Effective Partnering of Academic and Physician Scientists with the Pharmaceutical Drug Development Industry

SCOTT P. KENNEDY*,[1] AND B. J. BORMANN†

*Drug Safety Research and Development, Pfizer Global Research and Development, Pfizer Inc., Groton, Connecticut 06340; and †Strategic Alliances, Pfizer Global Research and Development, Pfizer Inc., New London, Connecticut 06320

This manuscript briefly addresses the drug discovery and development process. It is a long road from the formulation of a good discovery idea to the acceptance of a new drug in the marketplace, and there are many challenges faced along the way to the patient. Collaborations and partnerships are an important part of this process. There are a variety of partnering opportunities, ranging from the discovery of novel technologies and drug targets to lead discovery, compound gifts, and external sourcing. These partnerships help increase confidence and improve decision making on issues of safety and efficacy preclinically, which can reduce attrition and expedite the provision of new quality drugs to patients more quickly and at lower costs. Collaborations involve addressing multiple issues that include infrastructure, safety, regulatory matters, intellectual property, technical and personnel considerations, source document capture and data analysis issues, and legal and strategic alliances. A number of success factors are identified as important for quality collaborations in the drug development process. Exp Biol Med 231:1690–1694, 2006

Key words: academia; drug development, industry; partnering; physician scientist; safety

Despite significant increases in the number of dollars invested in pharmaceutical research and development over the last decade, the number of new Food and Drug Administration (FDA)–approved medicines reaching patients has continued to decline. Recent figures indicate that bringing a new medicine to market can take an average of 12 to 15 years and requires an investment greater than $800 million (Fig. 1). This cost generally is not associated with the development of a single compound; it is attributable to the extremely high industry program attrition resulting from unexpected or untoward safety issues or lack of sufficient efficacy to differentiate from existing therapies. On average, only one of every hundred discovery projects ever becomes a new medicine, with the result that over 75% of the cost of a launched product is due to the unpredictable failure of other programs. In addition, the time and cost associated with clinical trials in healthy volunteers and patients has escalated dramatically as regulatory agencies come under increased scrutiny and elevated public expectations regarding the safety of approved new medicines. This environment underscores the challenge and importance of leveraging all of the available scientific, preclinical, and clinical information to increase confidence in rationale (CIR) and confidence in safety (CIS), the two major root causes of program attrition throughout the drug discovery and development phases. One mechanism for potentially overcoming these challenges is to increase and leverage effective and appropriate partnering between academic and physician scientists with the pharmaceutical drug development industry. This summary will highlight the general activities associated with various drug discovery and development phases and will exemplify a variety of opportunities for academic and industry partnering along the long path from idea to new medicine. Although the illustrated examples are based on Pfizer experience, they are intended to represent similar types of partnering opportu-

[1]To whom correspondence should be addressed at Drug Safety Research and Development, Pfizer Global Research and Development, Pfizer Inc., Eastern Point Road, Groton, CT 06340. E-mail: Scott.P.Kennedy@Pfizer.com

