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Clinical Drug Development for the Treatment of Pulmonary Arterial Hypertension: Collaboration With the Pharmaceutical Industry and Regulatory Agencies

[Robyn Barst](#)

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"//connect.facebook.net/en_US/all.js#xfbml=1"; fjs.parentNode.insertBefore(js, fjs);
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Drug development is the entire process of introducing a new drug to the market. It involves drug discovery, screening, preclinical testing, an Investigational New Drug (IND) application in the US or a Clinical Trial Application (CTA) in the EU, phase 1-3 clinical trials, a New Drug Application (NDA), Food and Drug Administration (FDA) review and approval, and post approval studies required for continuing safety evaluation. Preclinical testing assesses safety and biologic activity, phase 1 determines safety and dosage, phase 2 evaluates efficacy and side effects, and phase 3 confirms efficacy and monitors adverse effects in a larger number of patients. Postapproval studies provide additional postmarketing data. On average, it takes 15 years from preclinical studies to regulatory approval by the FDA: about 3.5-6.5 years for preclinical, 1-1.5 years for phase 1, 2 years for phase 2, 3-3.5 years for phase 3, and 1.5-2.5 years for filing the NDA and completing the FDA review process. Of approximately 5000 compounds evaluated in preclinical studies, about 5 compounds enter clinical trials, and 1 compound is approved (Tufts Center for the Study of Drug Development, 2011). Most drug development programs include approximately 35-40 phase 1 studies, 15 phase 2 studies, and

3-5 pivotal trials with more than 5000 patients enrolled. Thus, to produce safe and effective drugs in a regulated environment is a highly complex process. Against this backdrop, what is the best way to develop drugs for pulmonary arterial hypertension (PAH), an orphan disease often rapidly fatal within several years of diagnosis and in which spontaneous regression does not occur?

Since 1938, every new drug requires an approved NDA before US commercialization. The NDA is the vehicle by which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the US. Data gathered during animal studies and human clinical trials of an IND become part of the NDA.

The documentation required in an NDA should “tell the drug's whole story,” including details of its composition; animal study results; its behavior in the body; clinical study reviews; and how it is manufactured, processed, and packaged. The NDA includes summaries of all efficacy and safety data with an in-depth discussion of the risk-benefit considerations for the given drug compared to drugs already approved for the same indication. The sponsor must provide sufficient evidence for the FDA to decide that: 1) the drug is safe and efficacious; 2) benefits outweigh risks; 3) the proposed labeling is appropriate; and 4) the manufacturing methods and controls maintain drug identity, strength, quality, and purity. Furthermore, the NDA review process is multifaceted. It includes medical review to evaluate the data generated from clinical protocols and safety; biopharmaceutical evaluation to assess absorption, distribution, metabolism, and excretion; pharmacological review to evaluate toxicity, clinical pharmacology, at-risk populations (elderly, children, etc); chemical review to assess chemical properties; and statistical assessment to determine if the results are statistically significant. As one would surmise, this process is expensive: on average, the cost is at least \$100,000 to \$1 million for phase 1 trials; \$10 million to \$100 million for phase 2; and more than \$50 million for phase 3 studies. Total cost for a full clinical drug development program is estimated at 1.0 to 1.8 billion US dollars.

Why is the drug development process so arduous? In the 1800s, the US was inundated with counterfeit, contaminated, diluted, and decomposed drug materials, resulting in the establishment of the Import Drugs Act in 1848 to enforce purity and potency standards. However, in the late 1800s, the marketing of drugs was still “a circus” (Figure 1).

Figure 1:

An example of drug marketing in the 1800's.

Milk was unpasteurized; cows were not tested for tuberculosis; the principal means of refrigeration was ice; and there were no restrictions on opium, morphine, heroin, or cocaine labeling or “marketing.”

In 1906, passage of the Pure Food and Drug Act prohibited interstate commerce of

misbranded and adulterated drugs, and permitted seizure and criminal penalties (Figure 2).

Figure 2:

The Pure Food and Drug Act was passed in 1906.

