Analyzing Analytical Outsourcing

Peter T. Kissinger, Ph.D.

Bioanalytical Systems, Inc.
2701 Kent Avenue
West Lafayette, IN 47906

email:
pete@bioanalytical.com

Over the last fifteen years, the pharmaceutical industry has outsourced an increasing number of analytical chemistry methods development and sample processing activities. These range from in vitro *screens to formulations development through all phases of clinical trials. This article suggests ways to make the process better through collegiality and attention to the key details.*

Businesses are participating more and more in the economic equivalent of an ecosystem. Vertical integration has clearly fallen out of fashion. Marketers outsource in order to focus on core competencies, but outsourcers face similar challenges. What we don't do well, we too must outsource. For us, that includes machine shop work, circuit board production, some business computer software: things that we desperately need, but don't necessarily want to do.

Key factors in successful outsourcing are selecting a small number of vendors, developing trust and working with them over time. Bioanalytical Systems has retained the same law firm for 18 years and the same primary circuit board subcontractor for 20 years. Both groups work with us every week. People on each side know one another, have watched their children grow up, seen the gray hairs appear, etc. Differences of opinion are solved quickly and professionally. We don't become complacent about our partners and they don't become complacent about us. Successful partnerships require give and take. Participants don't expect perfection, but they do expect mutual respect.

If You Do It Every Day, You Probably Do It Well...

One preferred vendor (for circuit boards) invests in automated equipment and spends 60 hours a week doing nothing else. If we bought the same equipment, we'd use it only three hours a week. On the other hand, we have 14 liquid chromatography/mass spectrometry (LC/MS/MS) units. We run them continuously for bioanalytical samples from clinical trials, as well as for some preclinical samples. We have become pretty good at this.

Sponsors must realize that what a contract lab does for Merck (for example) benefits what the lab does for Pfizer, which benefits what it does for GlaxoSmithKline, Abbott, Roche, Lilly and so on. Proprietary information must be kept totally confidential, of course, but the experience gained from one project helps labs perform other projects and refines their judgement.

BAS does a lot of work with HIV drugs and macrocyclic antibiotics, to name two examples. Our lab can do a better job with macrolides than the companies that make them, so those companies come to us and benefit from what we learned working for their competitor and *vice versa*. Similarly, suppose a law firm enters a patent dispute similar to ten other cases the firm has already seen. There are always new issues particular to the case, but experience gets the firm through them like nothing else can.

Analytical chemistry is a very creative activity when it comes to method development. There are usually a number of paths one can follow to achieve a satisfactory result. There can be many false starts. Success can depend on the creativity and experience of very few individuals, often a team of two or three.

Chemists at a company with 25,000 employees are no better at this than chemists at a company with 25 people. Trouble begins when the contract lab personnel are intimidated by the perception that Dr. Ego at Big Pharma, Inc. must know more about the problem than they do. Dr. Ego tends to agree with this assessment, but Dr. Shy at the contract lab should not be reluctant to ask questions and show some skepticism about documented methods, especially those published in the literature. These behaviors slow the process, inhibit creativity and break down communication. The best ap-

proach is to solve the problem as partners. What matters is getting the work done so the NDA comes through and both consumers and shareholders benefit!

There are big differences in how pharma companies manage analytical projects. In some cases, there is a near-total lack of trust in what the contractor is doing. Every little detail becomes a concern and much time is wasted that could be better invested in meeting the objective. In such cases, it sometimes becomes unclear as to why the contractor was hired at all. People don't expect their lawyers to follow their legal advice; they pay lawyers for that advice. People must work closely with lawyers, not micromanage them. Otherwise we'd be better off going to law school ourselves.

Continuity Is Everything

With all the up-front costs of QA inspections, getting blanket agreements signed, visits back and forth between sites, learning the format requirements of the sponsoring company, transferring methods that we develop and revalidating methods a sponsor develops, it is virtually impossible for the sponsoring company to get what it needs (or for the contract lab to get what it needs) with small projects that start and stop. It makes no sense to "farm out" (or should I say, "pharm out"?) an isolated study to determine drug concentration in 50 plasma samples, unless the contract lab has already done 500-2000 samples and these 50 are part of an ongoing study with a validated method in place.

