Industry and Academia Collaboration Creates Timely and Cost-effective Preclinical Outsourcing Solutions

Lee M. Cera, Comparative Medicine, Loyola University Medical Center, Maywood, IL
Philippe Baneux, Center for Comparative Medicine, Northwestern University, Chicago, IL
Donald P. Waller, Department of Biopharmaceutical Sciences, University of Illinois at Chicago, Chicago, IL
Thomas J. Welsh, Center for Comparative Medicine, Northwestern University, Chicago, IL
Boris Predovich, PreLabs, LLC, Oak Park, IL

Introduction

Global Bio-Pharma, Chemical and Medical Device companies are increasingly dependent on Contract Research Organizations (CROs) for accurate, timely and affordable preclinical outsourcing solutions. Escalating drug and device development costs and the recent economic downturn have created an environment where drug, biotechnology and chemical companies are searching for more cost effective options. Typical CRO's must make significant financial investments to support compliant vivaria, state-of-the-art instrumentation and equipment, and highly-trained technical staff to effectively complete drug and device development processes.

Sophisticated and costly systems are difficult to justify and cost prohibitive for small to mid-sized companies. New areas of research such as nanopharmacology/toxicology and gene therapies also demand expertise not readily found in most preclinical contract research organizations. This has led to increased outsourcing of preclinical and early drug and biologics development to CRO's. Expanded research capabilities in Asia are also beginning to attract customers based solely upon less expensive testing and research options.

Most outsourced testing involves the utilization of vivaria which are expensive to build, operate and maintain. Substantial funds have been devoted during the last decade to building and staffing vivaria within the US academic community to support ongoing university research programs.

Characteristics of Facilities Based on Allocation of Use

We recently polled both private and public academic research institutions to determine facility accreditation, types of facilities available, and level of use. All of the responding laboratories were AAALAC International accredited, indicating a high level of commitment to quality facilities operated with a high standard of animal care, use and welfare. These vivaria dedicated a majority of their space to maintain and house rodents and small animal species. Most of them also had significant space dedicated to larger animals and non-human primates.

% Space Dedicated	Small Animals/ Rodents	Larger Animals	Non-human primates
Mean(std)	82.0(11.4)	14.0(11.5)	4.5(4.0)
Low-High	65-100	0-29	0-12
# w/dedicated space	22/22	21/22	17/22

Facilities must be maintained and made available to the academic research community, but are often underutilized resulting in significant inefficiencies and increased costs. High occupancy rates are essential to minimize financial losses to vivarium operations in any setting. Academic institutions leverage multiple users to justify and support such resources but often require institutional subsidies to operate. The academic setting usually provides a significant baseline of research activities to support facility operation costs. However, an opportunity to increase occupancy greatly reduces per unit costs for all users and also provides additional revenue for the academic institution.

Many institutions provide opportunities for outside investigators to utilize their facilities. However, the use of such facilities by outside investigators is usually a small part of their total operations (less than 5%). GLPs (Good Laboratory Practices from the Food and Drug Administration or the Organization for Economic Cooperation and Development) were implemented in six of the institutions, but most (15) did not. Interestingly, one of the institutions performing GLP studies did not have any outside investigators. The GLP compliant studies for almost all of the institutions were performed by investigators within the academic faculty.

	Allow Outside Investigators	Follow GLP
Yes	14	6
No	8	15

Facility Occupancy

In most cases vivaria occupancy for a 24 month period was significant, although few facilities reached the full capacity level. The mean occupancy for the 24 months and forward projections for 24 months were about the same. However, there was significant capacity not utilized for small animals and larger animals when evaluating how many facilities were operating at 85% or greater capacity. Less than half of the institutions housing non-human primates were operating at that higher level.

Past 24 Months	Small Animals/ Rodents(%)	Larger Animals (%)	Non-human primates
Mean (std)	**76.5(14.5)**	**48.1(33.1)**	**64.6(39.4)**
Range	**50-100**	**2-100**	**1-100**
>=85% Occupancy	**7**	**3**	**8**
<85% Occupancy	**14**	**17**	**9**

Projected 24 Months	Small Animals/ Rodents(%)	Larger Animals (%)	Non-human primates
Mean (std)	**76.5(14.5)**	**48.1(33.1)**	**64.6(39.4)**
Range	**50-100**	**2-100**	**1-100**
>=85% Occupancy	**7**	**2**	**8**
<85% Occupancy	**14**	**18**	**9**

A similar situation applies to surgical space as well as animal housing and procedural space. In almost all institutions, surgical suites are also underutilized. In a recent polling of several Chicago institutions the surgeries were almost all at less than 50% utilization, providing opportunities for development of training programs where surgical facilities are required. As an example, emergency room residency training for local hospitals without vivaria has been conducted with great success. Other institutions are utilizing their surgical facilities to support product development for the medical device and pharmaceutical companies.