Despite this advance, the Act did not address drug standards, false advertising, or drug facility inspection. Also, existing laws did not require that any pharmacological studies be performed to demonstrate that a drug was safe. In 1937, the liquid form of sulfanilamide was manufactured using diethylene glycol (antifreeze) as the solvent; 107 people died (mostly children being treated for streptococcal infections). This resulted in the FDA Act of 1938, requiring new drugs to be *safe* before marketing, eliminating the requirement to prove intent to defraud in drug misbranding cases (fraudulent claims), providing standards and safe tolerances, and authorizing factory inspections. Despite these safeguards, in 1961, the thalidomide crisis occurred. Hailed as a wonder drug for sleeplessness, thalidomide also relieved morning sickness in many pregnant women; however, it was not appreciated that thalidomide crossed the placenta. Multiple defects, including peripheral neuritis deafness, blindness, severe disfigurement, and phocomelia occurred. As a result of this tragedy, in 1962, the FDA required drug manufacturers to prove drug *effectiveness and safety* before marketing. In addition, advertisements had to disclose complete information on benefits and risks and adverse effects had to be reported to the FDA pre- and post approval. These amendments resulted in thousands of drugs being removed from the market. One such drug was diethylstilbestrol (DES), which was promoted to prevent miscarriage, despite a large, randomized, controlled study in 1953 that demonstrated no effect for this use. By the time the devastating, multigenerational reproductive effects of DES became apparent in the 1960s and 1970s, 5-10 million American women and their children had been needlessly exposed.

What about the history of clinical trials? The first trial is considered the study performed by James Lind in 1747 at sea on the *Salisbury*.

“On the 20th of May 1747, I took 12 patients in the scurvy.... Their cases were as similar as I could have them. They all had putrid gums, the spots and lassitude, with weakness of their knees ... and had one diet in common, viz. water-gruel sweetened with sugar in the morning; fresh mutton often times for dinner; at other times puddings, boiled biscuit with sugar, etc.... Two of these were ordered each a quart of cider a day. Two others took 24 gutts of elixir vitriol three times a day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took 2 spoonfuls of vinegar three times a day, upon an empty stomach: having their gruels and their other food well acidulated with it, as also the gargle for their mouths. Two of the worst patients, with the tendons in the ham rigid (a symptom none of the rest had) were put under a course of sea-water. Of this, they drank half a pint every day.... Two others each had two oranges and a lemon given them every day. These they ate with

greediness.... The remaining patients took the bigness of a nutmeg three times a day, of an electuary recommended by a hospital-surgeon, maden of garlic, mustard-feed, raphan, balsum of Peru and gum myrrh; using for common drink barley water well acidulated with tamarinds.... The consequence was that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of 6 days fit for duty...."

In spite of the relatively straightforward nature of his findings, Lind still advised that the best treatment for scurvy involved placing stricken patients in "pure dry air." Undoubtedly, the reluctance to accept oranges and lemons as treatment for the disease was biased by expense compared to the "dry air" treatment. It was another 40 years before the British Navy supported lemon juice for the crew of its ships at sea. Once again the question of cost became an issue (limes were substituted for lemons, thus condemning British sailors as "limeys" for the next 200 years).

Most of the early "clinical trials" involved arbitrary, nonsystematic methods for assigning patients to treatments. The concept of randomization was first introduced in 1948; the first trial with a properly randomized control group evaluated streptomycin as treatment for pulmonary tuberculosis. However, not all clinicians were convinced of the need for such trials. A letter published shortly thereafter attacked a proposed trial for the treatment of depression: "There is no psychiatric illness in which bedside knowledge and long clinical experience pays better dividends; and we are never going to learn about how to treat depression properly from double blind sampling." Nevertheless, since World War II, the clinical trial has become a standard procedure in the evaluation of new drugs with the FDA having a statutory standard for effectiveness from well-controlled, randomized clinical trials.

What about drug development in PAH? Development began in the late 1970s with the acute testing of intravenous (IV) epoprostenol in adult patients with idiopathic or familial PAH (previously termed PPH). The objective was to determine if acute administration of this agent could predict those patients who could be considered for long-term calcium channel blockade (CCB). Prior to that point, many patients started empirically on CCBs died from sudden cardiogenic shock due to the long half-life of the CCB. At least with the short half-life of epoprostenol (3-6 minutes), patients could be "rescued" safely from acute vasodilator testing if the trial proved unfavorable. Following a 1984 case report from the UK of a young woman successfully treated with IV epoprostenol while awaiting transplantation, the feasibility of long-term IV epoprostenol as a "palliative bridge" to transplantation was evaluated. Clinical trials began in the US in 1987, and ultimately resulted in approval of epoprostenol in 1995 (based on improved survival over 12 weeks in the first pivotal trial performed in PAH). From that time, a small cadre of pioneers in academia persuaded key individuals in industry to become involved in PAH treatment. As such, a sometime contentious collaboration has been developed over the past several decades among academia, industry, and the FDA and has resulted in 8 drugs attaining approval for the treatment of PAH.

