaining to clinical observations, blood and clinical chemistry analyses, weights, and feed consumption statistics should be reviewed. Not all of these may apply and some studies will have more complex in-life observations than described here.

The laboratory's QA inspection reports should be reviewed at this time. These reports should demonstrate that QA inspections are being carried out according to QA SOPs. The content of the reports should be reviewed as a means of ensuring adherence to the study protocol and the laboratory's standard operating procedures.

The purpose of an in-progress monitoring visit is to review all the data collected since the last visit in order to ascertain that the study is progressing smoothly and without major problems. The data reviewed should be generally consistent with the sponsor's understanding of study progress to date derived from previous inspections or reports (written or verbal) from the laboratory. If the study appears to be changing in unsuspected ways, the sponsor and the study director should discuss the possibility of alteration of the study design: adding more or different observations, adjusting doses or dosing schedules, and inserting an unplanned interim sacrifice. The study protocol is designed to accommodate all reasonably foreseeable events in the study. However, some events may occur which were unexpected, particularly in a complex study. The monitoring visit allows the opportunity for the sponsor and study director to adapt the study design, if necessary.

If the study design has been changed since the sponsor's last visit, protocol amendments which clearly state the change, its scope, and the reason for the change should be found in the study documentation. If the amendment was authorized by the sponsor during a previous communication, this should be referenced.

The facility's SOPs should again be checked to ensure that relevant procedures are being followed (from cage washing to histological preparation). Most procedures generate some kind of documentation which should be reviewed.

When all available documentation has been reviewed, the sponsor will have a list of items for discussion with study management. Sponsor and study director, together with other pertinent laboratory staff (pathologist, animal care supervisor, quality assurance staff), should meet to discuss and resolve these issues.

Generally, the questions can be resolved fairly easily. Sometimes things go wrong which are beyond the control of facility management, such as temperature or humidity excursions in the animal room. If not numerous, extreme, or cyclical, such excursions are probably of little importance. However, if patterns of consistent difficulties are detected, facility management should be required to improve its control over environmental conditions. This may involve moving the study to a different room for completion or providing the facility maintenance staff with additional instruction and training. Whatever the cause, the desired effect is correction of excessive environmental variation.

Up to the point that the study initiates, inspections and auditing have been of a general nature as stated previously. But now things get specific. A useful tool and approach is that if a deviation from the protocol occurs, it is to use that specific incident and move forward and backward in time from it. This will generally reveal any systemic, compliance or operational problems that need to be addressed. As an example, if an animal is found dead, search through subsequent data to see if and how the animal appears in this data. It should not show up as alive at a later time. Then move back in time and see that all the appropriate care was delivered to the animal and that the descriptions of the animal's behavior up to the point of death are accurate and in compliance with laboratory standards. Look at the dosing records and evidence of the proper assessment of clinical signs during observation periods. Furthermore, look at environmental data.

Since the laboratory was selected on the basis of a thorough preplacement evaluation, now is the time to ask laboratory management to bring its expertise to bear on whatever problems have arisen in the study.

What if major problems arise which warrant aborting the study and restarting it? A frank discussion with study management (and your own management!) should be the starting point. If the sponsor's judgment to abort comes as the result of in-progress monitoring without any previous idea that such serious deficiencies existed, the sponsor's and the study director's expectations and understandings are apparently far apart. If, on the other hand, the sponsor's inspection is the result of the laboratory's report of problems, then the decision to restart the study may be easily and jointly reached. Despite a thorough prequalification audit, problems of a variety can develop.

The contract confers rights and responsibilities on both parties, and should therefore be consulted if study abortion and restart is contemplated. If the contract clearly permits the sponsor to judge at what point a major problem or a series of minor problems constitutes grounds for aborting the study, the decision to do so should be made expeditiously. Having learned from the experience, sponsor and study director should proceed to restart the study with as little delay as possible.

The Study Report

Most sponsors will want interim reports for major long-term studies. Since the interim reports will form the basis for the final report, they should be read carefully and critically. If misinformation, confidential business information, or poor interpretations of data are presented in the interim reports, they should be corrected at once. Interim reports may also be sought by regulators, so they should be held to the same exacting standards of thoroughness and accuracy as the final report.

The final report should be presented to the sponsor in draft form. Several years ago, this was a contested notion, with many contract laboratories objecting to draft reports. However, the current practice is for contract laboratories to submit drafts for review by sponsors.

The study report should contain all essential elements, generally those covered in the GLP regulations. Additional data may be included, for example, information about the test material, interpretative statements by sponsor scientists, references to other studies of the test material, or a host of other information. The sponsor should make such inclusions after receipt of the final report from the testing laboratory. For example, if previous study data are relevant, they might usefully be included in a discussion section.

Much report information required by GLPs deals with methodological details which should have been carefully described in the protocol. Appending the protocol to the study report can serve to fulfill these requirements. This saves time and retains the study plan as a historical document. If the protocol was not strictly followed or if it required extensive alterations, a new description of methodology may be preferable. A listing of any GLP amendments to the protocol and deviations from the protocol is essential to be included, with adequate dating, signatures, and descriptions of the situation and impact on the study scientifically as well as from a regulatory perspective.

The final study report should contain in the signatures of all required parties: study director, QA inspector, pathologist, statistician, clinical chemist, and any other scientists who contributed significantly to the work. It is also a good idea to list the study personnel. Such personnel can change frequently, and personnel lists may not be available if there is a need to identify study staff at some time in the future.

The sponsor or their representative (such as a consultant) should review actual data as soon as it has been prepared in tabular manner. The study report should take no more than *two* drafts in order for sponsor and contract laboratory to agree on a final version. If the sponsor feels that additional drafts are needed, this should be resolved quickly with the contract laboratory. Frequently, there is a reluctance to rewrite reports many times, and the zeal with which the perfect report is pursued will diminish with time. A qualified scientist is entitled to disagree with conclusions reached by another in an addendum to the report, although agreeing on the conclusions drawn from the study at the outset is a less awkward means of presenting conclusions in the report. Nevertheless, it is not uncommon for a sponsor's final report to include statements of opinion differing from those offered by the contract laboratory.

Subcontracted Services

The contract laboratory may not have available all the services needed to complete the study. For example, some laboratories use contract pathology services. Archiving of raw data, specimens, samples, and interim and final reports may be done at a commercial archiving operation rather than at the laboratory. Prior to contracting, decisions need to be made concerning services which the laboratory itself will not provide. In the case where pathology is subcontracted, the sponsor should be able to specify, if desired, a pathology laboratory other than the one the contract laboratory usually uses. Likewise, if the contractor does not have their own archive space, the samples could be retained by the sponsor, rather than having the materials sent to a

commercial archivist or warehouse. These issues should be anticipated and addressed in the contract. If circumstances require a change in the planned provider of these services, sponsor and contract laboratory should keep each other informed.

Ongoing Contracts or Master Service Agreement

Having successfully completed a contracted study, if the sponsor anticipates a continuing need, developing an ongoing contract with this laboratory for future work should be considered. Establishing a continuing relationship with one or several laboratories enables the sponsor to familiarize the laboratory thoroughly with the sponsor's study methods as well as with any idiosyncrasies of reporting or data gathering. In addition, economies can usually be affected on the basis of volume and/or regular scheduling. Very importantly, establishing an ongoing relationship with a contract laboratory may improve the turnaround time of "rush" studies, since the laboratory might be able to accommodate such a request more easily for an established than for a onetime customer.

Many sponsors have found it useful to establish such ongoing testing contracts with several laboratories simultaneously. Some advantages of this approach are expanding the possibilities of squeezing in a "rush" study, extending the standardization of test methodology from the sponsor's perspective, and increasing the objectivity of the overall testing program by bringing several observation and judgment capabilities to bear on similar methods and data sets.

A fourth advantage is that failures of individual contract laboratories will not leave a sponsor's testing program grounded so that the process of finding a suitable laboratory must be begun from ground zero again.

Some specialties are well practiced in only a handful of laboratories. In these cases, the objective must be to get a good study done each time. More and closer oversight may be required in such cases than if several laboratories are adept and ready to do the required testing.

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Chapter 9
Common Problems and Solutions

Despite the best efforts and intentions of all involved, there will always be an incidence of problems involved in even successful subcontracting (many if not all of these problems are also present when work is performed using internal resources, but such are not the subject of this volume). What can be done is to be aware of the potential of such problems and to be prepared to solve them if they arise. Preferably the initial step to a solution is knowledge of how others have previously solved similar problems.

In each of the cases that follow, a first step might well be to avoid the situations in the first place. So for each of the common problems that are considered, a history of how some arose is provided.

Changes in Key Personnel

Part of the initial selection process for a contractor is based on the experience and qualifications of their staff. Unfortunately, such assumptions may not hold true in at least two cases.

In the first case, key personnel may leave the organization through changing jobs, disability, or death. In the second situation, a key individual (such as a study director in a toxicology study) may prove to look better on paper than in reality and not be up to the task at hand (this is not uncommon). In either of these cases, a central figure involved in the completion of desired work is no longer present or involved.

Avoiding the occurrence of this problem is difficult, as there is really no advance warning in the situations cited as examples. Solution options here are limited. Other than the provision of the highest degree of assurance by the CRO that the on-the-job (as opposed to on paper) competence of replacement key individuals will not reduce the quality of the study, there are few options.

When faced with this situation, there are three potential solutions. The first is to have the vendor reassign another suitable individual to fill the vacancy – should such a person

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be available. Unfortunately, it is uncommon that such a solution is possible due to limited human resource redundancy within the vendor organization or nowadays any organization.

The second approach is to hire (or, rather, have the vendor organization hire) a suitable person for the completion of the task. The vendor may know such individuals, or do a search of the appropriate Web site (http://www.toxconsultants.com for a toxicologist or http://www.chemconsultants.com for a chemist), as examples. This is the more common approach, with the effective subcontract being limited to the period of need. The third approach (generally viable if a project has not yet actually been initiated) is to delay the start or completion of a project until a full-time replacement or adequate substitute is hired.

Client Signing Protocols

When work is contracted out, there is a tendency in many organizations to maintain (and even delimit) control and authority even though technical skills are not present. This is most commonly experienced by sponsors as well as contracted experts (consultants/monitors) being signatories for protocols, amendments, and other documents. This leads to (at best) a lack of clarity in lines of authority and responsibility for decisions, and perhaps much worse. In such a situation, most contractors will take no action until there is consensus or clarity, which in nonclinical and clinical studies many times becomes an (unintended) decision itself.

The means of avoiding this problem are clear, having only a single technical signatory from the sponsor regardless of whether said individual is internal to the sponsor or a consultant at project initiation. The worst case, by the way, is rare in the pharmaceutical industry but common in other industries (such as chemicals) – a committee in charge. Enough said. If, however, this problem cannot be avoided then ensuring open and continuous communications through a well-understood line of authority with clarified responsibilities is essential.

Time Slippage

The most valuable asset in the development of new products in the industries that we are concerned with is not money, but rather time. This leads to most activities being precisely scheduled (to ensure either the quickest time to overall project completion or the optimal use of resources such as money). While (as was made clear earlier) a clean set of expectations for project completion must be part of the contracting process, the nature and the course of human events may preclude on-time completion. Any extra time available between the initiation of an activity and its scheduled or required completion (delivery of a report or drug substance or for

alternate dosage form) constitutes "float" in the terminology of project management, and must be carefully monitored and controlled. Small delays which on their own seem trivial all too often accumulate over the course of a program to produce a painful protraction in completion. A frequent admonition to clients and contractors is "don't eat my float and I won't eat yours."

Delays can arise from a vast number of causes, but usually these translate to a shortage of a resource (availability of equipment, test animals, manpower, or an essential skill set such as expertise with using a specific instrument or the performance of a necropsy on test animals or delivery of materials (especially test article and/or vehicle)). When such are identified, their impact is commonly significantly underestimated. The key to avoiding or minimizing the impact of these is to ensure that causative factors and events are identified as soon as they occur, and that corrective actions are initiated as rapidly as possible. A second step is to allow some level of redundancy of resources to be included in plans. Extra starting material for synthesis or a few extra animals on hand over the minimal requirements are cheap insurance for on-time completion of the projects in question.

If such events still come to pass, then the best means of minimizing their impact is to provide a supplement or replacement for the limiting (critical path) resource in the completion of the entire project (i.e., drug or device approval).

Regulatory Noncompliance

The industries with which we are concerned here are heavily regulated in virtually all aspects. Seemingly small occurrences of noncompliance with such regulations (such as not taking samples of dosing solutions for analysis or not following quality assurance procedures can invalidate entire studies or activities) lead at best to a need for the repeat of the same study or performance of additional work, costing money and time.

All such regulated activities now must have some form of quality system (QS) in place. Regulatory noncompliance in such situations can occur only if the QS was incomplete (overlooked in the initial system set up) or failed. Procedures to avoid such occurrences are best discussed in the preaward phase of a contract work. Initially, insure that necessary systems are in place as evidenced by SOPs, validation reports, operative quality assurance unit (QAU), and the existence of a Quality Program effective for the critical points/activities involved in the work to be performed. Subsequent to this there should be a program for monitoring any ongoing work. Consider having a full systems (GLP/GMP/GCP) audit performed on any facility, which is either doing a large, critical project or is providing services on a number of separate projects.

If a noncompliance issue is identified, the solution is to document both the problem and corrective action in a timely manner (What happened? Why did it happen? What steps have been taken to prevent it from happening again?).

Quality Control/Assurance Failures

Again, there are several aspects of this topic. The first is if quality assurance and control procedures are not followed. An example is when plasma samples from a group of volunteers, subjects, or animals are analyzed and samples demonstrate erroneously high or low reported levels of the agent of interest. The second is when the understanding of regulatory quality assurance or study design requirements on the part of contractor personnel are different than those of the sponsor. Such differences of opinion can be legitimate, but the impact on cost, quality, and timing are potentially enormous.

This issue has some degree of overlap with regulatory noncompliance. Here we wish to focus on the following aspects not covered under that other topic: (1) that there is a significant disagreement between the contractor's quality assurance and the client's professional opinion (experience) or (2) that a QC/QA failure caused actions to be taken which cannot be solved simply by documenting the event and taking post action.

The first of these can take several forms: that a quality problem has or has not occurred or in some contract organizations, what is or is not presented in a final report. For these, both the client and vendor management must work to arrive at a mutually acceptable solution.

The second case is harder. If an erroneous finding has caused an irreversible action to be taken (such as shutting down a clinical trial or making a regulatory filing which was incorrect), fixing the matter has two separate aspects. First, all involved must be notified in writing of the error. Second, a legal issue of restitution of damages will need to be resolved between the client and vendor.

Inappropriate Technology

This may be due to decisions by the sponsor or the contractor (or both). The former may have an existing analytical method which served them well during earlier work on a project (such as an RIA method for measuring drug levels instead of a more sensitive LC/MS/MS method) and do not want to spend the money or delay progress on work while a better method is developed.

Contractors, on the other hand, usually play to their strength. If they have certain equipment and methods on hand, such are likely to constitute the recommended means of addressing a problem. An example here might be using a mass balance approach with a limited number of organs to evaluate the distribution of a drug and its metabolites throughout the body, as opposed to using whole body auto radiography.

It behooves both the client and vendor to ensure either that technologies involved in project conduct are according to the current industry norm, that the data from such work will provide answers to the desired questions, or that there is a well-documented reason for otherwise to be the case.

If it is found that the methodology employed does not meet current regulatory expectations (despite the rationale behind their use being good), then the performance of a bridging study establishing that results comparable to those from the desired method (or animal species) is advisable.

Facility Shutdown

Sometimes a facility will cease operations while work on a study or projects are still ongoing. Causes of such situations in the best of circumstances have included financial failure, death of essential personnel, and an acquisition of the facility by new management. The performance of thorough due diligence before the award of the contract is the best means to avoid this problem. Make sure the financial stability and other factors cited here are evaluated before an award.

Such an occurrence, if detected in a timely manner, can be addressed in one of two manners. Either the means may be acquired or negotiated (in the case of an acquisition) to resume operations and continue then until the contracted task is completed, or the work can be moved to another facility for completion. The past has documented the relocation of entire colonies of laboratory animals in just such circumstances.

Acts of Nature

Natural disasters do happen. Floods, hurricanes (wiping out animal colonies, remember Houston, TX in the late 1990s), fires, and earthquakes are all possibilities that can disrupt or totally discontinue the conduct of development activities. The occurrence of these cannot be either predicted or avoided, but the ability of a facility to withstand such occurrences and continue operations can and must be evaluated as a part of preaward considerations.

CROs May Stretch the Truth

While in our experience this has become much less of a problem than it once was, it still occurs that contractors may represent that they have capabilities that they do not have or can meet timelines, which have more of a spiritual than managerial basis. Avoidance of this problem is best pursued by careful review of past performance. While asking for and checking with provided reference clients is a useful step, a sponsor should also seek to use their professional contacts to seek out and query a broader range of prior clients. Alternatively, a strict financial penalty clause can be included in the contract with regard to the achievement of timed milestones.

The degree of the problem dictates the appropriate response. If the contractor has been overly optimistic about their ability to provide timely results, this can be addressed as previously discussed under time slippage. But if an actual untruth is detected, the problem is much more serious. Impact and corrective actions after such a breach of faith must be carefully considered.

Silent Subcontractors

Just as sponsors subcontract, so do contractors. Very common cases for toxicology labs, for example, include pathology, cardiology, ophthalmology, bioanalytical and analytical chemistry, and statistical analysis. It may not be made clear to the client that such is the case before a project is initiated. It is thus essential that documents such as protocols clearly disclose any subcontractors and their specific responsibilities, as well as provide sufficient contract information to allow independent sponsor contract and follow-up.

Alliances

Again, just as with client organizations, informal or formal arrangements may exist between contractors which can influence, complicate, or impede progress on a project. Examples include (1) a data entry analysis CRO which will not provide support to phase I studies initiated at other than their "partner" clinical facility once work has been done at that facility and (2) a GMP synthesis facility which has an arrangement with specific formulation and CTM manufacturing organizations.

Such arrangements do not inherently cause any harm, but also should be disclosed at the beginning of the study or project and in no way bind the sponsor to use (or even consider) the contractor's related organizations. Any "alliance" organization must be evaluated on its own independent merits.

Sponsors must insist on full and timely disclosure of any such arrangements and evaluate any resulting impact.

Too Many Eggs in a Basket

While there are both good reasons and a natural tendency to "reward" a vendor that performs well with additional work, it is always a sound practice to have more than a single contractor available to conduct a particular type of work (if at all possible). There are several reasons for this.

Even the best of contract service providers have limits on how much work they can do, and also will be subject to circumstances beyond their control from time to time.

These occurrences can easily lead to (1) having to accept delays or compromises in study or task performance or (2) in some cases finding that you are (in effect) competing against yourself for resources on different projects.

