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Foundation-Industry Relationships - A New Business Model
Joint-Venture Philanthropy in Therapy Development

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Abstract: The business model for medical therapy development has changed drastically. Large companies that once conducted their own Research and Development (R&D) and funded all the preclinical studies, all phases of clinical development and marketing of the products are increasingly turning to others for more and more of the earlier work in hopes of being able to in-license a de-risked program well downstream, take it through the final phases of clinical development and into the marketplace. This new paradigm has required patient-advocacy foundations, especially in the rare-disease space, to become far more effective in building relationships with all the players along the therapy-development pathway -- academic scientists, government agencies, other foundations with overlapping interests, biotechs, small biopharmaceutical entities and even the larger industry companies. From the perspective of the patient-advocacy community, these increasingly essential public-private partnerships have taken on the nature of what could be called joint-venture philanthropy and involve a broad spectrum of collaborations and financial relationships between foundations and industry partners that are not without concerns about potential conflicts of interest.

Keywords: Patients, patient-advocacy organization, patient registry, natural history, clinical trial design; clinical endpoints, public-private partnership, joint-venture philanthropy, industry partners, government agencies, de-risking, Valley of Death, conflict of interest, benefit-risk evaluation.

INTRODUCTION

During the extended period of time when the major biopharmaceutical and medical device industry players could and did operate as nearly independent actors in the therapy-development arena, there was little need for meaningful relationships between those large entities and patient-advocacy foundations. The large companies had robust in-house R&D divisions on which they depended to produce the lead candidates the companies would then advance through clinical development. These companies were accustomed to funding everything from the basic discovery science through preclinical studies, all phases of clinical development and marketing of the product. Increasingly, however, the large companies are leaving the R&D to others, turning to academic scientists for the discovery science and to biotechs, small biopharmaceutical companies and venture capitalists to "de-risk" therapy development by funding the preclinical requirements and the early clinical phases so larger companies can select from various in-licensing options at the later phases of clinical development.

Because the biotechs and small biopharmaceutical companies frequently do not have the resources required to move a discovery though its preclinical studies and through a phase I or phase II clinical trial and often are unable or unwilling to find a venture-capital company ready to provide those resources, they increasingly appeal to patient-advocacy foundations for help. And, because few foundations have sufficient resources to fund multiple programs through these expensive early stages, the chasm often described as the "Valley of Death" appears between the large companies waiting at one end of the Valley for de-risked programs and the foundations and small companies at the other end doing all they can to move programs further across the Valley.

Even more than the other entities struggling to get across the Valley, patient-advocacy foundations know that they cannot accomplish this transition alone. They understand that therapy development is now a team sport and that they can be a key player to the extent that they can help bring other players to the team and facilitate teamwork. The core strength of most foundations lies in the quality of their relationships with the patients and patient families. On those relationships is usually based a foundation's ability to assemble sufficient resources to support the basic discovery research of the disease-specific academic scientific community. It is on the basis of those relationships, too, that a foundation can seek support from government agencies such as the National Institutes of Health (NIH), the Food and Drug Administration (FDA) and congressional representatives as well as from other foundations with overlapping interests. A foundation with well-nurtured ties to those various entities is in a good position to bring together important pieces of a new business model that potential industry partners are likely to find attractive.

What are Foundations Doing to Get the Team Across the Valley?

Just a few years ago, as the biopharmaceutical industry's interest in the rare disease space was intensifying, an indus-

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try CEO in a conference presentation confirmed that increasing interest but added that he and his industry colleagues were "looking for low-hanging fruit." In that context, much of what foundations are doing in this challenging environment can be seen as attempts to grow such low-hanging fruit on their side of the Valley in hopes that potential industry partners will pick that fruit earlier in the process and help move it across the chasm into further clinical development and into patients. Especially with therapy development in the more common diseases an increasingly crowded and competitive space, the current environment is presenting even the larger, common-disease foundations with similar challenges.