What can the investigator community do to improve drug development for PAH? Collaboration requires melding the expertise of individuals with different skills; it is imperative that industry, academia, and regulatory agencies work together as each has different skill sets. By working together, drugs can be developed in a more efficient and cost-effective manner. The goals of

each group are the same: to improve survival and improve overall quality of life. The pharmaceutical industry does a vast amount of work before initiating clinical trials. How can academia contribute in this drug discovery and preclinical process? Basic scientists and clinical investigators must provide honest opinions regarding novel molecules being considered as therapeutic agents for the treatment of PAH. Utilize insights to assess whether developing another drug in a given class is beneficial; for example, tadalafil vs sildenafil—its longer half-life and once-daily dosing can be important for some PAH patients but might be seen by others as only a “me too” drug.

Future therapies for PAH must address the underlying molecular defects. Identification of BMPR2 and determinants of penetrance in families with a BMPR2 mutation has provided such a mechanism. Understanding these defects and determining correct points for intervention are required for development of more effective treatments for PAH. The basic science provided by physicians and researchers can provide industry with focus for drug discovery and preclinical studies. Realistically, collaboration between industry and academia is essential throughout the entire drug development process. There are some experts from whom translational medicine input is critical, but others from whom input is most important once a phase 3 program has been developed and implemented.

When should academia begin collaboration with industry? Clinical drug development is an arduous job with significant time and money often invested long before clinical investigators are asked to consult on study designs or to serve as members of a steering committee (SC), an advisory board, or a data safety monitoring board (DSMB). Clinical investigators are often first contacted when a company is organizing a SC and seeking recommendations for potential participating sites for the trial. This is unfortunate for all involved, especially if the first contact with academia is after the pre-IND meeting. The pre-IND meeting between the sponsor and the FDA establishes the framework for the phase 2 program and provides an overview for the phase 3 program. However, this can result in a sponsor agreeing to a study that clinically cannot be completed or cannot be completed in a timely and cost-effective manner—important factors to both the patient/investigator community and industry. Thus, the investigator community working with industry to design feasible studies that answer explicit prespecified objectives could be beneficial. Involving statisticians with experience and knowledge of PAH and regulatory requirements for drug approval is also invaluable. Moreover, collaboration should not end after the last patient has completed the final study visit, but should continue through the FDA approval process and beyond. Far too often, a wealth of important clinically relevant data are obtained during studies but are never fully evaluated because the FDA does not request specific additional analyses. For instance, the FDA convened an advisory committee in July 2010 to address whether pulmonary vascular resistance index could be considered an appropriate efficacy endpoint in children with PAH who are developmentally unable to exercise (if said drug has already been proven safe and efficacious in adult PAH). Based on the request of the FDA and further analyses by the sponsor, an agreement on how to evaluate drugs in childhood PAH is in sight. It is doubtful that these analyses would have been performed otherwise.

All patients are important, but this may be especially true for drug development in PAH because of the limited population to enroll in trials. As such, trials take longer to enroll, require a larger number of participating sites (many outside the US), and require a larger sample size because moving forward placebo-controlled trials in treatment-naïve patients are considered by many to be unethical. Additionally, as enrollment of more stable patients (functional class II instead of only functional class III or IV), becomes more prevalent, studies need longer

duration to demonstrate a treatment effect. All these factors affect the overall clinical development program; it will be more difficult to design a drug development program that is efficient, innovative, and robust for the next generation of PAH drugs. How can fragmentation of the field be stopped? Too many companies are performing small studies using standard endpoints that may not be clinically relevant. Collaboration is imperative; however, significant roadblocks exist, including endpoints, intellectual property, publication rights, etc. Organization is essential to achieve success over the next 10-15 years.

Clinical investigators must seize opportunities to learn as much as possible from all study patients and collaborate with industry to analyze databases and generate hypotheses for future study. It is important to avoid dependence on the FDA to request additional potentially informative analyses. Different aspects of clinical trial design can be gleaned from the FDA and industry, but these organizations can also learn from investigators. Although the investigator community may disagree with the FDA and/or with industry, it has the potential to be beneficial to the FDA and industry on PAH.

Industry has often asserted that the PAH community is very unusual. Is this because clinicians have created a specialty in an orphan disease when there was little promise for drug development even after epoprostenol was approved or because industry did not want to market epoprostenol as it was not considered a company priority? Is it because of the small number of very ill patients with this disease or because of the continued passionate advocacy for these patients? Is it because of the very collaborative relationship with colleagues? In effect, it is who the PAH community is and these attributes should be utilized to improve the clinical trial process in any way possible.