The essential solution to this problem is to be aware of viable alternative providers, and if possible to have the necessary preparation work (site visits, confidentiality agreements, and such) completed and set in place in advance. It is even well advised to split workloads between two separate vendors – while the cost of operations may be modestly increased in the short run, such an arrangement can be managed in such a fashion as to actually better control the project and even decrease costs in the long run.

Extraneous Event

Things happen in EVERY study and range from technique-associated animal deaths to sample loss to finding test article in the plasma of control animals. The best solutions are to rapidly identify such events, investigate causes, insure sound and effective communication, and document all the facts.

Appendix A
Toxicology Labs

S.C. Gad and C.B. Spainhour, *Contract Research and Development Organizations: Their Role in Global Product Development*, DOI 10.1007/978-1-4614-0049-3,

Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
ABC Labs.	Missouri, IA N. Ireland, UK Columbia, MO	(573) 474-8579 44 (0) 2870 320 639 (800) 538-5227	http://www.abclabs.com	Bio-analysis, methods development, radioactivity	X		X				X					X	X	
ADMETRx (Ceetox)	Kalamazoo, MI	(269)-372-3272	http://www.admetrx.com	Yes												X	X	
ADVINUS	Bangalore, India	+91-80-28394959 +91-80-28394015	http://www.rallis.co.in	Yes	X	X	X	X						X		X	X	
Aniclin Preclinical Services	Hollywood, FL	866-718-6284	Not available		X		X			X		X				X		
Apptec/Wuxi	St. Paul, MN	888-794-0077	http://www.apptec-usa.com	Biotech, biocomp/med devices, microbiology	X	X	X				X	X	X	X	X	X	X	
	Philadelphia, PA	800-622-8820	http://www.wuxiapptec.com															
	Marietta, GA	888-847-6633																
Aptuit	Ledbury, India, UK and US	44 (0) 131 451 2560 916-767-3900 (US) 44(0) 131 451 2451 (EU)	http://www.aptuit.com/	Yes, clinical, development, +	X	X	X	X	X		X	X	X	X	X	X	X	SP
Aurigon-Toxicoop Research	Germany	+49 (0) 8158 2597 30	http://www.atrc.eu	AMES, HPRT, chromosome aberration,	X	X	X	X				X					X	
Austrian Research Center	Seibersdorf, Austria	43(0) 50550-0	http://www.arcs.ac.at/		X	X			X		X							SP

Avanza	Gaithersburg, MD	240-364-6360	http://www.avanzalaboratories.com/	Program Management and Regulatory Consulting	X	X	X	X	X		X	X	X				X		
BASI	West Lafayette, IN	(800) 845-4246	http://www.basinc.com	Yes	X	X	X	X	X		X	X	X	X	X	X	X		
	Europe	44(0) 247 663 9574 (EU)																	
Battelle	Columbus, OH	(800) 201-2011	http://www.battelle.org	Yes	X	X	X	X	X	X	X	X	X		X	X	X		
	Richland, WA				X		X	X		X									
BEC Labs	Toledo, OH	(419) 693-5307 (888) BEC-LABS	http://www.lexamed.net	Yes											X				
BioAgri	Piracicaba, Campinas and Sao Paulo, Brazil	+55-19-3429-7720	http://www.bioagricorp.com/		X	X	X						X	X		X	X		
	Lost Angeles, CA	626-810-2823																	
Biocon	Farmington, MN	(651) 460 3330	http://www.bioconinc.com/																
	Bangalore, India	91 8028082808																	
	Rockville, MD	(301) 762-3202		Infection Models	X	X						X							
Bioduro	Beijing, China	86-1080768000	http://www.bioduro.com		X	X	X	X	X		X			X		X	X		
	US – East Coast	908 647 5012																	
	West Coast	855 779 9260																	
	NE Area	781 237 6688																	
Bio-Life	Neillsville, WI	(715) 743-3171	No	Yes											X				WL
Bio-Quant	San Diego, CA	(858)-450-0048	http://www.bio-quant.com	Tumor models, Disease models	X	X	X	X				X				X			

(continued)

Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
BioReliance	Rockville, MD UK, India, Japan	(800) 738-1000 (800) 553-5372	http://www.bioreliance.com	Full range Genotoxicity, Transgenic mouse CA models (p53)[a]	X	X		X			X		X	X	X		X	
BioSafety Research Center (BSRC)	Shizuoka, Japan	+81 538 58 3572	http://www.anpyo.or.jp	Immunotoxicity studies	X	X	X	X				X		X			X	
BioScience Laboratories	Bozeman, MT	877-858-2754	http://www.biosciencelabs.com	Microbiology, virology, cytotoxicity, pharmacokinetics													X	
Biotechnics	Hillsborough, NC	(919) 245-3114	http://www.biotechnics-inc.com	Yes	X	X	X				X	X		X				
BioTest	Czech Republic	+49 6103/8 01-0 (P) +49 6103/8 01-150 (F)	http://www.biotest.de	GLP Genetox , *Ames* Test, Chromosome aberration in vitro (human lympho-	X													
BRI	Vancouver, BC	(604) 432-9237	http://www.bripharm.com	Yes, Pharmaceutical, Development, +	X									X		X	X	
BRT	Raleigh, NC	(919) 851-4499		Specialty immunotox[a]	X	X									X			

BTC (Biological Test Center)	Irvine, CA	(949) 660-3185	http://www.biologicaltest-center.com	Ophthalmology, Pharmacokinetics, aseptic surgical model development, pediatric toxicity studies +	X	X	X				X	X	X	X	X	X			
Caliper Life	Hopkinton, MA	1-609-860-0806 1-410-712-4410 or 1-800-543-4141 508-435-9500	http://www.caliperLS.com													X			
Calvert	Olyphant, PA	(570) 586-2411	http://www.calvertlabs.com	Yes, Radioactivity Telemetry, Mouse Tumor Model, +	X	X	X	X	X		X	X	X		X	X	X	SP	
CBSET	Lexington, MA	(781) 541-5555	http://www.cbset.org/	GLP, disease models, pharmacokinetics, ADME											X				
CeeTox Inc. (ADMETRx)	Kalamazoo, MI	269-353-5555	http://www.ceetox.com	Chemistry, in vitro, cell culture												X	X	X	
CEDRA	Austin, TX	(512) 834-7766	http://www.cedracorp.com http://www.wwctrials.com	Yes													X		
Celsis	St. Louis, MO	(314) 487-6776	http://www.celsislabs.com	Yes, stability, methods	X	X	X	X	X	X	X	X		X	X	X	X	X	
Central Toxicology Labs. (Sygenta)	Alderley Park, Macclesfield SK10 4TJ, UK	+44 16255 15852 (p) +44 16255 17314 (f)	http://www.syngenta.com	Yes	X	X	X	X	X	X	X		X	X		X	X	SP	
Cerep	Redmond, WA	(425) 895-8666	http://www.cerep.com	Chemistry, in vitro														SP	

(continued)

Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
Chantest	Cleveland, OH	(216) 332-1665 (p) (216) 332-1706 (f)	http://www.chantest.com	HERG, ion channels														
Charles River	Reno, NV[a]	(775) 331-2201	http://www.criver.com	In general	X			X	X	X	X		X				X	
	Malvern Horsham, PA	(215) 443-8710		Phototoxicity, ferret emesis					X									
	Spencerville, OH	(419) 647-4196			X	X	X	X										
	Tranent, Scotland (Inveresk)	44 (0) 1875 614555		Clinical, ferret emesis	X	X	X	X	X	X	X	X		X		X	X	SP
	Piedmont, Morrisville, NC	(919) 206-7000		Tumor models, implant studies	X	X	X				X	X	X		X	X	X	SP
	Montreal, QU (CTBR)	(514) 630-8200		Clinical, ferret emesis	X	X	X	X	X	X	X	X	X			X	X	SP
Cirion	Canada	(450) 688-6445	http://www.cirion.ca	Yes, clinical	X	X	X				X	X		X	X	X		
CIT – Centre Internat. De Toxicologie	Cedex, France	+33 2 32 292626 (p) +33 2 32 678705 (f)	http://www.citox.com		X	X	X	X	X	X	X	X	X	X		X	X	SP
Clintox Bioservices	Hyderabad, India	91(40)55153222 91(40)23480666	http://www.clintoxbio.com	Phototox, Hamsters	X	X		X	X					X		X		SP
Commonwealth Biotechnologies Inc.	Richmond, VA	(804) 648-3820	http://www.cbi-biotech.com	Genomics		X												
Comparative Biosciences	Sunnyvale, CA	(408)-504-8871 (408) 738-9278	http://www.compbio.com	Special discovery, models[a]	X	X	X	X				X	X		X	X	X	

Comparative Ophthalmic Research Lab (CORL)	Madison, WI, University of Wisconsin	(530) 754-0216 (P) (530) 752-6042 (F)	http://www.vetmed.wisc.edu/research/corl/	Ocular Toxicity												
CorDynamics	Chicago, IL	(312)-421-8876	http://www.cordynamics.com	CV safety only												
Covance	Vienna, VA Madison, WI Harrogete, U.K. Muenster, FRG	(888) COVANCE (888) 541-LABS	http://www.covance.com	Clinical, consulting	X	X	X	X	X	X	X	X	X	X	X	X X 	 SP SP
CPTC	Fairfield, NJ	(973) 808-7111	http://www.cptclabs.com	Yes, clinical +	X	X								X		X	
CXR Biosciences	Dundee, UK Scotland, UK	44-1382-432163	http://www.cxrbiosciences.com	Humanized mouse models											X	X	
Dermtech	San Diego, CA LaJolla, CA	(800) 808-2774 858-450-4222	http://www.dermtech.com	Yes, consulting					X	X							
Enviro-Bio-Tech-Ltd.	Bernville, PA	(610) 488-7664	No	(chicken, cattle) (food animals)												X	WL
Estendart Limited/ Massey University	Palmerston North 4442, New Zealand	+64(0)6 350 0782 (P) + 64(0)6 350 0772 (F)	http://www.estendart.com	(sheep, cattle, chickens, horses)	X		X						X				
Eurofins	Dayton, NJ	732-438-5100 ext 270 Fax 732-355-3275 CelL 732-744-6579	http://www.eurofins.com											X	X		
Experimur	Chicago, IL	773-254-2700	http://www.experimur.com	PK	X	X	X	X	X		X	X	X			X	

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Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
Exygen	State College, PA	(800) 281-3219 (p) (800) 272-1019 (f)		Methods, development												X	X	
Fraunhofer ITEM	Nikolai-Fuchs Street, 30625 Hannover, Germany	+49 511 5353 0 (p) +49 511 5353 155(f)	http://www.item.fraunhofer.de		X	X	X	X	X	X				X		X	X	
Frontier Biosciences	China	US Office 301-251-0231	http://www.frontierbsi.com		X	X	X	X	X		X	X		X		X	X	SP
Genelogic	Gaithersburg, MD	800-436-3564	http://www.genelogic.com	Yes	X	X	X	X	X		X	X	X			X	X	SP
Gibraltar Laboratories, Inc.	Fairfield, NJ	(973)-227-6882(p) (973)-227-0812(f)	http://www.gibraltarlabsinc.com	Microbiology	X	X								X	X		X	
Gwathmey	Cambridge, MA	(617) 491-0022 (p) (617) 492-5545 (f)	http://www.gwathmey.com	Consulting, biology	X	X									X	X		
Harlan (RCC)	Rehovot, Israel	972 (0) 8-9409451	No	Bioproducts, Breeder	X		X									X	X	SP
	Zelgliweg 1, 4452 Itegen, Switzerland	(410) 385-1666 – US sales office +41 61 975 1111(p)	http://www.rcc.ch http://lchaney@harlan.com	In general	X	X	X	X	X	X		X	X	X	X	X	X	SP
	Germany		http://www.harlan.com	In vitro studies										X				
	Spain	34-937-190361			X		X			X	X	X	X				X	SP
	Madison, WI	317-806-6080 x2922		Non-naïve canines/ NHP			X				X		X			X		
	Indianapolis, IN	317-806-6080 x2922		Discovery support	X	X							X	X	X			

Haskell Dupont Laboratory		(306)-366-5200		Yes									X					
HemoGenix	Colorado Springs, CO	719-264-6250	http://www.hemogenix.com	In vitro tox/PK														
Huntingdon	East Millstone, NJ	(732) 873-2550	http://www.huntingdon.com	Discovery support	X	X	X	X	X	X	X	X	X			X	X	SP
	Cambridgeshire, UK	44 (0) 1480 892000		Radioactivity	X	X		X[b]	X	X				X			X	
Hurley Consulting Associates LTD	One Main Street, Chatham, NJ 07928	1-770-529-1154 (Phone) 1-770-529-3783 (Fax) 973-635-9898 (Phone) 973-635-9881 (Fax)	http://www.hurleyconsulting.com	Statistical analysis, Study design, preclinical assessments, data management, QA, regulatory affairs, pharmacovigilance, training, etc.											X	X	X	
Ibex	Logan, UT	435-752-4448	http://www.ibexpreclinical.com	Cardio telem.	X	X	X	X	X			X			X	X		
ICP Firefly	Sydney, Australia	+ 61-2 9310 3899	http://www.icpfirefly.com.au	Yes	X	X		X	X	X				X	X		X	
IIBAT	Padappai, India	04111-274246	http://www.iibat.com	ECOTOX	X	X		X	X				X	X				
IITRI	Chicago, IL McLean, VA	(312) 567-4000 (703) 918-4480	http://www.iitri.org	Yes	X		X	X	X	X	X			X		X	X	
ILS	RTP, NC Shardlow, Derbyshine	(919) 544-5857 44(0) 1332 793000	http://www.ils-limited.co.uk	Data analysis, ecotoxicology	X			X	X					X		X	X	SP

(continued)

Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
INA (Int. Non-clinical Assessment)	Nagano-ken, Japan	+81-265-72-6616(p) +63-49-541-2294(f)	http://www.ina-research.co.jp/en/	Pediatric toxicity	X	X	X	X	X		X			X	X			
Innostar Bio	China	(+86) 21 6328 8899	http://www.biotech-china.com	Biomedicine, gene-technology				X						X			X	
Industrial Toxicology Research Center (ITRC)	Lucknow Nadu, India	+91-522-2211547 Fax: +91-522 2228227	http://www.iitrindia.org	Irritation, behavioral	X	X		X	X	X				X			X	
Intox	Pune, India	+91 22923633 +91 2066548700	http://www.intoxlab.com	Irritation, Farm animals	X	X		X	X	X				X				
Inveresk	Tranent, Scotland	44 (0) 1875 614555	http://www.inveresk.com	Clinical, ferret emesis	X	X	X	X	X	X		X		X		X	X	SP
	Montreal, QU	(514) 630-8200			X	X	X	X	X	X	X	X	X			X	X	SP
Irvine Analytical Labs, Inc.	Irvine, CA	(877) 445-6554	http://www.ialab.com	Yes						X							X	
Intl. Inst. of Biotech and Toxicology	Tamil Nadu, India	+91-4111-274246 +91-4111-274455		Biotechnology, Entomology, Agronomy													X	
Intl. Hungary Ltd.	Veszprem, Hungary	+36-1-4314840 fax +36-88-545-301	http://www.trc.hu	Yes toxicology	X	X	X	X		X			X			X		
IPS Therapeutic	Sherbrooke, QC	Ph: 819-564-5391 Fax: 819-820-6831	http://www.ipstherapeutique.com/	hERG testing CV, safety pharm														

ITL Labs Ltd.	Delhi, India	91-11-27915654	http://www.itllabs.net													X		
ITR	Montreal, QU	(514) 457-7400	http://www.itrlab.com		X	X	X	X	X	X	X	X	X	X		X	X	SP
ITRI	Albuquerque, NM	(408) 428-9988	http://www.itri.com	Yes	X			X		X							X	
Jai Research Foundation International	Gujarat, India	912606540242	http://www.jrfonline.com		X	X	X	X	X	X				X		X	X	
JOINN Laboratories	Germantown, MD Beijing China	301-540-5988 86-10-67869966	http://www.joinn-lab.com	Pharmacokinetics, toxicokinetics, Ames test, micronucleus test, chromosome aberration test	X	X	X	X	X									X
JSW Research	Austria		http://www.jswresearch.com	Yes	X			X	X		X			X		X	X	
KIT (Korean Institute of Technology)	Korea	+82-42-610-8105	http://www.kitox.re.kr/eng_about.html	Yes	X	X	X	X			X	X	X	X				
LABS	Laval, Canada	(450) 973-2240	http://www.preclin.com	Yes	X	X	X	X			X		X			X		
	Veszprem, Hungary	(416) 815-0700	http://www.trc.hu		X	X	X	X		X			X			X		
Liberty Research	Waverly, NY	(607) 565-8131 (p) (607) 565-7420 (f)	No	Cats, Ferrets			X											
Litron Laboratories	Rochester, NY	877-454-8766	www.litronlabs.com											X	X		X	
Lovelace	Albuquerque, NM	(505) 348-9400	http://www.lrri.org	Clinical						X								

(continued)

Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
LPT	Hamburg, GE	49 40-70-20-20 49 40-70-20-22-99	http://www.LPT-pharm-tox.de		X	X	X	X	X	X	X	X	X	X	X	X	X	SP
LyChron	Mountain View, CA	650-938-3675	http://www.lychron.com	Pig Device Implant Studies					X			X			X			
Maccine	Singapore	+65-6778-7305 (Fax) +65 6622 9540 (Phone)	http://www.maccine.com	Yes	X						X		X			X	X	
MB Research	Spinnerstown, PA	(215) 536-4110	http://www.mbresearch.com	In vitro and alternative models	X	X	X			X		X		X	X			
Medicilon/MPI	Shanghai, China	8621-51-320228 8621-5859-1500	http://www.medicilon.com		X		X				X			X		X	X	
MicaGenix	Greenfield, IN	(888)-779-5500 317-468-1760	http://www.micagenix.com	Histology, Image analysis, Non-GLP												X		
Micro Test	Agawam, MA	(800) 631-1680	http://www.microtestlabs.com	Yes											X		X	
Midwest Bio Research	Evanston, IL Skokie, IL	866-416-6820(p) 847-972-2506(f)	http://www.midwestbioresearch.com	Consultation										X		X		
MPI	Mattawan, MI	(269) 668-3336	http://www.mpiresearch.com	Safety pharm, Transgenic mouse CA, Radioactivity	X	X	X	X	X		X	X	X		X	X	X	SP
MSI	Minato-ku, Tokyo, Japan	81 3 3454 7571	http://www.ankaken.co.jp	Yes				X		X	X					X		