So, what are foundations doing to grow low-hanging fruit attractive to industry? The spectrum of foundation activities and accomplishments in this regard is broad and varies with the resources available to each group, but the spectrum includes:

Basic Discovery Science: In many cases, foundations are funding the majority of the disease-specific basic research, especially in the current era in which budgetary constraints render government grants increasingly difficult to secure. As foundations fund individual academic scientists, they are consciously attempting to grow the field, assemble the field and facilitate -- even require -- healthy collaboration. In many cases, these foundation efforts result in discoveries that appear to promise potential therapeutic approaches and the foundation reaches out to industry in search of a suitable development partner. What the foundation too often hears in response is that the potential industry partner wants to see the program further de-risked before making a commitment, so the foundation has to dig deeper into its resources to ripen the fruit further.

Translational Science: Moving aggressively beyond basic science, foundations are providing more and more of the translational tools of therapy development. Many foundations support bio-repositories with a wide range of patient samples (e.g., blood, urine, DNA, RNA) as well as post-mortem patient tissues and organs. They have also funded an impressive array of cell assays, animal and cell models including disease-pertinent cell types derived from Induced Pluripotent Stem (IPS) cells. Many foundations are also performing the invaluable service of funding extensive natural history studies that produce rich databases that can, along with the bio-repositories, be mined for indicators of important translational tools such as biomarkers.

Clinical Research: Many foundations have even become indispensable partners in the clinical research enterprise. For example, these foundations have developed, refined and validated clinical endpoints for their diseases. Quite often in conjunction with their important work on natural history studies and clinical endpoints, they have, in effect, formed clinical networks consisting of clinicians and staff who see, in multiple visits over time, a significant number of the patients of interest to the foundations and are well prepared to conduct clinical research including trials of therapeutic candidates.

The rich databases populated by the natural history studies funded by foundations are also a valuable resource for industry partners as these databases are being mined by clinical trial sponsors, in concert with the foundations, to design their trials, write their protocols and select their subject populations. Some foundations have even discovered that conducting a natural history study, in addition to laying important groundwork for clinical development, can, by itself, lead to significant gains in patient care and survival

Once these clinical trials are ready for launch, a growing number of trial sponsors are discovering how much time and money they can save and how significantly the quality of their trials can be enhanced by foundations using the patient registries they have built and maintained to recruit subjects for trials. For example, in February 2013, Dr. David Lynch of the Children's Hospital of Philadelphia requested that the Friedreich's Ataxia Research Alliance (FARA) help him recruit the twenty subjects he required to conduct his site's portion of a phase IIb clinical trial in Friedreich ataxia. Using its patient registry, FARA notified the 245 patients who, from their registry entrees, appeared to meet the general inclusion criteria for the trial and to live within a reasonable distance of the site. The required twenty subjects were recruited in only two hours and forty-three minutes and many more responded but found the trial full [1].

Collaboration, Collaboration, Collaboration: Most foundations are fully aware of their limitations -- of the fact that they cannot get across the Valley alone. Consequently, they devote much of their time and effort to establishing and nurturing public-private partnerships they hope will evolve and grow into coalitions with sufficient resources and capabilities to complete therapy development successfully and deliver treatments to patients. These collaborations, especially in the United States, frequently begin with foundations reaching out to the government.

FOUNDATIONS, GOVERNMENT AND THE INDUSTRY

NIH: Most foundations recognize that the NIH is currently devoting more than 30 billion dollars annually to medical research and that, in a variety of ways, the foundations can help facilitate the beneficial impact of that funding on their disease communities. First, they can familiarize themselves with the NIH funding process and mechanisms so as to be able to serve as a conduit of information between the NIH and their academic scientists and biopharmaceutical development partners. They can keep their scientific and development communities current regarding a wide and evolving range of NIH funding opportunities. A foundation can enhance its NIH collaboration by becoming active with the pertinent NIH Institute's National Advisory Council and nurturing a good working relationship with the Institute's program director responsible for the foundation's disease group. Foundations can undertake to provide "seed" grants to investigators designed to enable them to prepare the preliminary data required to submit a successful application for an NIH grant. Foundations can also provide letters of support for applicants to the NIH and, in some cases, even become applicants or co-applicants themselves.