1535-3702/06/23111-1690$15.00

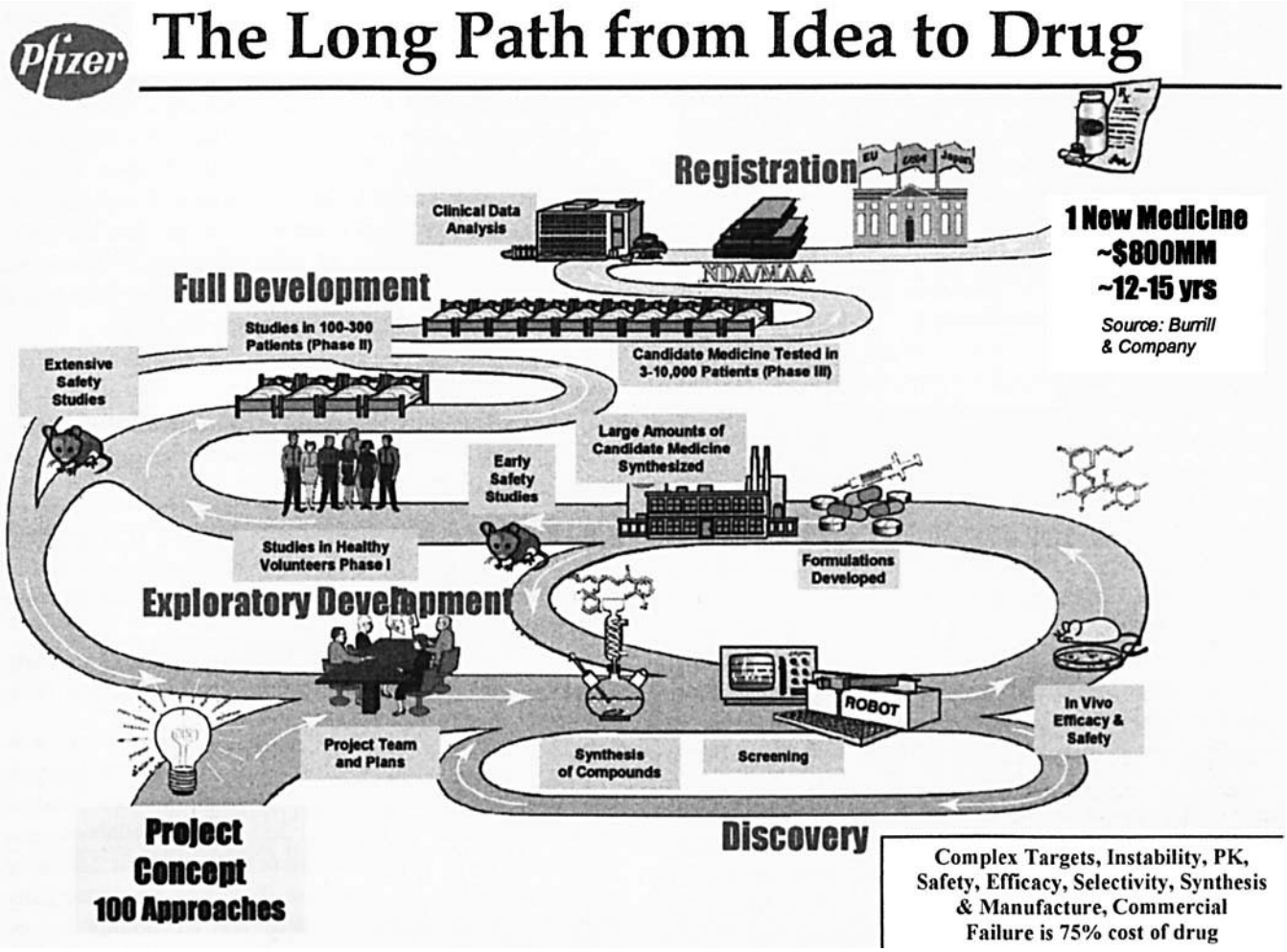


Figure 1. The long path from idea to drug. Turning quality drug target ideas into medicines that can treat patients is a long, risky, and expensive process. The majority of the cost of new medicines is due to the high attrition observed in the early phases of discovery and development, which stems from lack of efficacy or unacceptable safety. Effective partnering with academic and physician scientists can help with these challenges.

nities across the industry. Effective partnering depends not only on high-quality science and deliverables from both sides, but also on establishing expectations and behaviors that need to be discussed, understood, and adhered to before and during collaboration. Therefore, the authors also will discuss factors we believe to be important to partnership success.

Discovery and Development Primer

Project Conception. Drug development initiates with the identification of a therapeutic target which, if modulated via an agonist or antagonist drug molecule, could modify disease progression and/or undesirable symptoms of disease (Fig. 1). In the pharmaceutical industry, the therapeutic approach needs to be in an area of high medical need (i.e., no current therapies or an underserved patient population due to suboptimal efficacy or safety profiles). The approach has to be commercially attractive to return an investment to company shareholders and provide funding for continued research and development. In addition, modulation of the intended drug target must be scientifically approachable by small molecules (chemical compounds) or biologicals (antibodies, peptides, nucleic acids, etc.). Existing scientific information, whether generated internally or available through scientific and medical literature, needs to support a reasonable confidence in rationale—that is, that modulation of the target will produce the desired therapeutic effect and differentiate from existing therapies—and confidence in safety—that is, that an acceptable therapeutic index is achievable in the patient population. Furthermore, one must consider the cost, size, and timing of clinical trials designed to determine benefit of the drug.