MWRI	Kansas City, MO	(816) 753-7600	http://www.mriresearch.org	Yes	X			X									X	X		
Nia Life Sciences Inc.	Libertyville, IL 60048	847-573-1852	http://www.nialifesciences.com	Pharmacokinetics, GLP and non-GLP, Bioanalytical, Fungal and Tumor Model	X															
NAMSA	Toledo, OH	(419) 666-9455	http://www.namsa.com	Yes												X	X			
	Northwood, OH	866-666-9455																		
	Irvine, CA	(949) 951-3110														X	X			
	Kennesaw, GA	(770) 427-3101																		
NCDSER	Shanghai, China		http://www.ncdser.com	hERG safety pharma	X	X	X			X		X					X	X		
Nelson Labs	Salt Lake City, UT	(800) 826-2088	http://www.nelsonlabs.com		X	X										X	X		X	
Next Century, INC	Newark, DE	(302) 453-0571	http://www.nxtcent.com/	Yes	X	X	X	X		X	X	X	X			X				
Northern Biomedical Research	Muskegon, MI	(231) 759-2333	http://www.ntba.org	Yes, Surgery, Large animals	X	X	X			X	X	X					X			
Northview SGS	Northbrook, IL	(847) 564-8181	http://www.pharmardqc.sgs.com	Yes	X	X	X	X	X							X	X	X	X	
	Hercules, CA	(510) 694-9000																		
	Sparta, SC	(864) 574-7728																		
NOTOX	s'Hertogenbosch, The Netherlands	31073 640 67 00 (p) 31073 640 67 99 (f)	http://www.notox.nl	Yes, Birds, +	X	X	X	X	X			X	X	X	X	X	X	X		WL

(continued)

Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
Nucro-Technics	Scarborough, Canada	(416) 438-6727 (p) (416) 438-3463 (f)	http://www.nucro-technics.com	Microbiology	X	X	X	X						X	X		X	
Pacific Biolabs	Hercules, CA	(510) 964-9000	http://www.pacificbiolabs.com/home.htm	Yes	X	X	X	X	X	X		X		X	X	X	X	
Pathology Experts	Basel, Switzerland Rye, NY	44-61-422-09-29 888-473-4554	http://www.pathexperts.com	Histology and Histopathology										X				
Perry Scientific	San Diego, CA	(858) 560-9000 (p)	http://www.perryscientific.com	Yes; Large animals	X	X	X	X	X			X	X		X	X	X	SP
PharmaAdvance, Inc.	Jiangyin, China	(+86) 510 8641 7090	http://www.pharmaadvance.com	Pharmacology, Chemistry	X													
Pharmaron	Beijing, China	+650-859-3853 408 739 1572	http://www.pharmaron.com		X	X	X				X		X			X	X	
Porsolt & Partners	Boulougne-Billancourt, France	+33146109990	http://www.porsolt.com/	Yes	X	X	X				X		X			X	X	
PreClinical Services (Lab Research)	Canada	888-353-2240	http://www.labresearch.com	NHP, immunotoxicity, pharmacokinetics/ toxicokinetic studies	X			X		X		X	X	X		X	X	
PreLabs	Oak Park, IL	708-613-6000 Fax: 708-613-6100	http://www.prelabs.com	Transgenic Mouse, CA studies	X	X	X	X		X	X	X			X			

Product Safety Labs	Dayton, NJ	(732) 438-5100 (732) 254-9200	http://www.productsafety-labs.com	Environmental, Ferret Emesis Studies, Radioactivity	X	X	X	X	X	X	X	X	X	X	X	X	X	WL
Provident Preclinical, Inc	Doylestown, PA	215-348-3868(p) 215-348-5081(f)	http://www.ppicro.com	Yes	X	X	X	X		X	X	X			X			
QPS	Newark, DE Taipei	(302) 369-5601 800-237-1970	http://www.qps-usa.com	Yes Radioactivity	X	X	X		X		X			X		X	X	
Rallis Research Center	Bangalore, India Mumbai, India	+91-80-28394959 +91-80-28394015 +91-02266652700	http://www.rallis.co.in	Yes	X	X		X						X		X	X	
Ricerca	Concord, OH	(888) 763-4797	http://www.ricerca.com	Synthesis, product development, Radioactivity	X	X	X	X	X	X	X					X	X	
(MDS Pharma Services)	Lincoln, NE	(514) 333-0033	http://www.mdsps.com	Clinical, receptor screening										X		X	X	
	L'Arbresle, France				X	X	X	X	X		X				X	X	X	SP
	Geneva, Switzerland													X	X			SP
RTC S.p.A.	Via Tito Speri 12, 40 Pomezia (Rom), Italy	+39 06 910 951 (p) +39 06 910 5737 (f)	http://www.rtc.it	Yes, Consulting, Regulatory	X	X	X		X					X	X			WL
RTI	RTP, NC	(919) 541-6000	http://www.rti.org	Yes	X			X	X				X			X	X	
SafePharm	Derby, UK	00 44 (0) 1332 792896	http://www.safepharm.com (domain is for sale)	Yes, (fish +)	X			X	X	X				X	X	X	X	SP
SCANTOX	Hestehavevej 36a, 4623, Lille Skensved, Denmark	+45 56 82 12 02 (f) +45 56 86 15 00 (p)	http://www.scantox.com		X	X	X	X	X	X		X	X	X	X			

(continued)

Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
Sequani Limited	Bromyard Road, Herefordshire, HR8 1LH, Ledbury, UK	+44 1531 634121 (p) +44 1531 634753 (f)	http://www.sequani.com		X	X	X	X	X		X	X	X	X	X		X	
SGS Life Sciences Division	Fairfield, NJ	(800) 747-8782 (800) 777-8378	http://www.ustesting.sgsna.com	Implant, combustion, fish, industrial, consumer products	X	X		X						X	X		X	SP, WL
Sinclair	PO Box 658	573-387-4400	http://www.sinclairresearch.com	Radiolabeled; cats; other	X	X	X	X			X	X	X		X	X		
Sitek	Rockville, MD	(301) 926-4900	http://www.siteklabs.com	Yes	X	X								X	X	X		
SNBL	Tokyo, Japan	+ 81 355655001 (p) + 81 355656160 (f)	http://www.snbl.com	Yes, Clinical, +, Irritation	X	X	X	X	X	X	X	X	X	X				SP
SNBL USA Ltd.	6605 Merrill Creek Parkway, Everett, WA 98203	(425) 407 0121 (p) (425) 407 8601 (f)	http://www.snblusa.com/	Formulation	X			X	X		X		X				X	SP
Southern RI	Birmingham, AL	(888) 322-1166 (800) 967-6774	http://www.southernreasearch.org	Yes, formulation, development, tumor models	X	X	X	X	X	X	X	X	X	X	X	X	X	SP
SP1-bio Bertin Pharma	France	+ 33 139 30 62 60	http://www.spibio.com	Clinical	X											X	X	

Spring Valley Lab.	Woodbine, MD	(800) 864-1839	http://www.svlab.com	Ferrets	X	X		X	X			X			X				
SRI	Menlo Park, CA	(650) 859-2000 866-451-5998	http://www.sri.com	Formulation, CTM	X	X	X	X	X			X		X	X	X	X		
Stillmeadow Inc.	Sugarland, TX	(281) 240-8828	http://www.stillmeadow.com	Companion animal studies	X	X	X			X		X				X	X		
STS duo Tek Ethox	Rush, NY Henrietta, NY	(800) 836-4850	http://www.stsduotek.com	Yes, ocular	X	X							X	X	X		X		
SYNECOR	RTP, NC Durham, NC	(919) 541-9977	http://www.synecor.com/	Surgical			X					X			X				SP
Tandem Labs	West Trenton, NJ	(609) 434-0044	http://www.tandemlabs.com	Yes												X	X		
TNO Pharma	Utrechtseweg 48, 3700AJ Zeist, 3704 HE, The Netherlands	+31 30 694 4806 (p) +31 30 694 4845 (f) +31 30 694 4144	http://www.voeding.tno.nl	Yes, packaging, food and nutrition, clinical	X	X	X	X	X	X	X	X	X	X	X	X	X	SP, WL
Torrent Pharmaceuticals Ltd.	Gujarat, India	91 (0) 79-26585090/3060	http://www.torrentpharma.com		X	X		X	X					X		X	X		
Toxicology Research Labs	Chicago, IL	(312) 996-9185	http://www.uic.edu/labs/tox/trlt.html	Pharmacokinetics, GLP	X	X	X						X				X		
TOXIKON Corp.	15 Wiggins Avenue, Bedford, MA 01730	(781) 275 3330 (p) (781) 271-1136 (f)	http://www.toxikon.com	Yes	X	X	X	X	X			X	X	X	X	X	X	WL	

(continued)

Lab	Location	Phone #	Website	Additional services	Rat/mouse	Rabbits	Dog	Carcinogenicity	DART	Inhalation	Primate	Pig	IV infusion	Genotoxic	Devices	Metabolism	Analytical	Special studies
UIC Tox Research Lab	Chicago, IL	(312) 996-9185	http://www.uic.edu/labs/tox	Yes Radioactivity	X	X	X		X	X	X		X			X	X	
Valley Biosystems	West Sacramento, CA	916-374-2735									X							
Vanta Biosciences	Belgium	+32.2.709.2920	http://www.vantabio.com	Biotechnology, agri-food, nutritional supplements											X		X	
VIMTA	Hyderabad, India	+91-40-2726 4141	http://www.vimta.com	Clinical	X	X	X	X	X					X		X	X	
Vivo Bio Tech, Ltd.	Hyderabad, India	+91 4066784714 +91 405776112 (f)	http://www.vivobio.com	Immuno-deficient Mice	X	X	X	X	X					X		X		
VIZON SciTec	Vancouver, BC, Canada	604-224-4331	http://www.vizonscitec.com	Ecotox												X		
	Mississauga, ON	905-288-2150 866-611-1118	http://www.cantest.com															
WIL Research Labs, Inc.	1407 George Road, Ashland, OH 44805	(419) 289 8700 (p) (419) 289 3650 (f)	http://www.wilresearch.com	Yes Radioactivity	X	X	X	X	X	X	X	X	X			X	X	SP, WL

WuXi Pharmatech	288 FuTe ZhongLu, WaiGaoQiao, Shanghai 200131, P.R. China	+82(21) 5046-1111	http://www.pharmatechs.com http://www.wuxiapptec.com	Rodent toxicity (oral, iv, and PK)	X	X	X		X		X	X	X	X	X
XenoBiotics	Plainsboro, NJ	(609) 799-2295 (609) 799-7497	http://www.xbl.com	Formulation Radioactivity	X	X	X		X					X	X
Xenotech	Lanexa, KS	(913) 438-7450	http://www.xenotechllc.com	Yes	X	X	X		X	X				X	

A “Yes” or “+” listed in the additional services column indicates that there are more services available than just those listed
SP in the special studies column indicates safety pharmacology, *WL* in this column indicates wildlife/environmental testing is available
[a]Limited
[b]Hamster carcinogenicity is available (149 Organizations, 182 Facilities)
Wildlife and Biodegradation CROs:
Smithers-Viscient/Springborn- Wareham, MA
Wildlife International- Easton, MD
ABC Laboratories- Columbia, MO
AquaSurvey- Flemington, NJ
Ricerca- Painesville, OH
Stevens Ecology, Mosier, OR
Harlan Labs (Safe Pharm)- UK
Huntington Life Sciences- UK
NOTOX- Netherlands
Covance- UK
Harlan (RCC)- China

Appendix B
Medical Device Labs

Vendor	Location	Phone #	Website	Pharmacology	Metabolism	Contract device manufacturing	Contract sterilization	Physical testing	Additional services
ABC Laboratories	Columbia, MD	(573) 474-8579	http://www.abclabs.com		X				Manufacture, stability, validation
Advanced Polymers, Inc.	Salem, NH	(603) 327-0600	http://www.advpoly.com/default.aspx			X			
Aircom Manufacturing, Inc.	Indianapolis, IN	(317) 545-5383	http://www.aircommfg.com			X			Distribution, prototyping, supply chain management
AMF Technologies	Rockland, MA	(781) 982-0137	http://www.amftechnologies.com			X			Project management
ANPRO	Haw River, NC	(800) 523-1276	http://www.anpro.com				X		
Applied Tech	Calhoun, GA	(706) 629-4624	http://www.applied-technologies.com					X	
Balchem Corporation (ARC Specialty Product)	New Hampton, NY	(845) 326-5600	http://www.balchem.com/arc				X		Packaging, distribution
BASi	W. Lafayette, IN	(800) 845-4246 (765) 463-4527	http://www.basinc.com					X	Method validation, stability,
BD Biosciences	San Jose, CA	(408) 432-9475	http://www.bdbiosciences.com		X				ADME
Biolene	Buenos Aires, Argentina	+54 11 43 08 49 63	http://www.biolene.com				X		Manufacture
Biopharmaceutical Research Inc.	Vancouver, Canada	(604) 432-9237	http://www.bripharm.com		X				Stability, label, QA, QC
Calvert Preclinical	Olyphant, PA	(570) 586-2411	http://www.calvertlabs.com	X	X				Pharmacokinetics, QA, ADME

Cardinal Health	Dublin, OH	(614) 757-5000	http://www.cardinal.com				X	Development, manufacturing, stability
Case Medical	South Hackensack, NJ	(888) 227-CASE	http://www.casemed.com			X		Validation, product development, manufacture
Cecon Consulting Group	Wilmington, DE	(302) 994-8000	http://www.cecon.com				X	
Charles River Laboratories	Wilmington, MA	(877) 274-8371	http://www.criver.com		X			Manufacturing
Chemir	Maryland Heights, MO	(314) 291-6620	http://www.chemir.com				X	Stability, method development, bioanalytical
Covance	Princeton, NJ	(888) COVANCE	http://www.covance.com	X	X			Stability, clinical design and management, consulting
CTBR	Quebec, Canada	(514) 630-8200	http://www.ctbr.com		X			Method validation, analysis
CXRbiosciences	Scotland, UK	+44 (0) 1382 432163	http://www.cxrbiosciences.com		X			Development, consulting
Dalton Chemical Laboratories, Inc.	Toronto, ON	(800) 567-5060	http://www.dalton.com			X		Scale up, development
DEKA Research and Development Corporation	Manchester, NH	(603) 669-5139	http://www.dekaresearch.com			X		Design
Drug Safety Eval. Consulting, Inc.	Birmingham, AL	(205) 995-9545	http://www.dseconsulting.com		X			Stability, method validation
Eclipse Scientific Group	Cambridgeshire, UK	01354 695858	http://www.eclipsescientific.co.uk				X	Method development, stability
ETC sterilization Systems	Southampton, PA	(215) 355-9100	http://www.etcsterilization.com			X		Validation, manufacturing
Ethox Corp.	Buffalo, NY	(716) 842-4000	http://www.ethoxcorp.com			X	X	Lab services

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Vendor	Location	Phone #	Website	Pharmacology	Metabolism	Contract device manufacturing	Contract sterilization	Physical testing	Additional services
Exygen Research	State College, PA	(800) 281-3219	N/A		X				Method validation, chem. analysis, stability
Galbraith	Knoxville, TN	(865) 546-1335	http://www.galbraith.com					X	Validation, method validation
Geneva Medical Products, LLC	Walworth, WI	(866) 383-3323	N/A			X			Design, testing
Gibraltar Laboratories	Fairfield, NJ	(973) 227-6882	http://www.gibraltarlabsinc.com			X			Method development, validation
Gwathmey, Inc	Cambridge, MA	(617) 491-0022 ext22	http://www.gwathmey.com		X				Consulting
Harlan Laboratories	Indianapolis	(888)-265-2953	http://www.harlan.com	X	X				Inhalation, phase II, III
Huntingdon Life Sciences Group Plc	England	+44 148-089-2000	http://www.huntingdon.com		X				Phase II, III
IBA	CA, IL, OH, TX, NC, NJ, MD, AK, GA, NM, NY, UT		http://www.iba-worldwide.com				X		Packaging
IMI (TAMI)	Haifa Bay, Israel	972-4-8469550/ 8469546	http://www.tami-imi.com					X	Development
In Vitro Technologies	Baltimore, MD	(410) 455-1245	http://www.invitrotech.com		X				Validation
INA Research Inc.	Japan Philippines	0265-72-6616	http://www.ina-research.co.jp	X					Consulting
Innoventor Engineering, Inc.	Saint Louis, MO	(314) 785-0900	http://www.innoventor.net			X			Testing

Inveresk Research	Scotland, UK	+44 (0) 1875 614545	http://www.inversek.com		X			Validation, phase II, III, IV, stability, storage, inhalation
Isotron	Wiltshire, UK	+44 (0) 8456 889977	http://www.isotron.co.uk				X	
ITR Laboratories Canada Inc	Quebec, Canada	(514) 457-7400	http://www.itrlab.com		X			Method validation, development
LAB	Quebec, Canada	(450) 973-2240	http://www.labresearch.com/location-canada.htm		X			Method validation
Lake Region Manufacturing	Chaska, MN	(952) 361-2515	http://www.lakergn.com			X		Manufacture
LBR Scientific, Inc	Clifton, NJ	(973) 473-0039	http://www.Lbrscientific.com				X	Manufacture
Magellan Labs	RTP, NC	(919) 481-4855	http://www.magellanlabs.com				X	Stability, validation
MedSource Technologies Portlyn	Moultonboro, NH	(603) 476-5538	http://www.medsourcetech.com			X		Design
Meridan Medical Technologies, Inc.	Columbia, MD	(800) 638-8093	http://www.meridianmeds.com			X	X	Validation, develop
Metal Chem Industries	Mumbai, India	+91-22-2577 3780/81/65040650	http://www.metalchemindia.com				X	
Metrics, Inc.	Greenville, NC	(252) 752-3800	http://www.metricsinc.com	X				Validation, storage
Microbac	Pittsburgh, PA	(412)459-1060	http://www.microbac.com				X	Manufacture
Micro-Med Inc.	Tustin, CA	(714) 731-6803	http://www.micro-med.com			X		Packaging
Midwest Research Institute	Kansas City, MO	(816) 753-7600	http://www.mriresearch.org		X			Method Validation
MPI Research	Mattawan, MI	(269) 668-3336	http://www.mpiresearch.com	X	X			Inhalation
NAMSA	Northwood, OH	(866) 666-9455	http://www.namsa.com			X	X	Packaging
NASP	Franklin, NJ	(800) 392-6310	http://www.naspco.com				X	Packaging
Nelson Lab	Salt Lake City, UT	(801) 290-7503	http://www.nelsonlabs.com			X		Validation
Nucro Technics	Scarborough, ON	(416) 438-6727	http://www.nucro.com	X				Phase II, III, IV, method validation
NUTEK	Hayward, CA	(510) 429-2900	http://www.nutekcorp.com				X	
OSG Norwich Pharmaceuticals	Norwich, NY	(607) 335-3100	http://www.norwichpharma.com			X		Package, QA, stability, validation