ISSUES

Efficacy Assessments (endpoints, markers, outcomes, functional parameters, quality of life measures)

How to determine new endpoints? Industry has patient level data for its compounds, the FDA has all patient level data across compounds, and investigators have insight into what is clinically meaningful. The development of more sensitive and specific endpoints that are also prognostic of long-term outcomes requires collaborative efforts with both the FDA and industry now more than ever. Patients are likely to be on therapy before entering a clinical trial; they often have multiple concomitant diseases and are less ill than in previous studies. These and other factors make it more difficult to design a clinical program than it was 10 years ago. Primary endpoints must be clinically relevant, sensitive, measurable, and interpretable; secondary endpoints should complement primary endpoints by providing a more global view of drug benefit and by clarifying its risk-benefit ratio. Obviously, goals of treatment are to improve survival and symptoms. If a drug improves symptoms (however measured), there must also be reassuring survival data. However, if a drug improves symptoms but survival worsens, it is not approved.

How should an improvement be assessed? Using walk distance as an example: Should there be a threshold increase? Is it possible to say how much a given increase matters to patients? Maybe, but it is not the average that matters most. Means are used for historical and efficiency reasons, but the mean is not what individuals experience. Of greater interest is the effect on individuals, the distribution of effects. Why are mean effects problematic? A dramatic effect in 20% of patients may be preferable to a small effect in everyone. Thus, if a minimum

effect is set in a parameter, such as the 6-minute walk distance (6MWD), it should be interpreted in its distribution of effects. Optimally, the hope is that there would be a subset of patients with a substantial improvement, but what effect is large enough? Relative to initial disease severity? Relative to a more global measure, such as a “well-validated” quality of life tool? How can the influence of the trial circumstances, population, etc be assessed? Results regularly vary from one study to another. Should assay sensitivity be examined with an active control in addition to placebo? The reason for seeking a minimum effect is that use of any drug for a trivial gain does not, realistically, provide a favorable risk to benefit relationship. How can these questions be answered? In 2010, the FDA in collaboration with the Drug Information Agency and the Pulmonary Vascular Research Institute sponsored a “Debate on Clinical Trials for Pulmonary Arterial Hypertension.” It was unique in that there were presentations from members of the pharmaceutical industry, officials of the FDA, and members of academia. The last 2 world PH symposia (2003 and 2008) also included industry and regulatory agency participation. Meetings such as these will foster the collaboration needed to improve drug development for PAH and are critical to PAH drug development.

Biomarkers, Morphologic Parameters, Quality of Life Assessments

Whether the biomarkers are NT-proBNP, BNP, serum uric acid, troponin, plasma D-dimer levels, plasma endothelin-1 levels, urinary cGMP levels, norepinephrine, or genetic markers, investigators should consider including such assessments as exploratory supportive endpoints for efficacy and/or to elucidate mechanism(s) of disease. As PAH is a hemodynamic disease; ie, a disease of increased pulmonary vascular resistance (PVR) with subsequent development of PAH and right heart dysfunction, hemodynamic assessment is appropriate. In addition to PVR, right heart function is prognostic and cardiac index (CI) and mean right atrial pressure (mRAP) are important parameters. Imaging of the right ventricle is also valuable whether by echocardiography, cardiac MRI, radionuclide, CT, or PET. Additionally, developing and validating quality of life tools specific for adults and children with PAH can be invaluable. And sometimes the simplest parameters, such as resting heart rate or systemic pulse pressure, can be informative of disease severity and may prove beneficial as efficacy endpoints. Sensitive and specific endpoints can be simple. Basically, the FDA wants to determine if the patient is “better,” “worse,” or “unchanged.” Trust and utilize observations; do not try to generalize treatment responses. Look carefully at outliers; this is where exceptional breakthroughs might be found.

Utilizing insights derived from registries may also provide clinically meaningful endpoints. Investigators must be inventive by using results from prior trials and from observational studies; ie, registries, to develop more sensitive and specific endpoints to assess the effects of earlier treatment. Investigators have the clinical experience and access to patients to study novel approaches to assess disease severity, PAH pathobiology, and the genetics of PAH. It has been more than a decade since observations suggested similarities between cancer and PAH; yet, cancer research has been more successful than PAH research in identifying patient subgroups for specific targets, such as EGFR mutations in non-small cell lung cancer. Cancer studies highlight the importance of reviewing distribution of effects as opposed to mean effect. More rapid advances in understanding and therapeutic discoveries in PAH could be accomplished by cross-fertilizing endeavors with those of other medical specialties. The first

genetic defect associated with an increased risk of PAH was discovered over a decade ago; since that time, very little has been achieved to tailor therapies to genetic subgroups of patients. This is unacceptable.