Discovery. Once a project is considered to be a viable and high-priority option, a multidisciplinary discovery team is assembled to identify and optimize candidate leads. For small molecule (generally <500 mol wt) and other approaches (e.g., antibodies and peptides), this involves establishing an *in vitro* screen to identify leads that display the desired primary biologic activity. In addition, the project team needs to develop structure activity relationships so that the lead chemical structures can be further modified to

display appropriate and optimum selectivity, potency, safety, absorption, distribution, metabolism, excretion (ADME), or drug-like properties. Consideration also needs to be given to physicochemical properties that have an impact on employee safety, cost of synthesis, and stability. This discovery lead optimization process, which involves countless iterations of modifying chemical structures and assessing biologic activities, can take several years before a single compound is selected for advancement into development.

Exploratory Development. The decision to halt lead optimization and advance a single compound toward development is not a binary decision, but rather is based on confidence that the compound has the inherent properties needed to survive through development, the competitive environment, and the desire to gain human experience with the compound structural class and/or target in healthy volunteers and, eventually, patients. Before the initiation of Phase 1 clinical trials (the first exposure of drug to humans), extensive toxicity testing (general toxicity: 2–4 weeks in large and small animal species; genetic toxicity: assessing mutagenic and clastogenic potential; safety pharmacology: assessing impact on major physiologic systems such as the cardiovascular system, central nervous system, and pulmonary system) is performed in animals. Based on these studies, clinical trials are designed, and an investigative new drug (IND) application is discussed with and submitted to regulatory agencies (FDA in the United States). If approved, Phase 1 clinical studies, most often performed in healthy volunteers unless the indication is for a terminal disease, as in oncology, are conducted to generate toleration and safety information, pharmacokinetic/bioavailablity data, and, if possible, evidence that the compound is active in humans (proof of mechanism), often through the use of biomarkers. If safety, ADME, and biologic activity are acceptable, the compound progresses into Phase 2 clinical trials in patients. In Phase 2, dose ranging studies are designed to further evaluate and optimize efficacy, safety, and ADME properties. The studies often require hundreds of patients and prolonged lengths of treatment, and they focus on demonstrating a direct link between the initial mechanistic approach and medical outcome (i.e., proof of concept).

Full Development/Approval. Once proof of concept is achieved, investment in the development program increases substantially as chronic animal toxicology studies are initiated to support full development (Phase 3) and registration. These include extensive general toxicology studies (generally 6–12 months in small and large animal species), reproductive toxicology (to enable enrollment of women of childbearing potential in clinical trials), and, if for a chronic, nonterminal indication, rodent carcinogenicity studies (usually 2 years long and completed prior to registration). These Phase 3 studies can involve hundreds to tens of thousands of patients and can take several years to complete. The location and number of clinical trial sites used during the development of a drug like Pregabalin can be extensive and involved, enrolling subjects in major population areas throughout the world, including Canada, Europe, South Africa, Australia, and the United States. The studies are designed to provide pivotal efficacy and long-term, extensive safety information sufficient for registration by worldwide regulatory authorities. If definitive efficacy and safety are documented and agreed to by the appropriate authorities, the compound is approved for use (per the label) in patients. The amount of data collected to document efficacy and safety is extensive, literally occupying hundreds of feet of shelf storage space.

Opportunities for Partnership

Licensing and Research Collaborations. Up to and including the 1990s, collaborations were not the norm in the pharmaceutical industry.

"I'm amazed at the arrogance of some U.S. pharmaceutical companies like Merck and Pfizer who have hardly cut any deals with biotechnology companies. That's a very strange decision."