FDA: Foundations are playing an increasingly important role in the regulatory process, much to the benefit of their industry partners. Patients and patient advocates have long served as special government employee patient representatives at the FDA but, to date, have been restricted almost

exclusively to an advisory role in the New Drug Application (NDA)/market-approval review. Recently, however, especially in the context of discussions centered on the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, patients and patient advocates are assisting the FDA in an effort to improve communications with patient groups at all stages of the regulatory process beginning before the first meetings to discuss an Investigational New Drug (IND) submission and continuing through all the milestone meetings as well as the NDA review [2].

FDA officials have been meeting periodically with foundation representatives to discuss Patient-Focused Dug Development since well before enactment of FDASIA. At the center of these discussions have been the issues of risk tolerance, benefit-risk evaluation and education of FDA reviewers regarding the thousands of disease areas with which they must become familiar. The FDA clearly recognizes the importance of the patient and patient-advocate voices in these issues. In her opening remarks at the May 18, 2012 meeting with patient groups to discuss risk tolerance and benefit-risk evaluation, Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research (CDER), introduced the importance of hearing the patient's voice in drug development by stating, 'I would love to be able to tell you that our benefit-risk evaluation is completely data driven -- that we simply collect all the data, add up the numbers and the decision is made. But, I can't tell you that because, at the end of the day, benefit-risk evaluation is a value judgment.' Dr. Russell Katz, Director of CDER's Division of Neurology Products, told participants in the March 2, 2013 meeting of the American Society of Experimental NeuroTherapeutics that, 'Benefit-risk evaluation is not quantifiable. It is a judgment.'

Foundations are intent on helping educate FDA personnel regarding the severity of their diseases, their unmet medical needs, and the inadequacy of treatment or lack of any treatment for thousands of their conditions so that the FDA's benefit-risk value judgments are well informed by the patient perspective. It is obviously important that the diseases themselves and the patient's perspective be clearly understood at the earliest stages of drug development rather than being reserved for the NDA review. Far too few disease groups have gotten as far as an NDA review and far too many promising therapy opportunities may be lost in the early stages if the benefit-risk value judgments made at those early decision points are not as well informed as possible.

When industry officials are asked what would be most helpful in convincing them to commit resources earlier in the therapy-development process, they often reply, "reducing regulatory uncertainty." A growing number of foundations as well as their industry partners are beginning to conclude that all the work foundations are doing directly with the FDA, along with their contributions in such areas as biomarkers, clinical endpoints, natural history studies, assays, animal and cell models, databases and registries, etc., are accomplishing a great deal in terms of reducing regulatory uncertainty.

Congress: While all organizations involved in medical R&D in the United States recognize the important role played by the U.S. Congress, foundations vary as to the kind of congressional support they seek, and the variety of congressional support they receive results in differing impact on their relationships with the therapy-development industry. Many foundations, for example, take a very broad approach by seeking the most robust budgets possible for government agencies involved in medical R&D. Many of these foundations work together in umbrella groups such as Research!America to increase congressional support for agencies responsible for medical research, and the Alliance for a Stronger FDA, in which representatives from foundations and the industries regulated by the FDA advocate, together, for greater congressional support for the FDA.

FOUNDATIONS, ACADEMIA AND THE INDUSTRY

Many foundations devote a large portion of their resources, especially in their early years, to supporting academic investigators conducting basic discovery science and attempting to facilitate additional support for those investigators from government agencies and other foundations with overlapping interests. When such an investigator reports a breakthrough that appears to promise an effective therapeutic approach, the foundation often reaches out to potential industry partners. Foundations would be thrilled, of course, to see mid-sized or large therapy-development partners take up such discoveries from academia at the near side of the Valley. However, because this is not happening very often, many foundations spend considerable time and energy establishing and nurturing relationships with very small, start-up and virtual companies as well as venture capital firms in an attempt to match the interests of the company to those of the academic scientist.

Foundations are serving in this very important matchmaker role at the request of both sides of these partnerships. At times, the academic discovery scientist works with the foundation to find an industry partner while, at other times, it is the industry partner that appeals to the foundation to identify a promising academic discovery in its area of interest or to facilitate contact with an academic lab with the expertise and tools needed to test a potential therapeutic approach in the company's portfolio. In most cases, all three parties -- the foundation, the academic investigator and the industry partner -- want to collaborate so as to mature the program to a point at which they can market it to a therapy-development company with the resources needed to take it through the more expensive stages of clinical development.