Safety Assessments (size of safety database, duration of safety follow-up, patient subgroups of interest—including pediatrics)

Long-term observational follow-up in extension trials for all possible patients is critical. Specific pediatric concerns include effects on growth and development and sexual maturation; but again, risk-benefit considerations are crucial and DSMBs must understand the natural history of the disease when weighing “acceptable” risks, both short term and long term. The importance of such risks may be different for adults than for children. How aggressively children and adults are treated may differ. Collaboration between pediatric and adult investigators can also be useful in assessing safety signals.

Financial Relationships Between Physicians/Investigators and Industry

Participants in clinical trials accept risks primarily to advance scientific knowledge. Nonetheless, concern exists that financial conflicts of interest of investigators could compromise the well being of research subjects. Furthermore, conflicts of interest could lead to bias in the conduct of clinical trials and, thus, may undermine trust in results. Society traditionally has placed great trust in physicians and researchers, granting them considerable leeway to regulate themselves. However, there is increasing concern that extensive conflicts of interest in medicine may compromise clinical research. Responsible and reasonable conflict of interest policies and procedures should reduce the risk of bias and the loss of trust while avoiding undue burdens or harms and without damaging constructive collaborations with industry. Decisions about biomedical research, medical education, and patient care directly affect public health. The public must trust that physicians' decisions are not inappropriately influenced by their financial relationships with industry. Researchers should not conduct human research if they have a financial interest in the outcome of the research: for example, if they hold a patent on an intervention being tested. However, to prevent industry from supporting the preclinical research that provides the rationale for pursuing further drug development, or from supporting the clinical trials that determine if a new drug is safe and effective, or from supporting academia for collaborative efforts to optimize drug development, would only result in slowing the ability to develop new therapeutic options. It will not advance the goals of medical research to say that physicians should take nothing from industry. It is important to balance management of potential conflicts of interest against the possibility that overly restrictive policies (for example, prohibitions on physicians' use of drug samples for needy patients or the availability of industry funding for continuing medical education) could have negative consequences on patient care. Determining a consensus within the expert community to guide decisions about commencing or designing randomized clinical trials is critical. The well-known fallibility of expert opinion in support of the therapeutic

value of treatments without evidence from well-designed randomized clinical trials is reflected in notable examples of widely used treatments that were subsequently proven ineffective or harmful; for example, hormone-replacement therapy was shown to be ineffective in promoting cardiovascular health and to be associated with multiple serious adverse outcomes. Patients can benefit from physician-industry connections that move medical discoveries from research to clinical care. It is necessary to be cognizant of the concerns, act responsibly, and be appropriately transparent.

CONCLUSION

Vasodilator therapies have had an incredible effect on the lives of patients with PAH and have also been very successful for industry. But a new paradigm is now needed—it must dramatically slow the disease, stop it, or even reverse it. How can these goals be achieved? The PH community needs to collaborate more than ever. Relevant endpoints that are sensitive and specific must be defined to perform efficient, feasible, and adequately powered clinical trials. These endpoints will, by necessity, be discriminatory on a background of standard therapy (including currently approved vasodilator agents). Endpoints besides exercise must be defined, such as those that reflect disease modification. How can new targets be determined? Industry needs sound guidance from the investigator community. There must be a consensus on what the key targets are and where industry should focus efforts. Novel trial designs, such as using a Bayesian design, should be considered. Oncology has developed treatments that bring more benefit to fewer patients by targeting specific phenotypes, but in PAH, the “one-size-fits-all” approach perpetuates. The heterogeneity of PAH would seem to lend itself to a more personalized medicine approach. But how does this happen? Working together is the first step. Ultimately, the goals should be the same for clinical investigators, regulatory agencies, and industry; ie, to improve health care in the most efficient and safest manner possible. Clinical investigators, basic scientists, industry, and regulatory agencies each have specific areas of expertise that may overlap but are also sufficiently separate; expertise must be shared with one another to advance clinical drug development for PAH. Because PAH is a “rare disease” and pediatric PAH is a “rare disease within a rare disease,” there are more challenges to overcome in achieving goals than faced in other disorders. Achieving these mutual goals to improve quality of life and outcome for PAH patients of all ages is essential. Patients and their families have clearly demonstrated willingness to help; thus, they deserve that all respective strengths are used in a fully collaborative manner. Performance must be redefined not by how much is done but by how patients do. The investigator community, industry, and regulatory agencies must work together to cure PAH.

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