Tim Wilson, analyst, UBS Securities, New York, *BioWorld Today*, August 1996

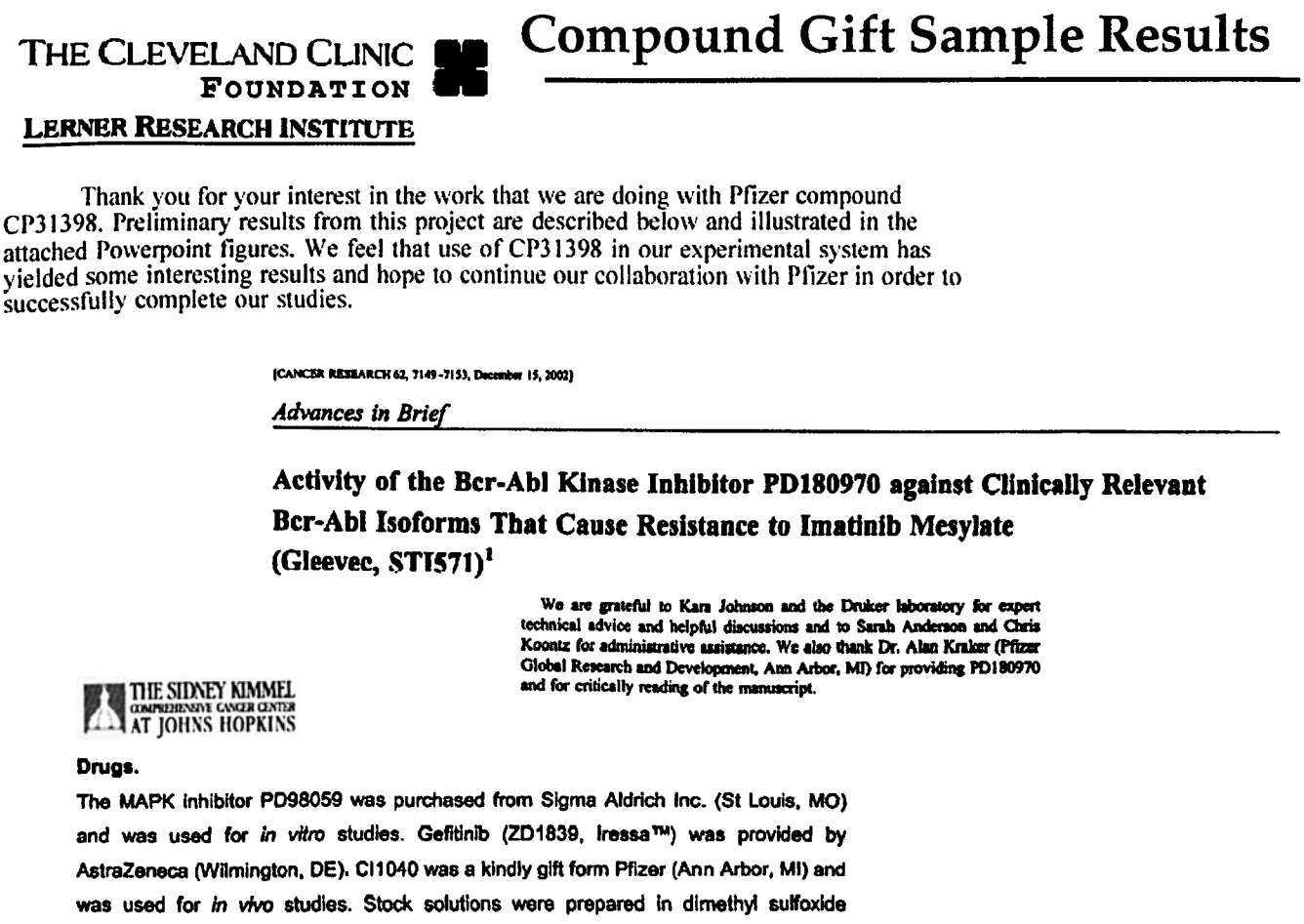
This culture certainly has changed, and Pfizer is now known as an active partner, seeking out collaborations in academia, biotechnology, and small- and midsized Pharma. In 2005 Pfizer entered into over 500 research collaborations, and our dynamic portfolio always holds at least 50 major collaborations (Fig. 2). These collaborations are strategically aligned with our therapeutic area and technology investments and provide our pipeline with some distinct advantages. For example, collaborations can focus on new assay development, novel animal models, new targets implicated in disease progression, and biologic tools such as knockout mice, cell lines, and cDNAs. Our collaborations save time and bring additional focus and thought into our drug discovery and development processes.