Underutilized academic resources provide an opportunity for the academic institution to increase utilization by working with drug development organizations. However, regulatory compliance, administrative hurdles, timeliness and intellectual property issues associated with private industry working within an academic institution, often prevent this collaboration from occurring.

An Emerging Academic and Industry Collaboration

Over the past eleven years, we have developed an academic/private industry collaboration resulting in increased occupancy of our vivarium, increased staff awareness of government regulatory requirements and sharing of technical resources.

This industry/academic relationship creates a unique client opportunity to interface with the drug development industry and take advantage of this emerging business model with benefits to the sponsor as well as the academic and private CRO collaborator.

PreLabs, LLC a GLP compliant preclinical CRO, operates within the Loyola University Medical Center facilities and business framework as an independent contractor providing GLP and non-GLP preclinical outsourcing. This relationship provides immediate access to the vivaria of the University. PreLabs utilizes the Loyola facilities and staff on a cost per use basis to perform a variety of tasks and help in subsidize g the institution's budgetary demands. This optimizes and leverages the in-house capabilities of the academic institution while providing variable capital and labor cost savings to the client. The PreLabs dedicated and trained scientific and operational staff is responsible for managing studies and preparing study reports to industry standards

This organization has performed hundreds of studies including two year carcinogencity studies in space which would have been underutilized and likely not generating revenues for the university. Trained staff has also been contracted from the facility to assist when additional staff were required to support the increased client demand.

Regulatory Compliance Training

This hybrid CRO employs dedicated Prelabs GLP-trained operational staff including Study Directors, Boarded Toxicologists, AAALAS trained technicians and a management team focused on delivering timely execution of studies while adhering to strict regulatory compliance.

Regulatory compliance is required for studies supporting drug, biologics and device development. The laboratory procedures are directed by Standard Operating Procedures (SOPs) to guide the performance of any study from initial protocol development to completed study reports. Established SOPs are created and followed by the CRO. All staff participating in studies must be trained to follow these SOPs.

GLP conditions require continuous training and updating of a CRO technical staff. Most academic institutions do not have the ability or desire to institute the required level of training and documentation for GLP compliant operations. One of the cornerstones of GLP compliance is documented training of all study participants.

Prelabs' close collaboration with Loyola provides an opportunity for experienced staff of the academic facility to participate in GLP studies. Although experienced, they usually do not have the documented training required for GLP compliance. PreLabs has an intensive training schedule to comply with the requirements of regulatory agencies. However, this training is not limited to those directly employed by Prelabs. The mandatory training sessions for the PreLabs staff and the

documentation of those attending the sessions are extended to all the staff in the academic facilities who may interact or directly participate in GLP compliant studies. The documentation and training of all staff provides an additional trained cadre of technical assistance which can be utilized whenever additional assistance is required.

Although post- doctoral and graduate students are available, they are not part of the process due to the temporary nature of their appointments and focus on specific research projects which do not require regulatory compliance.

The administrative understanding and support for all these activities and the release of staff for training have been negotiated for the benefit of both the academic institution and the private contract company. GLP training and compliance is an excellent mechanism to ensure good science.

Administrative Hurdles

The operation of an independent contract organization within an academic institution must be well coordinated with the higher administration of the institution. It is essential that the vision of the independent operation be accepted and encouraged. Without such support, the many requirements of efficient operation within the facility may be compromised. They need to have sensitivity and buy in to the vision and the requirements of the independent organization. Establishing the appropriate contracts and understanding between an independent contractor and the university for long term contracts is a difficult but a required part of the process.

Timeliness

The administrators of academic facilities, research staff and faculty do not normally work in the same environment as business entities focused on drug, biologic and device development. The ability to compete with other CRO's requires a new attitude of timeliness and streamlined procedures to allow work to be initiated and completed in the most time sensitive manner. Research grant preparation, review and awarding of funds usually have long timelines and have been the mainstay of academic institutions. Operating in the competitive CRO environment requires addressing issues quickly and with efficient pathways from IACUC approval to completion. Academic administrators must be willing to work within the needs of both the academic institution as well as the short response times required for operating in a business climate. Effective communication links with the administration are essential for efficient decision making.