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Vendor	Location	Phone #	Website	Pharmacology	Metabolism	Contract device manufacturing	Contract sterilization	Physical testing	Additional services
Pall Life Sciences	East Hills, NY	(800) 717-7255	http://www.pall.com/biopharmaceutical	X					Validation, liquids
PAREXEL Intl. Corp.	Boston, MA	(781) 487-9900	http://www.parexel.com	X					Phase II, III, IV, validation
Pathology Associates	Frederick, MD Durham, NC	(301) 663-1644 (919) 544-5257	http://www.paicriver.com	X	X				Software
Patrick Plastics Corp.	West Chicago, IL	(630) 639-5011	http://www.patrickplastics.com			X			
PCI Services	Philadelphia, PA	(215) 637-8100	http://www.pciservices.com	X					Manufacture, package, validation
Pharma Quality Control Testing	Geneva, Switzerland	+41 22 739 91 11	http://www.pharmardqc.sgs.com			X		X	
PPD, Inc.	Austin, TX	(512) 5819156	http://www.ppdi.com	X					QA, QC, pharmacokinetics
Primus	Omaha, NE	(402) 344-4206	http://www.primus-sterilizer.com				X		
QTI	Whitehouse, NJ	(908) 534-4455	http://www.QTIonline.com	X					Validation, stability, consulting
Quality Chemical Laboratories	Wilmington, NC	(910) 796-3441 Ext 109	http://www.qualitychemlabs.com	X					Development, validation, stability
Quest Pharmaceutical Services, L.L.C.	Newark, DE	(302) 369-5601	http://www.questpharm.com		X				Validation
Quintiles	RTP, NC	(919) 988-2000	http://www.quintiles.com	X	X				Package, manufacture
Resonetics, Inc.	Nashua, NH	(603) 886-6772	http://www.resonetics.com			X			

Ricerca	Concord, OH	(888) 763-4797	http://www.ricerca.com		X			Development, manufacture
Ruhof	Mineola, NY	(516) 294-5888	http://www.ruhof.com				X	Manufacture
Saphikon Inc.	Milford, NH	(800) 899-5831	http://www.saphikon.com			X		Manufacture
Source Precision Medicine	Boulder, CO	(303) 385-2750	http://www.sourcemedicine.com	X				Genomic outsourcing
Southern Research Institute	Birmingham, AL	(888) 322-1166 (205) 322-7472	http://www.southernresearch.com		X			Cancer, phase II, III
SRI International	Menlo Park, CA	(650) 859-2000	http://www.sri.com	X	X			QC, QA
Star Services, Inc.	Hayward, CA	(510) 782-8848	http://www.starservicesinc.com				X	
Sterile Technologies	Queensbury, NY	(518) 793-7077	http://www.steriletech.com				X	Manufacture
Sterilization Services, Inc.	Atlanta, GA	(404) 344-8423	http://www.sterilization-services.com				X	
Steris Isomedix Services Inc.	Mentor, OH	(888) 8STERIS	http://www.steris.com				X	
Stimtech, Inc.	Amherst, NH	(603) 880-5050	http://www.stimtech.net			X		Distribution
STS duoTEK, Inc	Rush, NY	(800) 836-4850	http://www.stsduotek.com				X	Stability, microbiology, package
TFX Medical Incorporated	Jaffrey, NH	(603) 532-7706	http://www.teleflexmedicaloem.com			X		
Tower Laboratories	Centerbrook, CT	(860) 767-2127	http://www.towerlabs.com			X		Packaging
Toxikon	Bedford, MA	(800)-458-4141	http://www.toxikon.com			X		Packaging , ADME, pharmacokinetics/toxicokinetics
University of Iowa, Division of Pharmaceutical Science	Iowa City, IA	(319) 335-8674	http://www.uiowa.edu/~cadd	X				Method validation
Vacudyne	Chicago Heights, IL	(708) 757-5200	http://www.vacudyne.com				X	
Ventrex, Inc.	Ventura, CA	(805) 658-2984	http://www.ventrexinc.com			X	X	
Vetter	Ranesburg, Germany	49-751-3700-0	http://www.vetter-group.com	X				Aseptically pre-filled applications, package, stable, valid
Vital Pharma Inc.	Riviera Beach, FL	(561) 844-3221	http://www.vitalpharma.com			X		Validation, stability
WellSpring Pharmaceutical	Oakville, ON	(866) 337-4500	http://www.wellspringpharm.com			X		Manufacture

Appendix C
Phase I Labs

Vendor	Website	Phone #
AAI international	http://www.aaipharma.com/	800-575-4224
ACE pharmaceuticals	http://www.ace-pharm.nl/ Location in The Netherlands	+31.36.5474091
ACM medical lab	http://www.acmlab.com/	1.800.525.5227
Algorithme Pharma	http://www.algopharm.com/ Canadian	514-381-ALGO (2546)
Almedica	http://www.almedica.com/	888-425-6334
Antigenics	http://www.antigenics.com/	781.674.4400
ARUP Labs	http://www.arup-lab.com/	800.242.2787
Biocor	http://biocor.org/	1-888-9-BIOCOR
BioSkin	http://www.bioskin.de/ Location in Germany (Specialized in dermatological testing)	+49 – 40 – 60 68 97-0
Bourn Hall Clinic	http://www.bourn-hall-clinic.co.uk/ Location in UK	+ 44 (0)1954 719111
CATO	http://www.cato.com	919-361-CATO (2286)
CharterHouse Clinical	http://www.charterhouse-clinical.com/ Location in London, UK	+44 (0)208 741 7170
Cirion	http://www.cirion.ca/ Location in Canada	(450) 688-6445
Clinical Horizons Research	http://www.horizonscrc.com/index.html	(303)399-4067
Clinical Research and Devel	http://www.clinicalrdservices.com/	973-696-0824
Clinimetrics	http://www.clinimetrics.com/	408.452.8215
CNS	http://www.cnswebsite.com/	954-266-1000
Cortrial	http://www.cortrial.com/	49 (30) 435 58 93 – 0
Covance	http://www.covance.com/	1.888.COVANCE
CRL	http://www.crlcorp.com/	(800) 445-6917
CTMS	http://ctmsinc.com/	888-422-3596
DP Clinical	http://www.dpclinical.com/	(301) 294-6226
Esoterix	http://www.esoterix.com/	(888) 333-3952
Essex Testing	http://www.essextesting.com/	(973) 857-9541

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Vendor	Website	Phone #
Frontage	http://www.frontagelab.com/	+1 201.678.0288
Genzyme Oncology	http://www.genzymeoncology.com/	Specializing in oncology
Huntingdon	http://www.huntingdon.com/index.html	
inVentive Clinical	http://www.inventivclinical.com/	877.559.6699
Inversek Research	http://www.criver.com/	(800) 988-9845
	Specialized in dermatological testing	
Lambda	http://www.lambdacanada-cro.com/	(416) 752-3333
MDS	http://www.mdsps.com/	610-239-7900
Medfiles	http://www.medfiles.ee/	+372 7 303 979
	Location in Estonia	
Medichem	http://www.medichem.co.uk/	44 – (0) – 1732 763 555
Millennix Inc.	http://www.millennix-inc.com/	(914) 694-4949
North Coast Clinical Lab	http://www.northcoastlab.com/default.htm	(419) 626-6012
Northwest Kinetics	http://www.nwkinetics.com	(253) 593-5304
Parexel	http://www.parexel.com/	781 487 9900
Patheon	http://www.patheon.com/home.htm	1-888-728-4366
Pharmaceutical Profiles	http://www.pharmprofiles.com/	609 951 2205
Pharmadata	http://www.pharmdata.com/	(770) 579.8812
PharmaResearch	http://www.criver.com/	919-465-6000
Philip Johnson Research Laboratory	http://stokes.chop.edu/programs/johnsonlab/	
PPD	http://www.ppdi.com/	910 251 0081
PRA International	http://www.prainternational.com/	703 748-0760
PRACS	http://www.pracs.com/	(701) 239-4750
Prime Trials	http://www.primetrials.com/	(604) 875-5122
	Canadian	
ProMedica CRC	http://www.promedicacrc.com/	617-782-6872
PSI	http://www.psi-cro.com/	+32 2 675 4890
	Locations in Brussels and St. Petersburg	
Quantum	http://www.quantum-intl.com/	(256) 971-1800
Schiff and Co.	http://www.schiffandcompany.com/	(973) 227-5330
SciAn	http://www.scian.com/	800-915-9315
Simbec	http://www.simbec.co.uk/	
Synteract	http://www.synteract.com/	(215) 283-9370
TNO BIBRA	http://www.tnobibra.com/	+44 (0)20 8652 1040
	Location in UK	
West	http://www.westpharma.com/	(800) 345-9800
Worldwide Clinical Trials	http://www.wwctrials.com/	+1 610 964 2000

Appendix D
Analytical Labs

Vendor	Location	Phone #	Website	Analytical	Bioanalytical	Additional services
Abbott	Abbott Park, IL	(847) 935-0945	http://www.abbottcontractmfg.com	X		Delivery, biologics
ABC Laboratories	Columbia, MD	(573) 474-8579	http://www.abslabs.com	X	X	Manufacturing, stability
Alturas Analytics Inc.	Moscow, ID	(208) 883-3400	http://www.alturasanalytics.com	X	X	Pharmacokinetics, validation
BASi	W. Lafayette, IN	(800) 845-4246 (765) 463-4527	http://www.basinc.com	X	X	Method validation, toxicology lab,
Battelle	Columbus, OH	(800) 201-2011	http://www.battelle.org	X	X	Toxicology lab
Baxter	Bloomington, IN	(800) 422-9837	http://www.baxter.com	X		Stability, packaging, biological
Bertin Pharma	Montigny le Bretonneux, France	+33 (0)1 39 30 62 60	http://www.bertinpharma.com	X	X	Formulation, manufacturing, packaging, toxicology lab
Biopharmaceutical Research Inc.	Vancouver, Canada	(604) 432-9237	http://www.bripharm.com	X	X	Stability, pharmacokinetics, ADME
BioReliance Corp.	Rockville, MD	(301) 738-1000	http://www.bioreliance.com	X	X	Manufacturing, stability, biologics
Boston Analytical Inc.	Salem, NH	(603) 893-3758	http://www.bostonanalytical.com	X		Method validation, stability
BTC	Irvine, CA	(949) 660-3185	http://www.biologicaltestcenter.com	X		Toxicology lab, pharmacokinetics, ADME
Calvert Preclinical	Olyphant, PA	(570) 586-2411	http://www.calvertlabs.com	X		Toxicology lab, QA, pharmacokinetics, ADME
Catalent	Somerset, NJ	(877) 587-1835	http://www.catalent.com	X	X	Method development, manufacturing
Celsis Lab Group	St. Louis, MO	(800) 523-5227 (312) 476-1200	http://www.celsis.com	X		Method validation, stability, safety, efficacy, pharmacokinetics
Charles River Laboratories	Wilmington, MA	(877) 274-8371	http://www.criver.com	X	X	Manufacturing

Chemir Analytical Services	Maryland Heights, MO	(800) 659-7659	http://www.chemir.com	X		Development, validation, stability
CIT	Evreux, France	+33 2 32 292626	http://www.citox.com	X	X	Toxicology lab, validation
Covance	Princeton, NJ	(888) COVANCE	http://www.covance.com	X	X	Stability, clinical design, consulting, toxicology lab
CPT Co.	Fairfield, NJ	(973) 808-7111	http://www.cptclabs.com	X		Method validation, stability, product testing, toxicology lab
CTBR	Quebec, Canada	(514) 630-8200	http://www.ctbr.com	X	X	Method validation, analysis
Dow Chemical (parent corp.)	Midland, MI Smithfield, RI	(800) 258-2436 (parent corp.)	http://www.dow.com (parent corp.)	X		Excipients, manufacturing
DPT	San Antonio, TX	(866) CALL DPT	http://www.dptlabs.com	X		Management, production, compounding, packaging, formulation
Elite labs	Northvale, NJ	(201) 750-2646	http://www.elitepharma.com	X		Manufacturing
Fraunhofer ITA	Hannover, Germany	+49 511 5353 0	http://www.item.fraunhofer.de/	X		Toxicology lab
Galbraith Labs, Inc	Knoxville, TN	(877) 449-8797	http://www.galbraith.com	X		Environmental, method validation
GEA Process Engineering	Hudson, WI	(715) 386-9371	http://www.niroinc.com	X	X	Validation, equipment
Glatt Contract Services	Ramsey, NJ	07621 – 664 319	http://www.glattair.com	X		Validation
Harlan Laboratories	Indianapolis, IN	(888) 265-2953	http://www.harlan.com	X	X	Microbiology, monoclonals
Hollister-Stier	Spokane, WA	(800) 655-5329	http://www.hollister-stier.com	X		Labeling, packaging, validation, manufacturing
Integrated Laboratory Services (ILS)	RTP, NC	(919) 544-5857	http://www.ils-inc.com	X	X	QA, toxicology lab
In Vitro Technologies	Baltimore, MD	(888) 468 3400.	http://www.invitrotech.com		X	Validation, stability
Irvine Pharmaceutical Services	Irvine, CA	(877) 445-6554	http://www.ialab.com	X		Validation, inhalation, QC, environmental, formulation
Irysis	San Diego, CA	(858) 623-1520	http://www.irisys.com	X	X	Liquid-filled capsules, peptides, organics, formulation

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Vendor	Location	Phone #	Website	Analytical	Bioanalytical	Additional services
Kendle Intl. Inc.	Cincinnati, OH	(513) 381-5550	http://www.kendle.com		X	Software, validation, project management
LabCorp	Burlington, NC	(336) 538-6595	http://www.labcorp.com	X	X	Phase I–III, DNA testing
Lancaster Labs	Lancaster, PA	(717) 656-2300	http://www.lancasterlabs.com	X	X	Stability, validation, microbiology, cell bank
Lyne Labs	Brockton, MA	(800) 525-0450	http://www.lyne.com	X		Manufacturing, stability, packaging
Magellan Labs	RTP, NC	(919) 481-4855	http://www.magellanlabs.com	X	X	Stability, validation
Maxxam Analytics Inc.	Mississauga, ON	(866) 611-1118	http://www.maxxam.ca	X	X	Method development
McKesson Bioservices	Rockville, MD	(888) 4-MBS-BIO	http://www.mckesson.com	X		Clinical management, package, label, store
MDS (parent: Nordion)	Quebec, Canada	(613) 592-2790	http://www.mdsps.com	X	X	Management
Medtox Laboratories Inc.	St. Paul, MN	(800) 832-3244	http://www.medtox.com	X	X	Biomarkers
Metrics, Inc.	Greenville, NC	(252) 752-3800	http://www.metricsinc.com	X		Validation, stability, manufacturing, formulation
Microbac Laboratories	Pittsburgh, PA	(412) 459-1060	http://www.microbac.com http://www.southerntesting.com	X		Method development, specification, stability
Micron Tech	Exton, PA	(610) 425-5100	http://www.microntech.com	X		Validation, stability
Midwest Research Institute	Kansas City, MO	(816) 753-7600	http://www.mriresearch.org	X	X	Method validation, pharmacokinetics
MiKart	Atlanta, GA	(404) 351-4510	http://www.mikart.com	X		Validation, stability, package, formulation
MPI Research	Mattawan, MI	(269) 668-3336	http://www.mpiresearch.com	X	X	Toxicology testing, formulation
Nucro Technics	Scarborough, ON	(416) 438-6727	http://www.nucro.com	X	X	Method validation, stability

OSG Norwich	Norwich, NY	(888) 674-7979	http://www.norwichpharma.com	X	X	Manufacturing, package, QC, validation
Patheon	RTP, NC	(919) 226-3200	http://www.patheon.com	X	X	Manufacturing, method development, validation
Pharma Medica	Mississauga, ON	(905) 624-9115 (888) PHARMA1	http://www.pharmamedica.com	X	X	Phase II, III, IV, development, validation
Pharmatek	San Diego, CA	(858) 350-8789	http://www.pharmatek.com	X	X	Formulation, manufacturing, stability
Pion	Wodburn, MA	(781) 935-8939	http://www.pion-inc.com	X		Permeability
Pisgah Labs Inc.	Pisgah Forest, NC	(828) 884-2789	http://www.pisgahlabs.com	X		Validation, manufacturing
PPD, Inc.	Wilmington, NC	(910) 251-0081	http://www.ppdi.com	X	X	Phase I–III, pharmacokinetics
Product Safety Labs	Dayton, NJ	(732) 438-5100	http://www.productsafetylabs.com	X	X	Method development, toxicology lab
QTI	Whitehouse, NJ	(908) 534-1054	http://www.QTIonline.com	X	X	Validation, stability, extractables/leachables
Quality Chemical Laboratories	Wilmington, NC	(910) 796-3441	http://www.qualitychemlabs.com	X		Development, validation, stability, microbiology, metals testing
Quest Pharmaceutical Services, L.L.C.	Newark, DE	(800) 237-1970	http://www.qps-usa.com	X	X	Validation, Phase I–II, pharmacokinetics
Quintiles	RTP, NC	(919) 998-2000	http://www.quintiles.com	X	X	Package, manufacturing, Phase I–III
Ricerca	Concord, OH	(888) 763-4797	http://www.ricerca.com	X	X	Development, manufacturing
RTI	RTP, NC	(919) 541-6000	http://www.rti.org	X	X	Pharmacokinetics, biostatistics
Sequani	Ledbury, UK	+44 (0) 1531 634121	http://www.sequani.com	X	X	Program management, toxicology lab, pharmacokinetics
SGS	Rutherford, NJ	(877) 677-2667	http://www.sgs.com	X	X	Toxicology lab, Phase I–III
Siegfried	Zofingen, Switzerland	+41 62 746 1212	http://www.siegfried.ch	X		Development, manufacturing
SL Pharma Labs	Wilmington, DE	(302) 636-0202	http://www.slpharmalabs.com	X		Method validation, stability, development, microbiology
SNBL USA Ltd.	Everett, WA	(425) 407-0121	http://www.snblusa.com	X	X	Toxicology lab, pathology
Source Precision Medicine	Boulder, CO	(303) 385-2700	http://www.sourcemdx.com		X	Genomics outsourcing

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Vendor	Location	Phone #	Website	Analytical	Bioanalytical	Additional services
Southern Research Institute	Birmingham, AL	(800) 967-6774	http://www.southernresearch.com	X	X	Cancer, phase II–III, medicinal chemistry
SRI International	Menlo Park, CA	(650) 859-2000	http://www.sri.com	X		QC, QA
Stiefel Laboratories	RTP, NC	(888) STIEFEL	http://www.stiefel.com	X	X	Topicals
Stillmeadow Incorporated	Sugar Land, TX	(281) 240-8828	http://www.stillmeadow.com	X	X	Inhalation, stability, pharmacokinetics, radio-tracing
STS duoTEK, Inc.	Rush, NY	(800) 836-4850	http://www.stsduotek.com	X		Stability, microbiology, package
Syngenta Central Tox. Labs.	UK	(302) 425-2000 (parent corp.)	http://www2.syngenta.com (parent)	X	X	Toxicology lab
TNO Pharma	The Netherlands	+31 88 866 00 00 (parent corp.)	http://www.tno.nl (parent)	X		Toxicology lab
Toxicology Research Laboratory	Chicago, IL	(312) 996-9185	http://www.uic.edu/labs/tox/trlt.html	X	X	Toxicology lab
U. Pharmacueticals of Maryland, Inc.	St. Baltimore, MD	(410) 843-3700	http://www.upm-inc.com	X		Formulation, manufacturing
Viromed Laboratories	Minnetonka, MN	(952) 563-3300	http://www.viromed.com	X	X	IVF testing, tissue (donor) testing
West Pharmaceutical Service	Lionville, PA	(800) 345-9800	http://www.westpharma.com	X		Device components, packaging, extractables/leachables