Compound Gifting. One of the most valuable assets of a pharmaceutical company, after its people, is its unique chemical compounds, which have been optimized for specific biologic/pharmacologic and drug-like properties after countless iterations and supporting experiments in preclinical species and humans. Pfizer now offers access to these "company jewels" through its compound gift program. Through this program we fulfill over 2000 requests for compounds at no cost to institutions seeking new paths of research, with the only requirement being acceptable scientific protocols, ownership of our compound intellectual property, and nonexclusive access, but not ownership, to novel discoveries. We supply these compounds to anyone around the world who requests them. These compounds are used to test basic hypotheses, uncover possible new treatments, and investigate public health applications (Fig. 3). Pfizer benefits from making these gifts by gaining a better understanding of the biologic

Figure 2. Licensing and development (L&D) and strategic alliance deals (2005). Academic and physician scientist collaborations with the pharmaceutical industry are important components in a successful drug discovery and development model. The left side of the figure demonstrates that alliances are frequent and plentiful, although high-quality deals are still in limited number. The right side of the figure illustrates a generic drug candidate licensing process, from initiation of company visits to finalization of a deal to develop and/or acquire a drug candidate. Likewise, the number of completed licensing deals is far less than the number of opportunities reviewed.

effects of their compounds and by learning of new clinical uses and markets for its compounds.

Drug Pfinder. Drug Pfinder was established to leverage discoveries and expertise from the academic and biotechnology communities to support new lead discovery programs. Novel potential discovery targets often are identified in the academic community; however, scientists lack the resources or experience to translate these targets into new medicines. Through a Drug Pfinder collaboration, the academic scientist gets access to Pfizer's extensive state-of-the-art high throughput screening (HTS) experience, including our compound file comprising millions of unique, drug-like structures. This collaboration also includes financial milestones, dedicated medicinal chemistry to turn "hits" into "leads," and a direct link to established teams dedicated to specific disease areas (Fig. 4). Of particular interest are targets that have yet to be published and/or have established intellectual property, targets in which our collaborator has extensive expertise and assay methods, and targets that may have numerous therapeutic applications or are in newly emerging areas of biology. Ultimately, the goal of a Drug Pfinder partnership is to generate a lead


THE CLEVELAND CLINIC FOUNDATION

LERNER RESEARCH INSTITUTE

Compound Gift Sample Results

Thank you for your interest in the work that we are doing with Pfizer compound CP31398. Preliminary results from this project are described below and illustrated in the attached Powerpoint figures. We feel that use of CP31398 in our experimental system has yielded some interesting results and hope to continue our collaboration with Pfizer in order to successfully complete our studies.

[CANCER RESEARCH 62, 7149–7153, December 15, 2002]

Advances in Brief

Activity of the Bcr-Abl Kinase Inhibitor PD180970 against Clinically Relevant Bcr-Abl Isoforms That Cause Resistance to Imatinib Mesylate (Gleevec, STI571)[1]

We are grateful to Kara Johnson and the Druker laboratory for expert technical advice and helpful discussions and to Sarah Anderson and Chris Koontz for administrative assistance. We also thank Dr. Alan Kraker (Pfizer Global Research and Development, Ann Arbor, MI) for providing PD180970 and for critically reading of the manuscript.

THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

Drugs.

The MAPK inhibitor PD98059 was purchased from Sigma Aldrich Inc. (St Louis, MO) and was used for *in vitro* studies. Gefitinib (ZD1839, Iressa™) was provided by AstraZeneca (Wilmington, DE). CI1040 was a kindly gift form Pfizer (Ann Arbor, MI) and was used for *in vivo* studies. Stock solutions were prepared in dimethyl sulfoxide

Figure 3. Compound gift sample results. The compound gift program offers a unique opportunity to access one of the industry's most valuable assets, its chemical compounds. These compounds offer a plethora of opportunities to test or uncover novel hypotheses, support confidence in target rationale, or improve confidence in program safety.