Intellectual Property

Academic institutions have awakened to the advantages of monitoring and maintaining ownership of new ideas and inventions. This has created a new hurdle for companies attempting to utilize the facilities and expertise within the academic setting. A clear understanding between the institution and the contract organization must be in place prior to any studies being performed. This is essential to prevent any potential legal issues regarding the data and the results generated in an outside funded contract. Even government contracts and grants have clear policies regarding intellectual property rights which must be in place prior to the start of any funded activities. Similarly,

any contract organization should have well defined intellectual property agreements in place which protect the sponsors. This must be clearly articulated in an agreement between the institution and the CRO. This protects the sponsor's intellectual property while performing research within an academic institution and minimizes delays in starting studies which include academic facilities and staff.

Entrepreneurship Success and Leading Edge Scientists

Academic institutions have a great deal of scientific expertise. A CRO can identify and leverage the expertise of the scientists for one or several studies to increase their breadth of studies. This may provide increased revenue to the faculty and/or increased exposure to the outside business community and lead to consulting arrangements both within our CRO and companies outside of the institutions.

A CRO can also foster staff entrepreneurship. Academic institutions are increasingly encouraging and supporting entrepreneurship. Although academic staff may have ideas and techniques which could be commercialized, they often lack the skills and the financial support to successfully enter the business arena. This expertise can contribute to the betterment of science and a potential revenue generating activity of a staff member. PreLabs has worked with the staff to identify opportunities for commercial development to benefit both the institution and the staff member.

One example is the development of genetic testing services used to refine non-human primate and other large model use in toxicology studies. There is a significant gap in information regarding the genetic background these animals used extensively in research studies. For instance, Cynomolgus monkeys used in research may derive from several geographical sources. Unfortunately, there are large genetic differences between animals derived from different sources (Figure 1). This can have a major effect on study results when small groups of non-human primates are utilized. Predictability and reproducibility of study data can be improved when genetic variability is reduced.

Prelabs currently offers genetic evaluations of both individual and group heterogeneity, geographic origin of matriline and individuals, and estimated relatedness common to individuals in a group for cynomolgus monkeys as a service to the research community. This will be expanded to other species as the value of the service to improve animal use in research is recognized.

This is a collaborative effort combining the skills and expertise of a staff/faculty member with the business contacts and marketing ability of Prelabs.

Conclusions

It is clear that a GLP contract laboratory can successfully meet industry study outsourcing standards when relevant details are addressed in an agreement at all levels of an academic institution and the CRO operating within its facilities. The benefits of this collaboration provide industry the opportunity to leverage academic collaborations resulting in cost effective outsourcing solutions while increasing business volume for the academic institution.

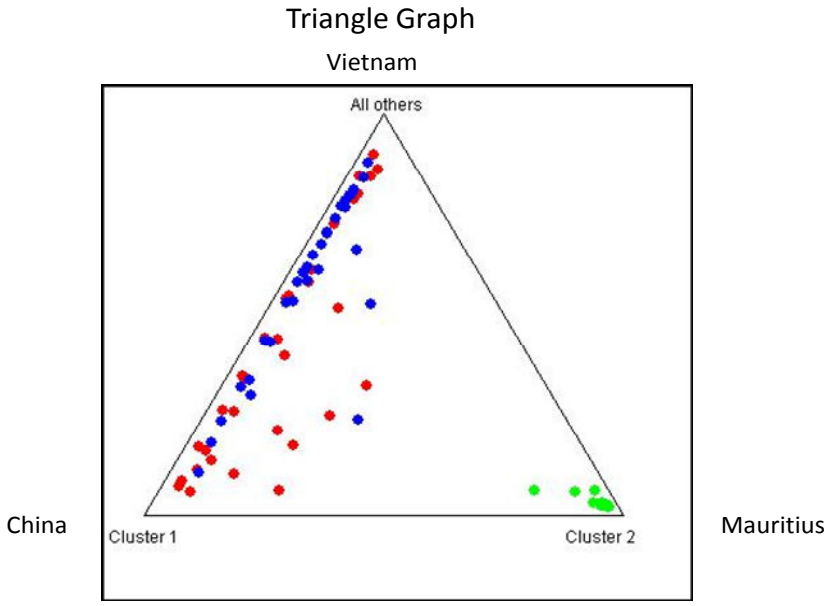

Figure 1. Bayesian Structure, version 2.1, analysis of individual cynomologus macaques using the admixture model with K set at 1 to 4. Results shown are for K = 3 populations. Histogram of assignments shows each individual as a vertical bar and clusters are identified with different colors. Triangular plot represents admixture between each of the three populations. China and Vietnam are represented with red and blue, Mauritius is green. The number of populations measured by Structure based on Delta K is 2