Appendix E
GMP Contract Facilities

Vendor	Location	Phone #	Website	CGMP synthesis	Synthesis of radiolabelled compound	Biologic product manufacture	Additional services
ABC Laboratories	Columbia, MD	(888) 222-4331	http://www.abclabs.com	X	X		Manufacture, stability, analytical, extractable, leachable
Accucaps	Ontario, Canada	(800) 665-7210	http://www.accucaps.com	X			Validation, development, gelatin, capsules
Akorn	Lake Forest, IL	(800) 932-5676 x6165	http://www.akorn.com	X			Solutions, sterile fill, injectables, controlled substance
Aptuit	Multiple	(816) 767-3900	http://www.aptuit.com	X	X		Discovery, analytical
American Radiolabeled Chemicals	St. Louis, MO	(314) 991-4545	http://www.arc-inc.com		X		
Boehringer Ingelheim	Germany	+49 6132-77-0	http://www.boehringer-ingelheim.com	X		X	Validation, formulations, microsystems
Cambrex Bio Science	Charles City, IA	866-286-9133	http://www.bscp.com	X			Development, QC, QA, validation
Cangene Corp.	Ontario, Canada	(416) 675-8290	http://www.cangene.com	X			Label and packaging, fermentation, purification, formulation, filling and lyophilization
Chromos Molecular Systems Inc.	Burnaby, BC, Canada	(604) 415-7100	http://www.chromos.com			X	
CPL	Ontario, Canada	(905) 821-7600	http://www.cplltd.com	X			Oral and topical, package, manufacture
Dalton Chemical Laboratories Inc.	Toronto, Canada	(416) 661-2102	http://www.dalton.com			X	Peptide synthesis, analytical, formulation development, aseptic filling
Doosan Serdary Research Labs	Ontario, Canada	(416) 742-0774				X	

Dow Chemical	Midland, MI Smithfield, RI	(800) 304-1488	http://www.dow.com	X			Excipients, manufacture
DSM Pharmaceutical Products	Parsippany, NJ	(973) 257-8011 (973) 257-8220 (Biologics)	http://www.dsmcatalytica-pharm.com	X		X	Method validation, stability
Formatech	Andover, MA	(877) 853-5397	http://www.formatech.com	X			Develop, manufacturing
Gelda Scientific & Industrial Developement Corporation	Mississauga, ON, Canada	(905) 673-9320	http://www.gelda.com	X			
Genzyme Pharmaceuticals	Cambridge, MA	(617) 252-7500	http://www.genzyme.com/pharmaceuticals	X			Manufacture
Girindus	Cincinnati, OH	(513) 679-3000	http://www.girindus.com	X	X		QA, QA, radiochemistry
Glatt Pharmaceuticals Services	Binzen, Germany Ramsey, NJ	07621-664 319 (201) 825-8700	http://www.glattpharmaceuticals.com	X			Validation
HyClone	Logan, UT	(800) 492-5663	http://www.hyclone.com	X			Liquids, package
Lyne Labs	Brockton, MA	(800) 525-0450	http://www.lyne.com	X			Manufacture, stability, package
Magellan Labs	RTP, NC	(919) 481-4855	http://www.magellanlabs.com	X			Stability, validation
Medicago Inc.	Quebec, Canada	(418) 658-9393	http://www.medicago.com	X		X	Plant growth, manipulation, product recovery and purification
MediChem	Barcelona, Spain	+34 93 477 64 40	http://www.medichem.com	X			Develop, project management
Microbix Biosystems Inc.	Toronto, ON, Canada	(416) 234-1624	http://www.microbix.com	X		X	
Midwest Research Institute	Kansas City, MO	(816) 753-7600	http://www.mriresearch.org	X	X		Method validation
National Cancer Institute	Bethesda, MD	(800) 4-CANCER	http://www.nci.nih.gov		X		
Nucro Technics	Scarborough, ON, Canada	(416) 438-6727	http://www.nucro.com	X			Phase II, III, IV, method validation

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Vendor	Location	Phone #	Website	CGMP synthesis	Synthesis of radiolabelled compound	Biologic product manufacture	Additional services
OctoPlus	The Netherlands	+31 (0)71 524 40 44	http://www.octoplus.nl	X			QC
Norwich Pharmaceuticals	Norwich, NY	(607) 335-3100	http://www.norwichpharma.com	X			Manufacture, package, QV, QC, validation
Pisgah Labs Inc.	Pisgah Forest, NC	(828) 884-2789	http://www.pisgahlabs.com	X			Validation, manufacture
PPD, Inc.	Austin, TX	(512) 581-9156	http://www.ppdi.com	X			QA, QC, pharmacokinetics
Quality Chemical Laboratories	Wilmington, NC	(910) 796-3441	http://www.qualitychem-labs.com	X			Development, validation, stability
RTI International	Research Triangle Park, NC	(919) 485-2666	http://www.rti.org		X		Radiochemistry, pharmacokinetics/ toxicokinetics
Sequani	United Kingdom	+44 (0) 1531 634121	http://www.sequani.com	X			QA, program management
SGS Group	Switzerland	+41 22 739 91 11	http://www.pharmardqc.sgs.com	X			
Sigma-Aldrich	St. Louis, MO	(800) 336-9719	http://www.sigma-aldrich.com/safe	X			Manufacture
Southern Research Institute	Birmingham, AL	(888) 322-1166	http://www.southernre-search.com	X			Cancer, phase II, III
University of Iowa Division of Pharmaceutical Science	Iowa City, IA	(319) 335-8674	http://www.pharmacy.uiowa.edu/uip/index.html	X			Method validation
University of Rhode Island	Kingston, RI	(401) 874-5842	http://www.uri.edu/pharmacy/		X		
Viromed Laboratories	Minnetonka, MN	(952) 563-3300	http://www.viromed.com	X			QA

Viron Therapeutics Inc.	Ontario, Canada	(519) 858-5109	http://www.vironinc.com		X	
Yale Pharmaceutical Research Institute	Bethesda, MD	(301) 571-2388	http://www.yalepharma.com	X		QA, QC, development
National Cancer Institute	Bethesda, MD	(800) 4-CANCER	http://www.nci.nih.gov	X		
Neurochem Inc.	Quebec, Canada	(514) 337-4646	http://www.neurochem.com		X	
NeuroMed Technologies Inc.	Vancouver, Canada	(604) 822-9970	http://www.neuromedtech.com		X	
New Life Resources	Northvale, NJ	(201) 750-7880	http://www.newliferecources.net	X		Manufacture, hard-gel caps
Nexia Biotechnologies Inc.	Quebec, Canada	(450) 424-3067	http://www.nexiabiotech.com		X	
Northview Biosciences	Spartanburg, SC Northbrook, IL Berkeley, CA	(864) 574-7728 (847) 564-8181 (510) 548-8440	http://www.northviewlabs.com	X		Biocompatibility, validation
Nucro Technics	Scarborough, ON	(416) 438-6727	http://www.nucro.com	X		Phase II, III, IV, method validation
OctoPlus	The Netherlands	+31 (71) 524 40 44	http://www.octoplus.nl	X		QC
Oncolytics Biotech Inc.	Calgary, Canada	(403) 670-7377	http://www.onloyticsbiotech.com		X	
OSG Norwich	Norwich, NY	(607) 335-3000	http://www.norwichpharma.com	X		Manufacture, package, QV, QC, validation
Pharm Eco	North Andover, MA	(978) 784-5000	http://www.pharmeco.com	X		Manufacture, development
Pharmacor Inc.	Quebec, Canada	(450) 973-1710	http://www.pharmacor.com		X	
Pisgah Labs Inc.	Pisgah Forest, NC	(828) 884-2789	http://www.pisgahlabs.com	X		Validation, manufacture
PPD, Inc.	Austin, TX	(512) 5819156	http://www.ppdi.com	X		QA, QC, pharmacokinetics
Quality Chemical Laboratories	Wilmington, NC	(910) 796-3441	http://www.qualitychemlabs.com	X		Development, validation, stability

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Vendor	Location	Phone #	Website	CGMP synthesis	Synthesis of radiolabelled compound	Biologic product manufacture	Additional services
RTI International	RTP, NC	(919) 485-2666	http://www.rti.org		X		Radiochemistry, pharmacokinetics/ toxicokinetics
RusGen	Moscow, Russia	007-095-253-92-36	http://www.rusgen.com		X		
Sequani	United Kingdom	+44 (0) 1531 634121	http://www.sequani.com	X			QA, program management
Siegfried Actives	Pennsville, NJ Switzerland	(877) 763-8630 +44 62 746 1212	http://www.siegfried.ch	X			QC, QA
Siegfried Exclusives	Pennsville, NJ Switzerland	(856) 678-3601 +41 62 746 1221	http://www.siegfried.ch	X			Storage, QC, QA
Siegfried Ventures	San Diego, CA Pennsville, NJ Switzerland	(858) 546-4346 (856) 678-3809 +41 62 746 1111	http://www.siegfried.ch	X			QC, QA
Sigma-Aldrich	St. Louis, MO	(800) 336-9719	http://www.sigma-aldrich.com/safe	X			Manufacture
Southern Research Institute	Birmingham, AL	(888) 322-1166 (205) 322-7472	http://www.southernresearch.com	X			Cancer, phase II, III
Stiefel Research Institute	Oak Hill, NY	(800) 633-7647	http://www.stiefelresearch.com	X			Topicals, development, validation
U. of Iowa Div. Of Pharm. Science	Iowa City, IA	(319) 335-8674 (319) 335-4096	http://www.uiowa.edu/~pharmaser http://www.uiowa.edu/~cadd	X			Method validation
University of Rhode Island	Kingston, RI	(401) 874-5842	http://www.uri.edu/pharmacy/		X		

Viromed Laboratories	Minneapolis, MN St. Paul, MN Marietta, GA Camden, NJ	(800) 582-0077 (800) 582-0077 (888) 847-6633 (800) 622-8820	http://www.viromed.com	X			QA
Viron Therapeutics Inc.	Ontario, Canada	(519) 858-5109	http://www.vironinc.com			X	
Vital Pharma Inc.	Riviera Beach, FL	(561) 844-3221	http://www.vitalpharma.com	X			Validation
Yale Pharmaceutical Research Institute	New Haven, CT	(301) 571-2388	http://www.yalepharma.com/ADME.htm		X		QA, QC, development

Appendix F
Formulation

Vendor	Location	Phone #	Website	Formulation	Additional services
AAI pharma	Wilmington, NC	(910) 254-7000	http://www.aaipharma.com	X	Method validation , project management, packaging, manufacturing, delivery, phase II, III, and IV
Accucaps	Ontario, Canada	(800) 665-7210	http://www.accucaps.com	X	Validation, OTC, health and nutritionals
Akorn	Decatur, IL	(800) 932-5676	http://www.akorn.com	X	Solutions, ophthalmic, ointments, delivery, manufacture
BAS	W. Lafayette, IN	(800) 845-4246 (765) 463-4527	http://www.basinc.com	X	Method validation
Baxter	Deerfield, IL	(800)422-9837	http://www.baxterdrugdelivery.com	X	Stability, packaging, manufacturing, solutions, drug delivery, irrigation products
Beckloff Associates, Inc. (a Cardinal Health Company)	Overland Park, KS	(913) 451-3955	http://www.cardinal.com/us/en/beckloff#	X	Development, publishing, compliance, manufacturing, training
Ben Venue Lab.	Bedford, OH	(800) 562-4797	http://www.benvenue.com	X	Package, method validation, stability, Product and dissolution, IVT
Biacore (GE Healthcare)	Piscataway, NJ	(800) 526-3593	http://www.biacore.com	X	
Bilcare	Phoenixville, PA	(610) 935-4300	http://www.proclinical.com	X	Packaging, stability, global clinical support
Boston Analytical Inc.	Salem, NH	(603) 893-3758	http://www.bostonanalytical.com	X	Method validation, stability
Cambrex Corporation	East Rutherford, NJ	(866) 286-9133	http://www.cambrex.com	X	QC, QA, validation
Cangene Corp.	Winnipeg, Canada	(204) 275-4200	http://www.cangene.com	X	Label and packaging, manufacturing, bio defense, donor programs

Celsis Lab Group	St. Louis, MO	(866) 468-3400	http://www.celsislabs.com	X	Method validation, stability, safety, efficacy, rapid detection, analytical, microbiological, QA
Charles River Laboratories	Wilmington, MA	(781) 222-6000	http://www.criver.com	X	Manufacture
CPL	Mississauga, ON, Canada	(905) 821-7600	http://www.cplltd.com	X	Oral and topical, package, manufacture
CPTC (Consumer Product Testing Company)	Fairfield, NJ	(973) 808-7111	http://www.cptclabs.com	X	Method validation, stability, product testing
CSC	New Castle, DE	(302) 427-4000	http://www.calscorp.com	X	Nano ITC, Nano DSC
Dow Chemical	International		http://www.dow.com	X	Excipients, manufacture
DPT	San Antonio, TX	(866) CALL DPT	http://www.dptlabs.com	X	Management, production, compounding, package, manufacturing, semi-solids, liquids
DSM Catalytica Pharmaceutical	Greenville, NC	(252) 707-2307	http://www.dsm.com	X	Method validation, stability
Elite Pharmaceuticals Inc.	Northvale, NJ	(201) 750-2646	http://www.elitepharma.com	X	Manufacture
Ferro	Waukegan, IL	(847) 623-0370	http://www.ferro.com	X	Manufacture, method validation
Formatech	Andover, MA	(877) 853-KEYS	http://www.formatech.com	X	Development, manufacture, formulation, cell culture, purification, Aseptic fill, lyophilization and finish
GEA Process Engineering Inc. Atlantic Pharm. Services	Columbia, MD	(410) 997-8700	http://www.niroinc.com	X	Chemical, evaporator, pharma systems, liquids
Genzyme Pharmaceuticals	Cambridge, MA	(800) 868-8208	http://www.genzyme.com/pharmaceuticals	X	Manufacture, lipids, amino acid derivatives, custom peptides.
Glatt pharmaceutical Services	Ramsey, NJ	(201) 825-8700	http://www.glattpharmaceuticals.com	X	Validation, manufacturing

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Vendor	Location	Phone #	Website	Formulation	Additional services
Irvine Analytical Laboratories, Inc	Irvine, CA	(877) 445-6554	http://www.ialab.com	X	Validation, inhalation, QC, environmental, analytical chemistry, development, biopharmaceuticals, stability, manufacturing
Irysis	San Diego, CA	(858) 623-1520	http://www.irisys.com	X	Liquid-filled capsules, peptides, proternal, organics, manufacturing
King Pharmaceuticals	Bristol, TN	(800) 776-3637	http://www.kingpharm.com	X	Packaging, liquid and topical, manufacturing
Laureate Pharma	Princeton, NJ	(609) 919-3400	http://www.laureatepharma.com	X	QC, package, development, Aseptic fill, preclinical production
Lyne Labs	Brockton, MA	(800) 525-0450	http://www.lyne.com	X	Manufacture, stability, package, validation, formulations
Magellan Labs	RTP, NC	(919) 481-4855	http://www.magellanlabs.com	X	Stable, validation
MERCK	Whithouse Station, NJ	(908) 423-1000	http://www.diosynth.com	X	Stability, scale-up, vaccines, discovery, development
Meridian Medical Technologies	Columbia, MD	(410) 309-6830	http://www.meridianmeds.com	X	Package
Metrics, Inc.	Greenville, NC	(252) 752-3800	http://www.metricsinc.com	X	Validation, storage
Midwest Research Institute	Kansas City, MO	(816) 753-7600	http://www.mriresearch.org	X	Method validation, GMP/GLP Bioanalytical services
MiKart	Atlanta, GA	(404) 351-4510	http://www.mikart.com	X	Validation, stability, package, manufacturing, product development
OctoPlus	The Netherlands	+31 (71) 524 40 44	http://www.octoplus.nl	X	QC, Delivery, ophthalmic, clinical trials
Pall Corporation	East Hills, NY	(800) 717-7255	http://www.pall.com	X	Validation, liquids, biochemistry, capsules, intravenous and solutions

Patheon	RTP, NC	(919) 226-3200	http://www.patheon.com	X	Manufacture, dosage from development and manufacturing services, Pharma and biotech, packaging
Pharmaceutics International, Inc.	Hunt Valley, MD	(410) 584-0001	http://www.pharm-int.com	X	Packaging, project management, stability, CTM, formulation, manufacturing
Pharmatek	San Diego, CA	(858) 805-6383	http://www.pharmatek.com	X	Pharma chem., small peptides, GMP manufacturing, stability, preformulation, cytotoxic/high-potency
Quintiles	International RTP, NC	(800) 7627-5381 (866) 267-447	http://www.quintiles.com	X	Package, manufacture, phase I–IV, biopharmaceuticals, devices, MBDD,
SAFC	International	(800) 244-1137	http://www.moleculARmed.com http://www.sigma-aldrich.com	X	Cell and gene bases therapeutics and vaccines, scale-up, supply chain, analytical testing, cell engineering, manufacturing, biopharmaceuticals, diagnostics
Southern Research Institute	Birmingham, AL	(800) 967-6774	http://www.southernresearch.com	X	Cancer, phase II, III, immunology, ADME, PK, pathology, bioanalytical
SRI International	Menlo Park, CA	(650) 859-4771	http://www.sri.com	X	Pharmacokinetics, QC, QA
Stiefel (A GSK Company)	RTP, NC	(781) 879-1200	http://www.stiefel.com	X	Topicals, development, validation, dermatology
University of Iowa Pharmaceuticals	Iowa City, IA	(319) 335-8674	http://www.uiowa.edu/~cadd	X	Method, validation, formulation, SA
UPM Pharmaceuticals	MD	(410) 843-3738	http://www.upm-inc.com	X	SUPAC Guidance, Training, formulation, manufacturing
Vital Pharma Inc.	Riviera Beach, Florida	(561) 844-3221	http://www.vitalpharma.com	X	Validation
Yamanouchi Pharma	Norman, OK	(888) 236-5553	http://www.ypharma.com	X	Manufacture, validation, stability, solid dose