The ideal situation is when the contract lab employees become virtual employees of the sponsor for six months, three years or however long. The sponsor still has the primary benefit of converting what would be fixed costs into variable costs (i.e., contract lab personnel are "fired" when no longer needed and there are no long-term vacation, insurance or retirement costs to deal with). It is not sensible to expect that the cost (per sample or per hour in a method development project) would be less than what sponsors pay for their own people to do the work. The immediate cost should be the same or perhaps even higher.

After all, contract labs must follow the same FDA regulations. They need to have good people who deserve to be paid well. The labs also need modern first-rate equipment and computer technology. The benefit to the sponsor comes from speed and the experience of the contract lab staff, not from paying a cheap fee. This flexibility allows the sponsor's staff to concentrate on more strategic projects.

It may be amazing to some (especially academics), but with small (perhaps all) projects, minor issues arise that can end up costing both the sponsor and the contract lab many thousands of dollars as reports must be redone to meet requirements that no one thought to specify up front. Seemingly trivial matters can evolve into tedious obstacles: the font chosen, the margins desired, the way certain words are spelled (reversed phase vs. reverse phase LC), labeling tables as Table II vs. Table 2, and the like.

Contract analytical labs want to do analytical chemistry. Redoing reports and duplicating QA effort is not "strategic" for them. Once a lab develops some history with a sponsor, these side issues are no longer points of contention.

Another baffling continuity problem occurs when projects are "thrown over the wall" from preclinical to development. That "wall" can be pretty high and not very transparent for some pharma companies. There are cases where the contracting liaison is a different person on both sides of the wall. It is frustrating to an analytical CRO to have developed and validated a high throughput preclinical LC/MS/MS method for monkey plasma, only to find out that another CRO was contracted to develop the same method for human plasma. The sponsor of the latter study may not even be aware that it has already paid for the former method. A lot of time can be saved (several months) with more coordination. Often a CRO will lose money on the preclinical work and hope to recover it on the (larger) clinical studies where the number of samples increases to many thousands.

Mutual Trust and Respect

If a person hires a lawyer or accountant and withholds information from him or her, the chance of getting good service is very limited. Likewise, if a sponsor hires analytical chemists and doesn't give them some ownership of the project by letting them in on why, how and when it needs to be completed, very poor results will often arise. A typical model that leads to poor communication works like this:

Sponsor bench scientist (A) to sponsor contract officer (B) to contract lab liaison (C) to contract lab study director scientist (D).

A→B→C→D

This sort of "straight-down-the-line" communication can be disastrous. Somewhere in the process there must be enough trust for the sponsor's chemist to talk directly to the CRO's chemist at the contract lab. They need to discuss many details that often don't show up in early documentation: where the trouble spots are, why solvents from one vendor might work and those from another might not, why the tubes need to be plastic and not glass or *vice versa*, how the internal standard was prepared and why the person who prepared the very limited supply is now retired or reassigned to the Singapore office...

We have found cases where working shoulder to shoulder with sponsor scientists can, for example, reduce an LC method from injections every 20 minutes to injections every seven minutes. With 6000 samples in the freezers, this can make a big difference! Naturally, all

involved parties need to be kept informed of relations with others, but this must be networked, not simply a linear progression, otherwise much time and value can be lost.

Often the chemist at the sponsor has not considered scale-up for "production" analytical chemistry and ends up transferring to the lab a method that is not robust. What was good enough for 100 samples often might not be good enough for 1000 or more.

Scale-up questions arise in strange ways. Suppose the sponsor's method defines a solution and says it must be prepared by weighing out a certain amount into a 1000 mL volumetric flask. The method is then transferred to the contract lab for production work. The lab needs 100 liters of the solution per week. Is it smart to be bound by regulatory matters to keep making the 1 L solution 100 times per week, or should the lab produce a larger volume one or two times per week? It is very prudent to consider such issues from the beginning so that apparent cGMP restrictions don't limit efficiency for years to come.

Schedule Within Reason

Analytical chemistry is a very creative activity, especially analytical chemistry at ng/mL concentrations and below in biological samples. Methods development can be fraught with surprises and false starts. It is very important to allow enough time to do the job right. Contract labs should avoid offering unrealistic completion times in order to win the assignment. After all, it may then be the last assignment the lab gets from that sponsor.