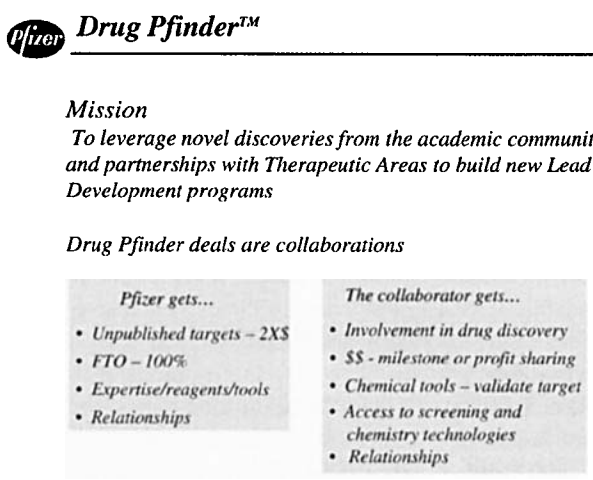


Figure 4. Drug Pfinder collaborations. Drug Pfinder collaborations provide a unique opportunity for industry to access novel potential drug discovery targets. They also enable academic scientists to experience the drug development process and gain access to novel screening and medicinal chemistry approaches.

molecule that can be further developed into a clinical candidate.

Effective Partnering Success Factors

Matching Quality Science with Strategic Objectives. Clearly, the first prerequisite in any partnership is that high-quality science on both sides is aligned with the strategic objectives of both partners. For industry, much of the focus is on investments that allow us to focus on fewer project concepts and get these concepts to the increased CIR and CIS stages, as described earlier in the Discovery section. This results in decreased time and cost to product launch (through the use of innovative clinical trials, biomarkers etc., to make better decisions earlier) and improved program survival to launch (through improving the quality of our programs). A thorough review of partner abilities, track record, facilities, management, and intellectual property should be expected as part of due diligence considerations.

Establishing Clear Expectations. Setting clear and transparent expectations before a partnership is formed is a necessary foundation for partnership return on investment, whether the collaboration is ultimately viewed as a success or not. For most collaborations these expectations are reflected by the research/work plan. This plan must clearly articulate who is responsible for performing what tasks, by when, and at what cost. Proactive scenario planning (decision trees) offers the most objective opportunity to help partners think through and agree to action plans and strategies ahead of actual data generation, and it allows for rapid decision making when timelines are tight.

Respect Your Partner. Recognizing and respecting that both partners are bringing unique value, perspective, skills, and resources to the collaboration is key to partnering success. Partners must have a shared vision, a collaborative spirit, and a visible commitment by both sides (i.e., not just mailing a check or having a fee-for-service relationship) built on integrity, trust, and transparency. Since the ultimate goals of academic and industrial science often differ (basic vs. applied research, respectively), partnerships should be win–win situations for both partners.

Contract Negotiation. Just as the research plan aims to meet the scientific and strategic needs of the partnership, the collaboration contract needs to reflect the business requirements. Expectations must be realistic and reflect the risks and rewards on both sides. A transparent and thorough awareness of where and how the collaboration deliverables fit into the overall discovery and/or development program can often aid in this understanding. The contract also must respect the fact that both partners may need or desire to collaborate with other partners. Each side must know what it really wants to get out of the deal, know when to walk away, and aim for a win–win situation. Deal terms on intellectual property (access vs. ownership), publication rights (ensuring freedom to publish), liability, and confidentiality often can be balanced so that both sides achieve what they really need to get out of the collaboration. Negotiation under short timelines is not recommended, as it often takes time to establish a relationship built on an understanding and appreciation of both partners' perspectives and aspirations.

Actively Manage the Collaboration. As mentioned above, mutual partner commitment to the collaboration is essential for deal success. The alliance cannot be treated as a hobby or sideline activity, and it needs to be visibly integrated into the business of both partners. Staff members need to share collaboration goals and be held accountable, and contract obligations need to be strictly followed. Appropriate governance structures for strategic, scientific, and tactical decision making needs to be effective, fair, part of the contract, and clear to all up front.

Conclusion

Getting new medicines to patients is a timely, expensive, and risky process. Even considering all the resources, skills, expertise, and talent in the pharmaceutical industry, program attrition due to safety and efficacy issues threatens to significantly impair our ability to provide new medicines to patients in areas of high medical need. Clearly, effective partnering with academic and physician scientists offers the potential to provide additional value to drug discovery and development. These partnerships must be well aligned around quality science and strategic objectives. They also must be built on transparency, integrity, and trust, which require effective communication, respect, understanding, and clear expectations. Ensuring the research plan and contractual framework matches the needs of both partners is essential, whether the collaboration ultimately is viewed as a success or not. Finally, signing the deal contract is only the first step in active management, engagement, and keeping the business and science on track to meet the goals of the collaboration.