FOUNDATIONS AND THE INDUSTRY -- DIRECT FINANCIAL RELATIONSHIPS

In addition to these diverse approaches being used by foundations to lay the groundwork for and enable collaborative, mutually beneficial relationships with industry partners, a wide range of direct financial relationships are being developed between foundations and the industry. Some of these relationships involve the flow of resources from the foundation to the industry partner. Some involve such flow from the industry partner to the foundation while, in others, the flow of resources is in both directions.

The very small companies with which foundations most often collaborate, frequently lack the full resources needed to take a program all the way to the tipping point at which it can be marketed to a larger company. Consequently, these small companies appeal to foundations for support. Of those

foundations who agree to provide support, some elect to award R&D grants to the company, while others choose to make investments in the company or a combination of the two approaches. In many cases, the two parties agree to a contract that calls for a return on investment, return of the grant monies if the company's program is sold or is approved for the market, or product royalties to the foundation upon successful launch.

The flow of resources is often in the other direction, with industry partners providing support to foundations. For example, some companies help foundations fund conferences to create a venue in which the company can present its work, meet with investigators with whom the company is collaborating or would like to collaborate, and interact with participating government personnel from agencies such as the NIH or FDA. Some companies provide funding to foundations for a variety of other reasons, including the development of patient registries to be used in recruiting for clinical trials and for educating the patient population regarding the particular condition and any available treatment options.

CONFLICTS OF INTEREST - REAL OR APPARENT

In the current therapy-development environment as outlined above, few foundations could hope to be successful in getting treatments to patients without doing all they can to establish and nurture productive, mutually beneficial relationships with industry partners -- relationships that include the flow of resources in one or both directions. That being the case, some degree of conflict of interest, or at least the appearance of conflict of interest, is likely inevitable. That reality leads some to conclude that, if you have no conflict, you have no interest.

Much attention has been paid and concerns raised about the conflicts of interest that are likely to result from the industry providing funding to academic investigators, physicians and government employees. etc. Some related concerns have been raised about potential conflicts of interest arising from industry providing funding to foundations. While there are no legal restrictions on such funding, the concerns usually raised revolve around such issues as the disclosure of these financial ties, the level of funding received from industry partners and the possibility that the funding might influence the foundation's policies, positions, website content, communications to the patient community, etc.

The *Chronicle of Philanthropy* reported in September 2010 that the office of Senator Charles E. Grassley, senior Republican on the Senate Finance Committee, had inquired of 33 foundations in the health and medical arena regarding the funding they had received from pharmaceutical, medical-device and insurance companies and that the *Chronicle* had asked those same foundations to share the information they had provided the Senator's office. From the information provided by those foundations, the *Chronicle* concluded that the level of funding, disclosures of such funding and the degree of any apparent conflicts of interest varied widely from foundation to foundation. Among the foundations that shared such information with the *Chronicle,* the percentage of total revenues represented by funding from the industry went as high as 78 percent. In terms of disclosing industry funding, the spectrum ranged from no disclosure on foundation website to full disclosure. Other foundation website content ranged from no representation of industry partners to industry advertising and endorsements of products [3].

The foundations' main concern regarding conflict of interest with the industry involves the vital importance of the trusting relationships the foundations have with their primary constituents -- usually patients, patient families and donors. As a foundation makes decisions about awarding grants, investing in therapy-development companies or programs and recruiting patient participants for clinical trials, for example, those primary constituents must be able to trust that the foundation is basing its decisions on the interests of the constituents rather than on any other interests of the foundation, its directors, officers or staff. If even the appearance of conflict begins to erode this essential trust, the foundation can begin to lose its credibility and ability to accomplish its mission.

With the near inevitability of at least the appearance of conflict of interest, foundations can not always avoid such conflicts and must take care to manage them as effectively as possible. Such management usually begins with disclosure. External disclosure can include public posting of the tax forms on which industry donations are reported and information provided on foundation websites, annual reports, and newsletters, etc. Internal disclosures include the foundation's officers, directors and staff disclosing any financial involvement with the industry such as investments, payments, grants, gifts, reimbursements, etc. It also includes any policy role the foundation member might play in the industry (e.g., serving on a board of directors or as an advisor). Some foundations prohibit such involvement while others require that such individuals disclose such involvement and be recused from any foundation decisions regarding the pertinent industry entity and any competing industry entities.