Appendix G
Dosage Forms

Vendor	Location	Phone #	Website	CTM	Label	Additional services
Akorn	Lake Forest, IL	(800) 932-5676	http://www.akorn.com	X		Solutions, ointments, delivery, manufacture
ARC	St. Louis, MO	(314) 991-4545	http://www.arc-inc.com		X	
Biopharmaceutical Research Inc.	Vancouver, Canada	(604) 432-9237	http://www.bripharm.com		X	Stability, QA, QC
Cangene Corp.	Winnipeg, Canada	(204) 275-4200	http://www.cangene.com		X	Packaging
CATO Research	Durham, NC	(919) 361-CATO	http://www.cato.com		X	
Chem Syn	Lenexa, KY	(800) 233-6643	http://www.chemsyn.com	X	X	Process, method validation
Dow Pharma	Petaluma, CA	(707) 793-2600	http://www.dowpharm.com		X	
DSM Catalytica Pharmaceutical	Parsippany, NJ	(973) 257-8011	http://www.dsmcatalytica-pharm.com	X		Method validation, stability
Elite Pharma	Northvale, NJ	(201) 750-2646	http://www.elitepharma.com	X		Manufacture
EMMCORP	Hempstead, NY	(800) 835-2393	http://www.easternmarking.com		X	
FLEXcon	Spencer, MA	(508) 885-8200	http://www.flexcon.com		X	
Formatech	Andover, MA	(877) 853-KEYS	http://www.formatech.com	X		Development, manufacture
Girindus	Cincinnati, OH	(513) 679-3000	http://www.girindus.com	X		Project management
Glatt Contract Services	Ramsey, NJ	(201) 825-8700	http://www.glattair.com	X		Validation
Hollister-Stier	Spokane, WA	(509) 489-5656	http://www.hollister-stier.com	X	X	Package, project management, validation
Irysis	San Diego, CA	(858) 623-1520	http://www.irisys.com	X		Liquid-filled capsules, peptides, proternal, organics
Lyne Labs	Brockton, MA	(800) 525-0450	http://www.lyne.com	X		Manufacture, stability, package
Magellan Laboratories	RTP, NC	(919) 481-4855	http://www.magellanlabs.com	X	X	Stability, validation
	Somerset, NJ	(732) 302-1400				
	San Diego, CA	(858) 547-7800				
	Albuquerque, NM	(815) 338-9500				
Meridian Medical Technologies	Columbia, MD	(410) 309-6830	http://www.meridianmeds.com	X		Package

Metrics, Inc.	Greenville, NC	(252) 752-3800	http://www.metricsinc.com	X		Validation, storage
Midwest Research Institute	Kansas City, MO	(816) 753-7600	http://www.mriresearch.org		X	Method validation
MiKart	Atlanta, GA	(404) 351-4510	http://www.mikart.com	X		Validation, stability, package, manufacture
Mova	Caguas, Puerto Rico	(800) 468-5201	http://www.movapharm.com	X		Manufacture, package
OSG Norwich	Norwich, NY	(607) 335-3000	http://www.norwichpharma.com	X		Manufacture, package, QV, QC, validation
Paragon Data Systems, Inc.	Cleveland, OH	(800) 211-0768	http://www.paragondatasystem.com		X	
Patheon	Ontario, Canada	(888) PATHEON	http://www.patheon.com	X		Manufacture, many dosage forms
PCI Services	Philadelphia, PA	(215) 637-8100	http://www.pciservices.com	X		Manufacture, package, validation
Pharmaceutical Research Company, Inc.	Exton, PA	(484) 875-9000	http://www.pharmaceuticalrc.com		X	
Pharmatek	San Diego, CA	(858) 350-8789	http://www.pharmatek.com	X		Pharma chem., small peptides
PPD, Inc.	Austin, TX	(512) 5819156	http://www.ppdi.com	X		QA, QC, pharmacokinetics
Quadrel Labeling Systems	Mentor, OH	(440) 602-4700	http://www.quadrel.com		X	
Quintiles	Kansas City, MO RTP, NC	(816) 767-3900 (877) 988-2100	http://www.quintiles.com	X		Package, manufacture
RCC	Switzerland	+41 61 975 11 11	http://www.rcc.ch	X		Inhalation, phase II, III
Ricerca	Concord, OH	(888) 742-3722	http://www.ricerca.com		X	
SAFC	San Diego, CA	(858) 523-9544	http://www.molecularmed.com	X		Cell and gene bases therapeutics and vaccines, scale-up, manufacturing
Schwarz	Seymour, IN	(812) 523-5490	http://www.schwarzusa.com	X		Manufacture, package, support, method
Siegfried Exclusives	Pennsville, NJ Switzerland	(856) 678-3601 +41 62 746 1221	http://www.siegfried.ch	X		Storage, QC, QA
Southern Research Institute	Birmingham, AL	(800) 967-6774 (205) 581-2000	http://www.southernresearch.com	X		Cancer, phase II, III

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Vendor	Location	Phone #	Website	CTM	Label	Additional services
SRI International	Menlo Park, CA	(650) 859-2000	http://www.sri.com	X		Pharmacokinetics, QC, QA
Star Labeling Products	Fairless Hills, PA	(800) 394-6900	http://www.starlabel.com		X	
Stiefel Research Institute	Oak Hill, NY	(800) 633-7647 (215) 295-3340	http://www.stiefelresearch.com	X		Topicals, development, validation
Tapecon	Buffalo, NY	(800) 333-2407	http://www.tapecon.com		X	
Taro	Hawthorne, NY	(800) 544-1449	http://www.tarousa.com		X	
Toxcon	Edmonton, Canada	(780) 435-9028	http://www.toxcon.com	X		Risk assessment
U. of Iowa Div. Of Pharm. Science	Iowa City, IA	(319) 335-8674	http://www.uiowa.edu/~cadd	X		Method validation
University Pharmaceuticals of Maryland, Inc.	St. Baltimore, MD	(410) 843-3700	http://www.upm-inc.com	X		SUPAC guidance, training

Appendix H
Clinical Testing

Vendor	Location	Phone #	Website	Clinical support	Phase I clinical	Clinical trial management	Clinical statistics	Additional services
AACT	Camperdown, Australia	+61 2 9993 4523	http://www.academicalliance.com		X	X	X	Project management, electronic data capture, Phase II–III
ABT Associates	Cambridge, MA	(617) 492-7100	http://www.abtassociates.com		X		X	Project management
ACE Pharmaceuticals	The Netherlands	+31 (0) 36 5227201	http://www.acepharmaceuticals.nl		X			Manufacturing, packaging
ACM Medical Lab	Rochester, NY	(800) 525-5227	http://www.acmgloballab.com	X	X	X		Phase II–IV, data management
Advanced Clinical Research	Salt Lake City, UT	(801) 355-4126	http://www.acr-research.com			X		
Advanced Clinical Services	Chicago, IL	(847) 267-1176	http://www.advancedclinical.com	X			X	Validation, programming, data management
Algorithme Pharma	Laval, Quebec	(450) 973-6077	http://www.algopharm.com		X			Phase I–IV, regulatory
Alquest	Minneapolis, MN	(763) 287-3830	http://www.alquest.com			X	X	Medical devices, data management
Aptuit	Greenwich, CT	(816) 767-3900	http://www.aptuit.com	X	X			Manufacturing, packaging
Arkios	Virginia Beach, VA	(757) 631-2114	http://www.arkios.com			X	X	Data management
ARUP Labs	Salt Lake City, UT	(800) 242-2787	http://www.arup-lab.com	X				
Barton and Polansky Associates, Inc.	New York, NY	(212) 759-6341	http://www.bpa-mcs.com				X	
BDH Clinical Research Services	Durham, NC	(919) 477-9542	http://www.bdhclinical.com			X		QA
Beardsworth Consulting Group, Inc.	Flemington, NJ	(800) 788-6046	http://www.beardsworth.com			X		QA, phase IV, development
BioClin Health Research, Inc.	British Columbia, Canada	(604) 276-2580	http://www.bioclin.ca		X	X		Phase II–IV

Biostat International, Inc	Tampa, FL	(813) 979-1619	http://www.biostatinc.com			X	X	SAS, validation, data management
Biotechnical Services, Inc.	North Little Rock, AR	(501) 758-6290	http://www.biotechnicalservices.com				X	Validation, data management, QA/QC
CAP Trials	Framingham, MA	(508) 620-2700	http://www.captrials.com			X		Training, educational materials
Cardinal Systems	Paris, France	+33 1 40 21 19 00	http://www.cardinal-sys.com			X	X	eCTD
Carolinas Research Associates	Charlotte, NC	(704) 503-3216	http://www.carolinasresearch.com		X	X		Phase II–IV
CATO	Durham, NC	(919) 361-CATO	http://www.cato.com		X	X	X	Phase II–IV, monitoring, regulatory
Cenetron	Austin, TX	(888) 834-6632 (512) 439-2000	http://www.cenetron.com	X				Trial supplies
Certus International, Inc.	Bedford, NH	(603) 472-8400	http://www.certusintl.com			X	X	Project management, imaging, monitoring
Chiltern International	Berkshire, UK	+44 (0)1753 512000	http://www.chiltern.com		X	X	X	Phase II–IV, regulatory filings
Cirion	Laval, QC	(450) 682-2231	http://www.cirion.ca	X				Biologics, immunology, microbiology
Clinical R&D Services	Wayne, NJ	(973) 696-0824	http://www.clinicalrdservices.com		X			Phase II–IV
Clinical Research Consulting, Inc.	Boston, MA	(508) 865-8907	http://www.eclinicalresearchconsulting.com			X		Project management, monitoring
Clinical Trial Management Services, Inc.	Bristol, TN	(800) 422-3596	http://www.ctmsinc.com			X	X	QA
ClinSmart	Longhorne, PA	(215) 710-3200	http://www.clinsmart.com				X	
ClinStat Consulting	Cardiff by the Sea, CA	(760) 207-5260	http://clinstatconsulting.com			X		Project management

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Vendor	Location	Phone #	Website	Clinical support	Phase I clinical	Clinical trial management	Clinical statistics	Additional services
Covance	Princeton, NJ	(888) COVANCE	http://www.covance.com		X	X	X	Stability, clinical design and management, consulting
CPT Co.	Fairfield, NJ	(973) 808-7111	http://www.cptclabs.com		X			Method validation. stability, analytical
CRL	Lenexa, KS	(800) 445-6917	http://www.crlcorp.com	X				Bioanalytical, data management
DATAMAP GmbH	Freiburg, Germany	+49 (761) 4 52 08-0	http://www.datamap.de				X	Programming, data management
DP Clinical	Rockville, MD	(301) 294-6226	http://www.dpclinical.com			X	X	Data management, regulatory, QA
DPT	San Antonio, TX	(866) CALL DPT	http://www.dptlabs.com			X		Analytical, clinical trial material
Ecron Acunova	Princeton, NJ	(973) 396-2742	http://www.ecronacunova.com	X	X	X	X	Phase II–IV
Emissary	Austin, TX	(512) 918-1992	http://www.sendemissary.com			X	X	QA, electronic data capture, regulatory
Emphusion	San Francisco, CA	(415) 776-0660	http://home.pdd.net			X		Statistics
EPS Company, Ltd.	Tokyo, Japan	+81-3-5804-7577	http://www.eps.co.jp				X	Programming, QA, data management
Estoerix Inc	Cranford, NJ	(877) 788-8861	http://www.esoterix.com	X				Project management
Frontage	Exton, PA	(610) 232-0100	http://www.frontagelab.com	X		X	X	Regulatory, pharmacokinetics
Genzyme	Cambridge, MA	(617) 252-7500	http://www.genzyme.com	X	X	X	X	Phase II–IV
Global Pharma Alliance	Bridgewater, NJ	(908) 672-3686	http://globalpharmalliance.com			X		Project management
GNB Limited	UK	NA	http://www.gnblimited.co.uk				X	Validation, trial design

Grayline Clinical Drug Trials	Wichita Falls, TX	(800) 782-0895	http://www.graylinecdt.com	X	X		Phase II–IV
Gulf Coast Research Associates, Inc.	Baton Rouge, LA	(225) 757-1084	http://www.gulfcoastra.com	X			Phase II–IV
Health Decisions	Durham, NC	(888) 779-3771	http://www.healthdec.com	X	X	X	Project management, electronic data capture, Phase II–IV
Health Research Associates, Inc.	Mountlake Terrace, WA	(425) 775-6565	http://www.hrainc.net			X	Consulting, project management
Healthcare Project Management (HPM)	Geneva, Switzerland	+41 22 596 44 44	http://www.hpmgeneva.com		X		
Huntingdon Life Sciences Group Plc	Cambridgeshire, UK	+44 (0) 1480 892 000	http://www.huntingdon.com	X			Phase II–III
ICON Clinical Research	Dublin, Ireland	+353 (1) 291 2000	http://www.iconclinical.com	X	X	X	Project management, QA, Phase II–IV
idv Data Analysis and Study Planning	Munich, Germany	+49 (89) 850 80 01	http://www.idvgauting.com			X	Programming, data management
INC Research	Raleigh, NC	(919) 876-9300	http://www.incresearch.com	X	X	X	Data management, Phase II–IV
Integrated Research, Inc.	Montreal, Canada	(514) 683-1909	http://www.iricanada.com			X	Regulatory, data management
International Drug Development Institute (IDDI)	Louvain-la-Neuve, Belgium	+32 (0)10 61 44 44	http://www.iddi.com		X	X	
inVentive Clinical	Houston, TX	(281) 829-1110 (877) 559-6699	http://inventivclinical.com/solutions/cro-services/default.aspx		X	X	
Kendle Intl. Inc.	Cincinnati, OH	(800) 733-1572	http://www.kendle.com	X	X		Software, validation, project management
Köhler GmbH, Dr. Manfred	Freiburg, Germany	+49 761 50318	http://www.koehler-freiburg.de			X	Data management, randomization

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Vendor	Location	Phone #	Website	Clinical support	Phase I clinical	Clinical trial management	Clinical statistics	Additional services
Lovelace Respiratory Research Institute	Albuquerque, NM	(505) 348-9400	http://www.lrri.org		X			Phase II–IV
MAJARO InfoSystems, Inc.	San Jose, CA	(408) 330-9400	http://www.majaro.com				X	Data management, project management
Medfiles	Helsinki, Finland	+358 20 7446 840	http://www.medfiles.fi	X	X	X		Phase II–IV, regulatory
MediMentum ApS	Hilleroed, Denmark	+45 48 22 9410	N/A				X	Consulting, programming
Medpace LLC	Cincinnati, OH	(513) 579-9911	http://www.medpace.com			X	X	Project management, regulatory
Microbiotest Laboratories	Sterling, VA	(703) 925-0100	http://www.microbiotest.com		X			QA/QC
Micromedex	Greenwood Village, CO	(303) 486-6400	http://www.micromedex.com	X				Electronic data capture
Msource Medical Development	Kraainem, Belgium	+32-2-768.01.66	http://www.msource-cro.com	X	X	X	X	Project management, Phase II–IV, QA/QC
NOCCR	New Orleans, LA	(504) 821-CARE	http://www.noccr.com		X			Phase II–IV
Northwest Kinetics, L.L.C.	Tacoma, WA	(253) 593-5304	http://www.nwkinetics.com		X			Phase I, II, pharmacokinetics, QA
Novella Clinical	Durham, NC	(919) 484-1921	http://www.novellaclinical.com			X		Staffing
Nth Analytics	Princeton, NJ	(908) 672-5649	http://www.nthanalytics.com				X	Validation, programming
Nucro Technics	Scarborough, ON	(416) 438-6727	http://www.nucro.com	X	X			Phase II–IV, method validation, QA
Omnicare Clinical Research	King of Prussia, PA	(800) 290-5766	http://www.omnicarecr.com			X	X	Project management, medical devices, Phase II–IV

Operatix Consulting Inc.	Waterdown, Ontario	(905) 690-1200	http://www.operatrix.com			X		Project management
P3 Research, Ltd.	Tauranga, New Zealand	+64 7 579 0453	http://www.p3research.co.nz		X			Phase II–IV
Paragon	Irvine, CA	(949) 224-2800	http://www.parabio.com				X	Programming, project management, QA, regulatory
PAREXEL Intl. Corp.	Boston, MA	(781) 487-9900	http://www.parexel.com	X	X	X	X	Phase II–IV, validation
Patheon	Mississauga, ON	(888) 728-4366	http://www.patheon.com	X				Packaging
Peirrel Research	Essen, Germany	+49 201 89900	http://www.pierrel-research.com			X	X	Data management, regulatory
Pharma Medica	Ontario, Canada	(905) 624-9115 (877) PHARMA1	http://www.pharmamedica.com	X	X	X	X	Phase II–IV, development, validation
PharmaNet	Princeton, NJ	(609) 951 6800	http://www.pharmanet.com	X	X	X	X	Phase II–IV, medical devices
Phase Forward	Waltham, MA	(888) 703-1122	http://www.phaseforward.com			X		Data management
PPD, Inc.	Wilmington, NC	(910) 251-0081	http://www.ppdi.com	X	X	X	X	QA, pharmacokinetics, Phase II–IV
PRA International	Raleigh, NC	(919) 786-8200	http://www.prainternational.com		X	X		Phase II–IV, QA
PRACS	Fargo, ND	(701) 239-4750	http://www.pracs.com		X			Phase II–IV, bioanalytical
Premier Research	Philadelphia, PA	(215) 282-5500	http://www.premier-research.com			X	X	Data management, QA
Prologue Research	Columbus, OH	(614) 324-1500	http://www.procro.com			X	X	Programming, project management, development
PSI	Zug, Switzerland	+41 41 228 10 00	http://www.psi-cro.com			X	X	Phase I, II, III, development, consulting

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Vendor	Location	Phone #	Website	Clinical support	Phase I clinical	Clinical trial management	Clinical statistics	Additional services
Research Dynamics Consulting Group, Ltd.	Pittsford, NY	(585) 381-1350	http://www.resdyncg.com			X		Consulting, monitoring
Research Pharmaceutical Services, Inc.	Fort Washington, PA	(215) 540-0700	http://www.rpsweb.com			X	X	Programming, project management, QA/QC
Rho, Inc.	Chapel Hill, NC	(919) 408-8000	http://www.rhoworld.com			X	X	Programming, randomization
SciAn Research Services	Toronto, Canada King of Prussia, PA Walnut Creek, CA	(416) 231-8008 (610) 945-1763 (925) 407-2069	http://www.scian.com		X	X	X	Consulting
Sequani	United Kingdom	+44 (0) 1531 634121	http://www.sequani.com		X			QA, management
SGS Biopharma	Wavre, Belgium	(877) 677-2667	http://www.sgsbiopharma.com		X	X	X	QA/QC
Simbec	United Kingdom	+44 1443 690977	http://www.simbec.co.uk		X			Phase II, III, QA
SMO-USA, Inc.	Big Timber, MT	(406) 930-1970	http://www.smo-usa.com		X	X		Phase II–IV
Southern Research Institute	Birmingham, AL	(888) 322-1166	http://www.southernresearch.com		X			Cancer, phase II, III
Statisticians WithOut Borders	Bahama, NC	(919) 477-4007	http://www.statisticinas-withoutborders.com				X	Programming
Statking Consulting Inc.	Fairfield, OH	(513) 858-2989	http://www.statkingcon-sulting.com			X	X	Programming, develop-ment, randomization
Symbiance, Inc.	Princeton Junction, NJ	(609) 243-9050	http://www.symbiance.com			X	X	Programming, project management, development
SyMetric Sciences	Lery, QC, Canada	(450) 691-0183	http://www.symetric.ca			X	X	