Sponsors must also be reasonable about their expectations. Poor planning on the sponsor's part doesn't excuse unreasonable expectations, forcing the CRO to work weekends and holidays unnecessarily. Sponsors must be realistic about the state of any method they want to transfer to the contract lab.

Professional pride can become an issue in an outsourcing setting. For example, the sponsor's method may not hold up under the scrutiny of experienced contract lab scientists working in a production environment. Sponsors should not be defensive about this; instead, they should work shoulder to shoulder with the contract lab to develop a more refined method. Partnership is key. Competition is silly. Arrogance is destructive from both sides. Collegiality is productive from both sides; teamwork is key to success.

Think Like A Business

Over the years I've had numerous exchanges like this one: "We have 750 samples of rat brain hypothalamus at -80° in a freezer. We want to determine [X]. Can you do it?" Typically this question comes from a bright M.D. I ask how the samples were prepared, if they went through any freeze-thaw cycles and how and in what were they homogenized. I get such answers as: "I'm not sure what my postdoc did; she left three years ago," "We made all the samples 1 M in hydrochloric acid because the guy down the hall told us everyone knows that will stabilize any analyte," and, "Can you do this for $10-15 per sample?" More than once I have pointed out that the method should have been optimized before the samples were collected and prepared. Looking at them now may be a waste of time. The above are extreme cases and not what we would expect from an established pharmaceutical company, but these things are not unusual. Asking a bioanalytical chemist to help in this manner is like asking an accountant to help balance your checkbook after you lost it and threw away all your receipts.

One key element of scheduling is economics. Contract labs usually have no source of revenue beyond the time expended with the available personnel and instrumentation. Such labs have no source of income to cover lost time, no billion dollar blockbuster drug putting coins in the bank. Thus sponsors can easily make or break such businesses. The sponsor who delays a 2000 samples/month project by a couple of months is the sponsor who may leave a Ph.D. and a couple of technicians with no source of revenue for their food and mortgage. Contract labs are like restaurants or airlines. They take reservations. They can overbook only by a certain amount in hopes of balancing cancelled/delayed projects and even (rarely) accelerated projects. Thus sponsors must take responsibility for giving contract labs the earliest possible warning of any change in schedule.

Sponsors should think of contract labs as businesses facing all the same problems they do. A delay in a contract lab receiving boxes full of Phase II clinical trial samples can be as damaging as a delay in a pharma company's NDA. To meet the agreed-upon timeline, all parties must adhere to the schedule. Moving a major project from one quarter to another impacts what Wall Street analysts might say about a contract lab, just as a failed Phase III trial might sink a biotech stock. This is a risk of new science and medicine. Contract labs need to know as soon as possible when such schedule changes occur.

Sponsors ask contract labs to bid on specific jobs, but CROs often find that the project bid is not the project ultimately carried out. Key information is often not shared. The method transferred may not be robust or the internal standard is not readily available. The goals might change three days before the project is to start. The number of samples bid was 6000, but the number received is 600. Science is not predictable. Changes are to be expected. With teamwork and mutual respect, they can be accommodated.

How significant is analytical chemistry as a business expense? I do not have the data for enough cases to be sure. My guess is that for a $100 million clinical trial, the total expense for both bioanalytical chemis-

try (blood) and pharmaceutical analysis (the formulation) is less than 2%. This will clearly vary with the complexity of the NCE, its potency and the type of dosage form. I would think that a company would want to get this work done properly and not put a $100 million project in jeopardy by short-changing components of the project that cost less than a few percent.

Lawyers or Lab-sters?

Contracting out analytical chemistry to a firm which has analytical chemistry as its strategic passion can be very worthwhile if certain key principles are considered. It can also result in much frustration if communications are inadequate and assumptions are made rather than protocols defined. Both sides must listen and arrive at a mutually agreed-upon set of objectives and procedures. They must work as a team.

Outsourcing pharmaceutical (bio)analytical chemistry has a relatively short history, but it already provides some clear lessons. Companies should consider their analytical vendors in a manner similar to how they consider outside lawyers and accountants. Cutting corners on any of these three positions can have adverse consequences for a company. Long-term, trusting relationships can be highly satisfying and productive.

One final thought: The pharma or biopharma company that hires its lawyers for $300/hour and its analytical chemists for $30/hour is going to need more lawyers. The cost of hiring the best people at the outset is less than the cost of correcting mistakes later.

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