THE RESULTING NEW BUSINESS MODEL - JOINT-VENTURE PHILANTHROPY

In 2012 and the first quarter of 2013, the news in the therapy-development community included a number of exciting developments that illustrated the power of the new business model that is attracting the larger companies to programs in which foundations played and continue to play major roles as a result of their relationships with patients, academic investigators, government, other foundations and industry partners. One of the most widely publicized of these developments involved the 2012 announcement of FDA approval (after a review that lasted just over three months) of Vertex's Kalydeco for a rare form of Cystic Fibrosis followed by the FDA's designation of Kalydeco in combination with a second Vertex drug - VTX 809 - as a "breakthrough therapy." CDER Director Janet Woodcock has described this new breakthrough designation as a call for "all hands on deck" to accelerate completion of therapy development from the early phases of clinical trials to approval [4]. The Cystic Fibrosis Foundation played an essential role, along with its public-private partners, in developing Kalydeco. "Kalydeco was discovered in a collaboration between Vertex and the Cystic Fibrosis Foundation that began more than a decade ago. The Foundation provided significant scientific, clinical and financial support throughout the development process, including a $75 million investment [5]."

JOINT-VENTURE PHILANTHROPY IN SPINAL MUSCULAR ATROPHY (SMA)

Because the Cystic Fibrosis Foundation's annual revenues in recent years have ranged between $250 million and $300 million [6], it is instructive to note that some foundations with much smaller treasuries have also been able to execute a very similar business model. For example, on January 3, 2013, Repligen Corporation announced, "that it has entered into an exclusive worldwide licensing agreement with Pfizer Inc. to advance Repligen's Spinal Muscular Atrophy (SMA) program, originally in-licensed from Families of SMA (FSMA). The SMA program includes RG3039, a small molecule drug candidate in clinical development for SMA, as well as backup compounds and enabling technologies. Under the terms of the agreement, Repligen is entitled to receive up to $70 million from Pfizer, commencing with an upfront payment of $5 million and total potential future milestone payments of up to $65 million as well as royalties on any future sales of SMA compounds developed under the agreement. ... 'This licensing deal demonstrates the innovative collaborations that Families of SMA has successfully implemented between non-profit, biotech and big pharma,' stated Jill Jarecki, Ph.D., Research Director for Families of SMA [7]."

FSMA reports that the foundation initiated this program in 2000 by performing drug screens with Aurora Bioscience/Vertex Pharmaceuticals, devoted $13 million to move the program through its pre-clinical requirements including testing in the animal models the SMA foundations helped develop, and secured FDA's Orphan Drug designation for the lead compound [8]. After Repligen in-licensed the SMA program from FSMA in 2009, an additional foundation, the Muscular Dystrophy Association, awarded Repligen $1.4 million for further development [9].

Meanwhile, the NIH was working with the SMA foundations and other public-private partners on a concerted SMA Project advised by a panel of senior experts from industry, academia, the NIH National Institute for Neurological Disorders and Stroke (NINDS) and the FDA. With the guidance of this Steering Committee, the SMA Project "established a preclinical drug-development effort, modeled after those conducted by large pharmaceutical companies, by funding a core group of industry Contract Research Organizations (CROs) and partners in academia. Under supervision of NINDS scientific staff, a primary contractor organization (SAIC) managed day-to-day activities of the Project, and a Lead Development Team with extensive pharmaceutical industry experience interpreted results and planned next steps [10]. In addition, the NINDS selected an SMA biomarker study as the first undertaking of its new Network for Excellence in Neuroscience Clinical Trials (NeuroNext) and began in December 2012 enrolling patients in that study [11].