Symfo	Boston, MA	(617) 577-9484	http://www.symfo.com	X	X		X	Project management, randomization
Synteract, Inc.	Carlsbad, CA	(760) 268-8200	http://www.synteract.com		X	X	X	Programming, project management, develop, randomization
Target Health Inc.	New York, NY	(212) 681-2100	http://www.targethealth.com			X	X	
Trial Form Support (TFS)	Lund, Switzerland	+46 46 280 18 00	http://www.trialformsupport.com	X	X	X	X	Phase II–IV
Trial Management Group, Inc.	Toronto, Canada	(416) 929-7717	http://www.tmginvestigators.com			X		Phase II–IV
University of Iowa Division of Pharmacueticals Science	Iowa City, IA	(319) 335-8674 (319) 335-4096	http://www.pharmacy.uiowa.edu/uip					Method validation
United Biosource	Chevy Chase, MD	(866) 458-1096	http://unitedbiosource.com	X	X	X		Phase IIIb–IV, health economics, project management
Uppsala Monitoring Centre	Uppsala, Sweden	+46 1865 6060	http://www.who-umc.org				X	
Virtu Stat, Ltd.	North Wales, PA	(215) 699-2424	http://www.virtustat.com				X	Validation, programming, randomization, Phase I through IV study design
Westat	Sarasota, FL	941-926-2922	http://www.westat.com				X	Consulting
West Pharmaceutical Service	Lionville, PA	(610) 594-2900	http://www.westpharma.com		X			Device and package components, drug-package, interactions
Worldwide Clinical Trials	King of Prussia, PA	(610) 964-2000	http://www.wwctrials.com	X	X	X		Phase II–IV

Appendix I
Regulatory Services

Vendor	Location	Phone #	Website	IND preparation	NDA preparation	Annual update preparation	Regulatory advisors	Additional services
Advanced Clinical Services	Bannockburn, IL	(847) 267-1176	http://www.advancedclinical.com	X		X	X	QA, SAS
Agallaco and Associates	Belle Mead, NJ	(908) 874-7558	Agallaco.com		X			Validation, manufacturing
Algorithm Pharma Inc.	Laval, QC	(514) 381-2546	http://www.algopharm.com				X	QA/QC, development
Allied Clinical Research	Ontario, Canada	(905) 238-0599	http://www.allied-research.com	X				Phase II, III, method development
AON	Chicago, IL	(312) 381-1000	http://www.aon.com				X	
ArisGlobal, LLC	Stamford, CT	(203) 588-3000	http://www.arisglobal.com				X	
Arkios Bio Development International	Virginia Beach, VA	(757) 631-2114	http://www.arkios.com	X	X		X	Project management
Beardsworth Consulting Group, Inc.	Flemington, NJ	(800) 788-6046	http://www.beardsworth.com	X	X			PLA prep, project management
Beckloff Associates, Inc	Overland Park, KS	(913) 451-3955	http://www.beckloff.com	X	X	X	X	Development
Brand Institute, Inc.	Miami, FL	(305) 374-2500	http://www.brandinstitute.com		X	X	X	Consulting, validation
Cambridge Regulatory Services Limited	Cambridgeshire, UK	+44 (0) 1480 465755	http://www.cambreg.co.uk				X	
CanReg Inc.	Dundas, ON	(866) 7CANREG	http://www.canreg.ca	X	X	X	X	Consulting, PLA prep
CCS Associates	Mountain View, CA Vienna, VA	(650) 691-4410	http://www.ccsainc.com	X	X			QA
Cerner	Kansas City, MO	(816) 221-1024	http://www.cerner.com					
Certus International, Inc.	St. Louis, MO	(636) 519-1699	http://www.certusintl.com		X		X	Development, project management
ClinForce, Inc	Durham, NC	(800) 964-2877	http://www.clinforce.com				X	Programming, project management
Covance Inc.	Princeton, NJ	(888) 268-2623	http://www.covance.com			X	X	Consulting

DataCeutics, Inc.	Pottstown, PA	(610) 970-2333	http://www.dataceutics.com		X			Validation, consulting, project management
Emissary Inc.	Austin, TX	(512) 918-1992	http://www.sendemissary.com	X				Development, project management
EMMES Corporation	Rockville, MD	(301) 251-1161	http://www.emmes.com	X				QC, project management
eResearch Technology	Philadelphia, PA	(215) 972-0420	http://www.ert.com		X			
EZ Associates	Washington, NJ	(908) 531-8148	http://www.ezassociates.com		X			Development
Gad Consulting Services	Cary, NC	(919) 233-2926	http://www.gadconsulting.com	X	X	X	X	
Galt Associates, Inc.	Sterling, VA	(703) 421-6720	http://www.DrugSafety.com			X	X	Consulting
Health Decisions	Oxford, UK	+44 1865 338005	http://www.healthdec.com				X	Project management
Icagen, Inc.	Durham, NC	(919) 941-5206	http://www.icagen.com	X	X			Development
ICON Clinical Research	North Wales, PA	(215) 616-3000	http://www.iconclinical.com		X			QA/QC, project management
IDRAC	Fort Washington, PA	(215) 386-0100	http://www.idrac.com	X	X		X	Validation
Image Solutions, Inc.	Morristown, NJ	(973) 560-0404	http://www.imagesolutions.com	X	X			BLA prep, consulting
IMIC	Colonia Roma Mexico, Mexico	(800) 292-8849	http://www.imicresearch.com				X	QA/QC
INC Research	Raleigh, NC	(919) 876-9300	http://www.incresearch.com				X	Project management, development
Integrated Research Inc.	Montreal, QC	(514) 683-1909	http://www.iricanada.com				X	Development
Inveresk Research	Cary, NC	(800) 988-9845	http://www.inveresk.com				X	Project management
Jarosz Regulatory Services, Inc.	Whitewater, WI	(262) 473-4255	http://www.jrsweb.com				X	CTX prep
Kendle International	Cincinnati, OH	(513) 381 5550	http://www.kendle.com	X	X		X	Phase II, III, IV
Kruse Consulting Group	Cheyenne, WY	(307) 634-7697	http://www.kruseconsultinggroup.com	X	X			QA, project management
Lineberry Research Associates	RTP, NC	(919) 547-0970	http://www.lineberryresearch.com	X	X			Development, IB
Liquent Inc.	Horsham, PA	(215) 328-4444	http://www.liquent.com	X	X	X	X	BLA prep, consulting
Lorenz Hoffman	Chapel Hill, NC	(919) 918-7707	http://www.larryhofmann.com	X	X			Consulting

(continued)

Vendor	Location	Phone #	Website	IND preparation	NDA preparation	Annual update preparation	Regulatory advisors	Additional services
Magellan Labs	RTP, NC Somerset, NJ San Diego, CA Albuquerque, NM	(919) 481-4855 (732) 302-1400 (858) 547-7800 (815) 338-9500	http://www.magellanlabs.com	X	X			Stability, validation
MAJARO InfoSystems, Inc.	Santa Clara, CA	(408) 330-9400	http://www.majaro.com		X			Validation, project management
McCarthy Consultant Services, Inc.	Newmarket, ON	(905) 836-0033	http://www.mccarthyconsultant.com	X	X	X	X	Consulting, QA/QC
Med Exec International	Glendale, CA	(818) 552-2036	http://www.medexecintl.com				X	QA/QC
MedFocus Clinical Research Consulting Opportunities	Chicago, IL	(800) 256-4625	http://www.medfocus.com		X			Consulting, project management
Medichem	Barcelona, Spain	+ 34 93 477 64 40	http://www.medichem.es	X				Develop, scale up
MEDISCRIBE, INC.	Cary, NC	(919) 468-8518	http://www.mediscribe.com	X	X		X	IB, development
Medpace LLC	Cincinnati, OH	(513) 579-9911	http://www.medpace.com		X		X	Project management, programming
MedSource Consulting, Inc.	Houston, TX	(281) 286-2003	http://www.medsource.com	X			X	Project management
MORIAH Consultants	Yorba Linda, CA	(714) 970-0790	http://www.moriahconsultants.com	X	X	X	X	BLA prep, consulting
Nucro-Technics Inc.	Scarborough, Ontario	(416) 438-6727	http://www.nucro-technics.com				X	QA/QC, stability
NuGenesis Technologies Corporation	Milford, MA	1-888-246-1888	http://www.nugenesis.com				X	Validation, project management, QA/QC
Omnicare Clinical Research	King of Prussia, PA	(800) 290-5766	http://www.omnicarecr.com				X	Project management

ORA Clinical Research and Development	Andover, MA	(978) 685-8900	http://www.oraclinical.com				X	Project management
Paragon Biomedical	Irvine, CA	(949) 224-2800	http://www.parabio.com				X	Programming, project management, QA/QC
Pharmaceutical Regulatory Services, Inc.	Princeton, NJ	(609) 497-9694	http://www.pharmregservices.com	X		X	X	Consulting
PharmaNet	Princeton, NJ	(609) 951-6800	http://www.pharmanet-cro.com	X				Consulting
Phoenix Regulatory Associates, Ltd.	Sterling, VA	(703) 406-0906	http://www.phoenixrising.com	X	X		X	Validation
PPD Development	Morrisville, NC	(919) 462-5600	http://www.ppdi.com	X			X	Project management
PRA International	Charlottesville, VA	(434) 951-3924	http://www.prainternational.com	X	X		X	Project management
PSI International, Inc.	Fairfax, VA	(703) 352-9482	http://www.psiint.com			X	X	Consulting
RCN Associates, Inc.	Annapolis, MD	(410) 263-3355	http://www.rcnrx.com		X			
Recruitech International, Inc.	Horsham, PA	(215) 293-1300	http://www.recruitech.com				X	Project management, QA/QC
Regulatory Affairs, North America LLC	Durham, NC	(919) 479-9956	http://www.ranallc.com	X		X	X	Consulting, CTX prep, IB
RPS	Plymouth Meeting, PA	(866) RPS-1151	http://www.rpsweb.com				X	Programming, project management, QA/QC
Simbec Research Limited	South Wales, UK	+44 (0) 1443 690977	http://www.simbec.co.uk				X	Project management, phase I
Smith Hanley Consulting Group	Lake Mary, FL	(407) 805-3010	http://www.smithhanley-consulting.com		X			Programming, project management
SRI	Menlo Park, CA	(650) 859-2000	http://www.sri.com	X				QA, pharmacokinetics
Target Health Inc.	New York, NY	(212) 681-2100	http://www.targethealth.com	X	X		X	Data management
TRI	Bethesda, MD	(301) 564-6400	http://www.tech-res.com/tri/	X				
TriPharmSafety, Inc	Raleigh, NC	(919) 870-5772	http://drugsafety.home.mindspring.com	X	X			Project management
Wainwright Associates Limited	Berkshire, UK	+44 (0) 1628 530554	http://www.wainwrightassociates.co.uk			X	X	Consulting, CTX prep
Weissinger Solutions, Inc.	Las Vegas, NV	(702) 294-3134	http://www.weissinger.com	X	X	X	X	BLA prep, consulting, IB

Appendix J
Contract Laboratory Audit Check List

Client	Revision:	Title: CONTRACT LABORATORY AUDIT CHECKLIST (GLP)	Page 1 of 5

Audit#:_____ Date: _____ Auditor:_____

1. Study Title:_____
2. Laboratory:_____
3. Address:_____
4. Date of Audit:_____
5. Auditor:_____
6. Date of Last FDA Inspection of Laboratory:_____
7. Date of Last CarboMedics Audit of Laboratory:_____
8. Facility Manager:_____
9. Study Director:_____
10. Quality Assurance Unit:_____

		Unaccept	Needs Imp.	Accept	Excellent
11.	**Protocol:**				
	a. Title and Purpose of Study				
	b. Identification of Test and Control Articles				
	c. Name of Sponsor and Name and Address of Testing Facility				
	d. Description of Animal Model				
	e. Rationale for Animal Model				
	f. Procedure for Identification of Test System				
	g. Description of Experimental Design				
	h. Description of Animal Diet				
	i. Administration of Test or Control Article				
	j. Type and Frequency of Tests, Analyses, and Measurements				
	k. Records to be Maintained				
	l. Date of Approval and Dated Signature of Study Director				
	m. Statistical Methods to be Used				
	n. Changes (with Reasons) Approved and Maintained with Protocol				
12.	Master Schedule Sheet (Test system, Nature of Study, Date Study was Initiated, Current Status, Identity of Sponsor, and Name of Study Director)				

Client	Revision:	Title: CONTRACT LABORATORY AUDIT CHECKLIST (GLP)	Page 2 of 5

		Unaccept	Needs Imp.	Accept	Excellent
13.	Current Summary of Training and Experience and Job Description for Each Individual				
14.	Personnel Qualifications				
15.	**Quality Assurance (QA) Unit:**				
	a. Independent of Personnel Engaged in Study				
	b. Written Procedure for Operation of QA Unit				
	c. Maintains copy of Master Schedule Sheet				
	d. Maintains Copy of All Protocols				
	e. Inspections at Intervals Adequate to Assure Integrity				
	f. Written Reports of Periodic Inspections				
	g. Significant Problems Reported to Study Director and Management				
	h. Written Status Reports on Each Study				
	i. Reviews Final Study Report				
	j. All QA Unit Records are Kept in One Location				
16.	**Written Procedures:**				
	a. Animal Care				
	b. Animal Care Facilities				
	c. Animal Transfer and Identification				
	d. Characterization of Test and Control Articles				
	e. Handling of Test and Control Articles				
	f. Methods of Synthesis, Fabrication, or Derivation of Test and Control Articles				
	g. Determination of Stability of Test and Control Articles				
	h. Determination of Stability of Carrier Mixtures				
	i. Test System Observations				
	j. Laboratory Testing				
	k. Handling of Moribund or Dead				
	l. Necropsy or Postmortem Examination of Animals				
	m. Collection and Identification of Specimens				
	n. Histopathology				
	o. Inspection, Cleaning, Maintenance, Testing, Calibration, and Standardization of Equipment				
	p. Data Handling and Storage				
17.	Testing Facilities of Suitable Size and Construction				
18.	Spaces for Cleaning, Sterilizing, and Maintaining Equipment and Supplies				
19.	**Equipment:**				
	a. Adequate Equipment Including Environmental Control Equipment				
	b. Equipment Cleanliness				
	c. Adherence to Cleaning, Maintenance, Calibration, and Standardization Schedules				

Client	Revision:	Title: CONTRACT LABORATORY AUDIT CHECKLIST (GLP)	Page 3 of 5

		Unaccept	Needs Imp.	Accept	Excellent
	d. Records of All Inspection, Maintenance, Testing, Calibration, and Standardization Operations				
	e. Records Include Defects, How and When Defects were Found, and Remedial Action				
20.	Labeling of Reagents and Solutions (Identity, Titer or Concentration, Storage Requirements, and Expiration Date)				
21.	**Test and Control Articles:**				
	a. Records of Identity, Strength, Purity, and Composition of Each Batch				
	b. Stability Determined				
	c. Records of Stability Testing				
	d. Labeling of Storage Containers				
	e. Storage				
	f. Retention of Reserve Samples				
	g. Handling				
	h. Testing of Carrier Mixtures				
	i. Records of Stability Testing of Carrier Mixtures				
	j. Labeling of Carrier Mixtures				
22.	**Animal Facilities:**				
	a. Sufficient Number of Animal Rooms and Areas:				
	(1) Separation of Species and Test Systems				
	(2) Isolation of Individual Projects				
	(3) Isolation of Newly Received Animals				
	(4) Routine and Specialized Housing of Animals				
	(5) Isolation of Studies Using Biohazardous Materials				
	(6) Separate Areas, as appropriate, for Diagnosis, Treatment, and Control of Animal Diseases				
	b. Facilities for Collection and Disposal of Animal Waste and Refuse				
	c. Storage Areas for Feed, Bedding, Supplies, and Equipment				
	d. Areas for Handling Test and Control Articles				
	e. Space for Aseptic Surgery, Intensive Care, Necropsy, Histology, Radiography, and Handling of Biohazardous Materials				
23.	**Animal Care:**				
	a. Isolation of Newly Received Animals				
	b. Animals Free of Any Disease or Condition that Could Interfere with Study				
	c. Records or Diagnosis and Treatment of Animal Disease				
	d. Animal Identification				
	e. Separation of Different Species				
	f. Cleaning of Cages and Equipment				
	g. Records of Periodic Analyses of Feed and Water				
	h. Bedding Does Not Interfere with Study Purpose or Conduct				
	i. Records of Use of Pest Control Materials				

Client	Revision:	Title: CONTRACT LABORATORY AUDIT CHECKLIST (GLP)	Page 4 of 5

		Unaccept	Needs Imp.	Accept	Excellent
	j. Pest Control Materials Do Not Interfere with Study				
24.	Identification of Specimens (Test System, Study, Nature, and Date of Collection)				
25.	Records Available to Pathologists when Examining Specimens Histopathologically				
26.	Records of All Deviations from Written Procedures, Including Authorization				
27.	All Records Specified in Protocol are Maintained				
28.	Data Entries (Manual and Computer)				
29.	Availability of Laboratory Manuals and Written Procedures				
30.	Study Conducted in Accordance with Protocol				
31.	Test Systems Monitored in Conformity with Protocol				
32.	Personnel Report Adverse Health or Medical Condition				
33.	Final Study Reports Include (as a Minimum) Name and Address of Facility Performing Study, Start and Completion Dates of Study, Objectives and Procedures Stated in the Protocol, Changes to Protocol, Statistical Methods for Data Analysis, Test and Control Articles Used, Stability of Test and Control Articles, Methods Used, Test System Used, Dosage and its Administration, All Circumstances That Could Have Affected the Data, Names of Key members of Study Team, Operations Performed on the Data, Summary and Analysis of Data, Conclusions Drawn, Signed and Dated Reports of Key Members of Study Team, Data and Specimen Storage Locations, Statement Prepared and Signed by QA Unit, Dated Signature of Study Director, and Corrections and Additions (in the Form of Amendments) to Final Study Reports				
34.	**Data Handling and Storage:**				
a.	Retention of All Raw Data, Documentation, Protocols, Required Specimens, and Final Study Reports				
b.	Archives Orderly and Minimize Deterioration of Documents and Specimens				
c.	An Individual is Responsible for Archives				
d.	Index of Material in Archives				
e.	Historical File of all Obsolete Documents				
f.	Retention Period of at Least 2 Years from Date of Approval by FDA of a Research or Marketing Permit or from Study Termination Date for Studies that are not included in an FDA Submission, Except at Least 5 Years from Date of Submittal to FDA if in Support of an IND or IDE				