JOINT-VENTURE PHILANTHROPY IN FRIEDREICH ATAXIA (FRDA)

Another illustration of the new business model in which a foundation with modest revenues is playing a key role involves FRDA. On March 29, 2013, privately held Edison Pharmaceuticals, a small U.S. biotech developing compounds for FRDA and other inherited mitochondrial respiratory chain diseases announced an R&D and commercialization agreement with Dainippon Sumitomo Pharmaceuticals (DSP). Under the terms of the agreement, DSP is to develop Edison's lead candidate, EPI-743, and its follow-on molecule, EPI-589, in Japan while Edison retains all rights to the compounds elsewhere. Edison is to receive $35 million up front and $15 million in R&D support and is eligible for $10 million to $35 million in development milestones per indication and $460 million in commercial milestone payments as well as royalties on commercial sales.

In early 2005, Edison, then a start-up biotech beginning to seek its initial financing, had a small library of molecules it had identified as promising in potentially addressing the mitochondrial respiratory chain defects that characterize FRDA and a number of other disorders. Edison's management approached the Friedreich's Ataxia Research Alliance (FARA) with a request for collaboration in testing the Edison molecules. After receiving exciting results from tests conducted by FARA-funded academic scientists in FARA-funded FRDA cell assays, FARA awarded Edison a $3.3 million R&D grant to advance the compounds, and the Muscular Dystrophy Association's Seek a Miracle program added $100,000 to that grant. In Edison's first round of financing in late 2005, FARA also invested $1.1 million in the company's Series A preferred shares.

Also in 2005, FARA teamed with Edison and a leading academic FRDA investigator as co-applicants to the Rapid Access to Intervention Development (RAID) program that was part of the NIH Roadmap for Medical Research initiative launched in September 2004 and has evolved into the current NIH/NCATS program called Bridging Interventional Development Gaps (BrIDGs). In July 2006, the NIH accepted this joint-venture project into the RAID program, which provided some of the drug-development guidance and contract resources needed to enable an Investigative New Drug Application (IND) to be filed with the FDA. FARA later participated in the project's pre-IND meeting at the FDA along with Edison, the academic principle investigator and representatives of the NIH RAID team.

Edison's lead molecule was then in-licensed by a small company -- Penwest Pharmaceuticals -- that worked closely with FARA to advance the molecule through successful phase I and phase II FRDA clinical trials. Endo Pharmaceuticals then acquired Penwest to obtain its other assets, outside the neurodegenerative arena, and decided to return Penwest's lead neurodegenerative candidate to Edison.

In early 2013, working closely with FARA, Edison launched a phase IIb pivotal study in FRDA at three sites -- all of which participate in the FARA-supported clinical network that has conducted extensive FRDA natural history studies and in which a large number of FRDA patients are seen annually. Using the on-line patient registry it developed in collaboration with Electronic Data Systems and students at the Rochester Institute of Technology, FARA was successful in fully recruiting the 60 patients needed for Edison's phase IIb trial in only a few hours. This rapid subject recruitment, of course, will save Edison much time and money over the course of the trial. In collaboration with a number of

other foundations, Edison has also launched phase II trials of the same lead compound in Leigh syndrome, Leber's hereditary optic neuropathy, cobalamin C deficiency, MELAS, metabolism or mitochondrial disorders, Tourette syndrome and Rett syndrome [12].

CONCLUSION

The foundations involved in cystic fibrosis, spinal muscular atrophy and Friedreich ataxia are only a few of the many organizations working hard to build the new joint-venture philanthropy business model they hope industry partners will find sufficiently attractive to "pick the low-hanging fruit" earlier in the therapy-development process. The experiences of these three foundations do seem to include illustrations of many of the building blocks foundations are putting into place so as to construct this new business model and to establish and enhance their important relationships with industry partners. The continuing development of this new business model is clearly a validation of the principle, "necessity is the mother of invention" in that the current R&D environment severely limits any public or private organization's ability to advance a therapy from bench to bedside without effective public-private partnerships that include creative, mutually beneficial foundation-industry relationships.

CONFLICT OF INTEREST

The author has no personal conflicts of interest related to his relationships with industry partners. He has no personal financial involvement with any industry entities. He has not received any funding from or made any investments in any such entities. FARA, the organization of which the author is Co-Founder and President, is actively and transparently involved in the kind of joint-venture philanthropy that is discussed above and specifically described in the above section, "Joint-Venture Philanthropy in Friedreich Ataxia (FRDA)." All such FARA involvements are fully disclosed.

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