Client	Revision:	Title: CONTRACT LABORATORY AUDIT CHECKLIST (GLP)	Page 5 of 5

35. Comments:_____

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36. Auditors Signature:_____ 37. Date:_____

cc: _____

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References: **Singer, D.C.; Upton, Ronald P.; *Guidelines for Quality Auditing*; ASQC Quality Press, 1993**
Robert E. Spinock Consultants; Sample Audit Checklist, 1988

Audit Coordinator Approval:

_____ _____
Audit Coordinator Date

Appendix K
Contract Manufacturer Audit Check List

Client	Revision:	Title: CONTRACT MANUFACTURER AUDIT CHECKLIST (GMP)	Page 1 of 5

Audit#:_____ Date: _____ Auditor:_____

1. Project Title:_____
2. Facility:_____
3. Address:_____
4. Date of Audit:_____
5. Auditor:_____
6. Date of Last FDA Inspection of Facility:_____
7. Facility number:_____
8. Facility Manager:_____
9. Study Director:_____
10. Quality Assurance Unit:_____

		Unaccept	Needs Imp.	Accept	Excellent
11.	**Batch Records:**				
	a. Title and Purpose of Synthesis				
	b. Identification of Drug and Devices Articles				
	c. Name of Sponsor and Name and Address of Facility				
	d. Description of Process				
	e. Rationale for Process				
	f. Procedure for Identification of Process				
	g. Description of Process Design and Equipment				
	h. Description / Specification on Drug				
	i. Initiation of Synthesis				
	j. Type and Frequency of Tests, Analyses, and Measurements				
	k. Records to be Maintained				
	l. Date of Approval and Dated Signature of Manager				
	m. Analytical Methods to be Used				
	n. Changes (with Reasons) Approved and Maintained with Batch Record				

Client	Revision:	Title: CONTRACT MANUFACTURER AUDIT CHECKLIST (GMP)	Page 2 of 5

		Unaccept	Needs Imp.	Accept	Excellent
12.	Current Summary of Training and Experience and Job Description for Each Individual				
13.	Personnel Qualifications				
14.	**Quality Assurance (QA) Unit:**				
	a. Independent of Personnel Engaged in Study				
	b. Written Procedure for Operation of QA Unit				
	c. Maintains copy of Master Schedule Sheet				
	d. Maintains Copy of All Protocols				
	e. Inspections at Intervals Adequate to Assure Integrity				
	f. Written Reports of Periodic Inspections				
	g. Significant Problems Reported to Study Director and Management				
	h. Written Status Reports on Each Study				
	i. Reviews Final Study Report				
	j. All QA Unit Records are Kept in One Location				
15.	**Written Procedures:**				
	a. Starting Materials				
	b. Retology				
	c. Materials Acceptance Transfer and Identification				
	d. Characterization of Reagents and Intermediates				
	e. Handling of Reagents and Intermediates				
	f. Methods of Synthesis, Fabrication, or Derivation of Intermediate Test and Final Articles				
	g. Determination of Stability of Process and Final Molecules				
	h. Determination of Stability of Carrier Mixtures				
	i. Test System Observations				
	j. Laboratory Testing				
	k. Handling of Intermediate				
	l. Personnel Safety				
	m. Collection and Identification of Samples				
	n. Analytical Processes				
	o. Inspection, Cleaning, Maintenance, Testing, Calibration, and Standardization of Equipment				
	p. Data Handling and Storage				
16.	Testing Facilities of Suitable Size and Construction				
17.	Spaces for Cleaning, Sterilizing, and Maintaining Equipment and Supplies				
18.	**Equipment:**				
	a. Adequate Equipment Including Environmental Control Equipment				
	b. Equipment Cleanliness				
	c. Adherence to Cleaning, Maintenance, Calibration, and Standardization Schedules				

Client	Revision:	Title: CONTRACT MANUFACTURER AUDIT CHECKLIST (GMP)	Page 3 of 5

		Unaccept	Needs Imp.	Accept	Excellent
	d. Records of All Inspection, Maintenance, Testing, Calibration, and Standardization Operations				
	e. Records Include Defects, How and When Defects were Found, and Remedial Action				
19.	Labeling of Reagents and Solutions (Identity, Titer or Concentration, Storage Requirements, and Expiration Date)				
20.	**Test and Control Articles:**				
	a. Records of Identity, Strength, Purity, and Composition of Each Batch				
	b. Stability Determined				
	c. Records of Stability Testing				
	d. Labeling of Storage Containers				
	e. Storage				
	f. Retention of Reserve Samples				
	g. Handling				
	h. Testing of Carrier Mixtures				
	i. Records of Stability Testing of Carrier Mixtures				
	j. Labeling of Carrier Mixtures				
21.	**Production Facilities:**				
	a. Sufficient Number of Rooms and Areas:				
	(1) Separation of Materials and Processes				
	(2) Isolation of Individual Projects				
	(3) Isolation of Newly Received Materials				
	(4) Routine and Specialized Housing of Materials				
	(5) Isolation of Projects Using Biohazardous Materials				
	b. Facilities for Collection and Disposal of Waste and Refuse				
	c. Storage Areas Before Cleaning				
	d. Cleaning Procedures				
22.	**Care of Drug Substance/ API:**				
	a. Isolation of Newly Produced Drug				
	b. API Tracking				
	c. Stability Analysis				
	d. Records of Periodic Analyses				
	e. Records of Use of Pest Control Materials in Facilities				
	f. Environmental Records (Humidity and Temperatures)				

Client	Revision:	Title: CONTRACT MANUFACTURER AUDIT CHECKLIST (GMP)	Page 4 of 5

		Unaccept	Needs Imp.	Accept	Excellent
23.	Identification of Specimens (Test System, Study, Nature, and Date of Collection)				
24.	Records of All Deviations from Written Procedures, Including Authorization				
25.	All Records Specified in Batch Record are Maintained				
26.	Data Entries (Manual and Computer)				
27.	Availability of Laboratory Manuals and Written Procedures				
28.	Systems Monitored in Conformity with Protocol				
29.	Personnel Report Adverse Health or Medical Condition				
30.	Final Batch Record Include (as a Minimum) Name and Address of Facility Performing Synthesis, Start and Completion Dates of Project, Objectives and Procedures Stated in the Batch Record, Changes to Protocol, Statistical Methods for Data Analysis, Test and Control Articles Used, Stability of Test and Control Articles, Methods Used, Equipment Used, All Circumstances That Could Have Affected the Data, Names of Key members of Project Team, Operations Performed on the Data, Summary and Analysis of Data, Conclusions Drawn, Signed and Dated Reports of Key Members of Study Team, Data and MAterial Storage Locations, Statement Prepared and Signed by QA Unit, Dated Signature of Project Manager, and Corrections and Additions (in the Form of Amendments) to Final Project Reports, Release Criteria and Documents				
31.	**Data Handling and Storage:**				
a.	Retention of All Raw Data, Documentation, Protocols, Required Specimens, and Final Study Reports				
b.	Archives Orderly and Minimize Deterioration of Documents and Specimens				
c.	An Individual is Responsible for Archives				
d.	Index of Material in Archives				
e.	Historical File of all Obsolete Documents				
f.	Retention Period of at Least 2 Years from Date of Approval by FDA of a Research or Marketing Permit or from Study Termination Date for Studies that are not included in an FDA Submission, Except at Least 5 Years from Date of Submittal to FDA if in Support of an IND or IDE				

Client	Revision:	Title: CONTRACT MANUFACTURER AUDIT CHECKLIST (GMP)	Page 5 of 5

35. Comments:_____

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36. Auditors Signature:_____ 37. Date:_____

cc: _____

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References: **Singer, D.C.; Upton, Ronald P.; *Guidelines for Quality Auditing*; ASQC Quality Press, 1993**
Robert E. Spinock Consultants; Sample Audit Checklist, 1988

Appendix L
Contract Laboratory Audit Check List (GCP)

Coordinator:		Review Type:	
Sponsor:	Protocol #:	Subject Initials:	Subject #:
Visit Type Screen		YES/NO	If answer is no, then document findings:
Prescreen Report	All Sections Addressed:		
Informed Consent Process	Appropriate # of consents:		
	Appropriate version:		
	All pages initialed:		
	Signed & dated by:		
	Patient:		
	CRC:		
	PI/Sub-I:		
	Process documented:		
	Peer review of consent form:		
Source Checklist	Appropriate procedures completed:		
Cross-reference with applicable source document	Order of procedure evident(if applicable)		
Ratings/Diagnostic Tools	Appropriate, certified rater:		
	Tally(if applicable) meets all inc./no exc.		
	Scales support diagnosis		
PI/Sub-I Progress Note	ICF process documented		
Cross-reference with all	Diagnosis meets all inclusions/no exclusion		
Applicable source documents	History of presenting illness		
	Medical history		
	Concomitant medications		
	Physical examination		
Medical History	Prescreen report		
Cross-reference with all	PI/Sub-I progress note		
applicable source documents	Medical records (if a available)		
	Concomitant medications		
	Medical history meets all inclusion/no exc.		
Concomitant Medications	Prescreen report		
Cross-reference with all	PI/Sub-I progress note		
Applicable source documents	Previous medication log		
	Con med log		
	Con meds do not meet exclusion		
	If no, was waiver obtained?		
Safety	Vitals (performed per protocol)		
EGG	EGG (performed per protocol)		
	ECG demographics accurate?		
	Timely review of ECG by PI/Sub-I?		
	Any repeats ordered?		
	If so, repeat completed?		
Labs	Labs (performed per protocol)		
	Lab Requisition Demographics Accurate?		
	Timely review of Labs by PI/Sub-I?		
	Any repeats ordered?		
	If so, repreat completed?		
Inclusion/Exclusion	Documented and complete through screening		
Protcol Adherence	Any protocol deviation/ violations?		
	Documented?		
	Sponsor/CRO notified?		
	Receipt of approval from sponsor/CRO?		
	Reported to IRB (If applicable)		
Appearance	Source intact and legible?		
	Filing completed?		
	Documented and complete through screening		
	Any protocol deviation/violations?		
	Documented?		
	Sponsor/CRO notified?		
	Receipt of approval from sponsor/CRO?		
	Reported to IRB (if applicable)		
Appearance	Source intact and legible?		
	Filing completed?		
	Headers complete and accurate?		
	CRF completed?		
Reviewed By:			
	Name:	Date	

Coordinator:		Review Type	
Sponsor:			
Visit Type: Randomization			
Source Checklist	Appropiate procedures completed:	**YES/NO**	
Cross-reference with	Order of procedures evident (if applicable)		
Applicable source documents			
Ratings/Diagnostic Tools	Appropriate, certified rater:		
	Rater changes? If so, explanation provided?		
	Tally (if applicable)meets all inc./no exc.?		
	Scales support diagnosis?		
	Shifts in ratings are explained?		
PI/Sub-I Progress Note	Diagnosis meets all inclusion/ no exclusion		
Cross-reference with all	Confirms subject eligibility		
applicable source documents	Concomitant medications		
	Adverse events		
Concomitant Medications	PI/Sub-I progress note		
Cross-reference with all	Con med log		
applicable source documents	Con meds do not meet exclusion		
	If no, was waiver obtained?		
Adverse Events	PI/Sub-I progress note		
Cross-reference with all	CRC progress note		
applicable source documents	AE log		
	Medical history vs. adverse event		
Drug Accountability	Dispensing recorded		
	Dosing instructions evident (If applicable)		
Safety	Vitals (performed per protocol)		
ECG	Screening ECG available prior to randomization?		
	ECG (performed per protocol) if applicable		
	ECG demographics accurate?		
	Timely review of ECG by PI/Sub-I?		
	Any repeats ordered?		
	If so, repeat completed?		
Labs	Lab Reports available prior to randomization?		
	Labs (performed per protocol) if applicable		
	Lab requisition demographics accurate?		
	Timely review of labs by PI/Sub-I?		
	Any repeats ordered?		
	If so, repeat completed?		
Inclusion/Exclusion	Documented and complete through randomization		
Protocol Adherence	Any protocol deviation/violations?		
	Documented?		
	Sponsor/CRO notified?		
	Receipt of approval from sponsor/CRO?		
	Reported to IRB (if applicable)		
Appearance	Source intact and legible?		
	Filing completed?		
	Headers complete and accurate?		
	CRF completed?		
Reviewed By:			
	Name	Date	

Coordinator:		Review Type	
Sponsor:			
Visit Type: Interim Visit			
Source Checklist	Appropriate procedures completed:	**YES/NO**	
Cross-reference with	Order of procedures evident (if applicable)		
Applicable source documents			
Ratings/Diagnostic Tools	Appropriate, certified rater:		
	Rater changes? If so, explanation provided?		
	Tally (if applicable)meets all inc./no exc.?		
	Scales support diagnosis?		
	Shifts in ratings are explained?		
PI/Sub-I Progress Note	Concomitant medications		
Cross-reference with all	Adverse events		
applicable source documents	Dosage changes documented (if applicable)		
Concomitant Medications	PI/Sub-I progress note		
Cross-reference with all	Con med log		
applicable source documents	Con meds do not meet exclusion		
	If no, was waiver obtained?		
Adverse Events	PI/Sub-I progress note		
Cross-reference with all			
applicable source documents	AE log		
	Medical history vs. adverse event		
Drug Accountability	Returned drug recorded (if no, reason document?)		
	Dispensing recorded		
	Dosing instructions evident (if applicable)		
Safety	Vitals (performed per protocol)		
ECG	Screening ECG available prior to randomization?		
	ECG (performed per protocol) if applicable		
	ECG demographics accurate?		
	Timely review of ECG by PI/Sub-I?		
	Any repeats ordered?		
	If so, repeat completed?		
Safety (continued)	Random. lab reports available prior to current visit?		
Labs	Labs (performed per protocol) if applicable		
	Lab requisition demographics accurate?		
	Timely review of labs by PI/Sub-I?		
	Any repeats ordered?		
Protocol Adherence	Any protocol deviation/violations?		
	Documented?		
	Sponsor/CRO notified?		
	Receipt of approval from sponsor/CRO?		
	Reported to IRB (if applicable)		
Appearance	Source intact and legible?		
	Filing completed?		
	Headers complete and accurate?		
	CRF completed?		
Reviewed By:			
	Name	Date	

Coordinator:		Review Type	
Sponsor:			
Visit Type: EOS/ET			
Source Checklist	Appropriate procedures completed:	**YES/NO**	
Cross-reference with	Order of procedures evident (if applicable)		
Applicable source documents			
Ratings/Diagnostic Tools	Appropriate, certified rater:		
	Rater changes? If so, explanation provided?		
	Tally (if applicable)meets all inc./no exc.?		
	Scales support diagnosis?		
	Shifts in ratings are explained?		
PI/Sub-I Progress Note	Concomitant medications		
Cross-reference with all	Adverse events		
applicable source documents	Dosage changes documented (if applicable)		
	Reason ET (if applicable)		
Concomitant Medications	PI/Sub-I progress note		
Cross-reference with all	Con med log		
applicable source documents	Con meds do not meet exclusion		
	If no, was waiver obtained?		
	Ongoing meds closed out or noted “ongoing”		
Adverse Events	PI/Sub-I progress note		
Cross-reference with all			
applicable source documents	AE log		
	Medical history vs. adverse event		
	Ongoing AEs closed out or noted “ongoing”		
Drug Accountability	Returned drug recorded (if no, reason document?)		
	Dispensing recorded		
	Dosing instructions evident (if applicable)		
Safety	Vitals (performed per protocol)		
ECG	Screening ECG available prior to randomization?		
	ECG (performed per protocol) if applicable		
	ECG demographics accurate?		
	Timely review of ECG by PI/Sub-I?		
	Any repeats ordered?		
	If so, repeat completed?		
Safety (continued)	Random. lab reports available prior to current visit?		
Labs	Labs (performed per protocol) if applicable		
	Lab requisition demographics accurate?		
	Timely review of labs by PI/Sub-I?		
	Any repeats ordered?		
Protocol Adherence	Any protocol deviation/violations?		
	Documented?		
	Sponsor/CRO notified?		
	Receipt of approval from sponsor/CRO?		
	Reported to IRB (if applicable)		
Appearance	Source intact and legible?		
	Filing completed?		
	Headers complete and accurate?		
	CRF completed?		
Reviewed By:			
	Name	Date	

About the Author

Shayne C. Gad, B.S. (Whittier College, Chemistry and Biology, 1970) and Ph.D. in Pharmacology/Toxicology (Texas, 1977) DABT, ATS, is the principal of Gad Consulting Services, an 18-year-old consulting firm with 6 employees and more than 450 clients (including 120 pharmaceutical companies in the United States and 50 overseas). Prior to this, he served in director-level and above positions at Searle, Synergen, and Becton Dickinson. He has published 41 books and more than 350 chapters, articles, and abstracts in the fields of toxicology, statistics, pharmacology, drug development, and safety assessment. He has more than 34 years of broad experience in toxicology, drug and device development, statistics and risk assessment. He has specific expertise in neurotoxicology, in vitro methods, cardiovascular toxicology, inhalation toxicology, immunotoxicology, and genotoxicology. Past President of the American College of Toxicology, the Roundtable of Toxicology Consultants and three of SOT's specialty sections, and recipient of the American College of Toxicology Lifetime Contribution Award. He has direct involvement in the preparation of INDs (92 successfully to date), NDA, PLA, ANDA, 510(k), IDE, CTD, clinical data bases for phase I and II studies, and PMAs. He has been a consultant for FDA, EPA, and NIH, and has trained reviewers and been an expert witness for FDA. He has also conducted the triennial toxicology salary survey as a service to the profession for the last 19 years.

Charles B. Spainhour, V.M.D., Ph.D., DABT, DABFS, DABFM received his B.S. from Michigan State University, veterinary degree from the University of Pennsylvania, and doctoral degree from Texas A&M University. Dr. Spainhour has over 42 years experience in the pharmaceutical industry and with various aspects of drug development. Currently, Dr. Spainhour is the Chief Scientific Officer for Calvert Holdings and is also the President and Chief Scientific Officer for Calvert Laboratories, where he works with clients in the design, conduct, and management of safety assessment programs. He has played a significant leadership role in the development of Calvert Laboratories into the highly respected CRO that it is today. Previously, he has worked in the areas of pharmacokinetics and metabolism, biochemical pharmacology, and process chemistry. His employment history includes

MDS Pharma Services, Phoenix International Life Sciences, Chrysalis International, Pharmakon, and SmithKline Corporation (presently GSK). Dr. Spainhour has also worked as a veterinarian in private practice and as a forensic toxicologist and independent consultant, founding The Summit Group, which has provided services in the areas of safety pharmacology, toxicology, and drug development. Dr. Spainhour is a Diplomate of the American Board of Toxicology, American Board of Forensic Science, American Board of Forensic Medicine, and is a member of numerous scientific and professional organizations, including the American College of Toxicology, Society of Toxicology, Roundtable of Toxicology Consultants, Society of Toxicologic Pathology, Drug Information Association, American Chemical Society, and the Regulatory Affairs Professionals Society.

Index