EDITOR'S MEMO

The Year of Firsts in Pulmonary Arterial Hypertension Treatments

The process of drug development can be a long and arduous road. To go from a "promising compound" to a marketable therapy can take anywhere from 8 to 15 years with resources ranging from $500 million to $2 billion.[1,2] The steps required include successful preclinical phase trials with an investigational new drug (IND) application to FDA followed by clinical phases 1, 2, and 3 that meet efficacy and safety criteria followed by the manufacturer's filing for a new drug application (NDA). Any of these steps can be terminated for myriad reasons, which is why only one drug for up to 10,000 compounds that enter the preclinical phase reaches the marketable stage.[3,4]

Therefore, it is an incredible accomplishment that 10 treatments have been approved for PAH in the past 18 years. The degree of innovation, dedication, and commitment from researchers, physicians, industry partners, regulators, and of course patients in working toward the common goal of curing pulmonary hypertension is evident in the remarkable achievement in having moved from a uniformly fatal orphan disease to a treatable condition with a wide array of treatment options. Indeed, 2013 topped the ranks in the list of incredible feats in that not only did we see 3 new therapies approved, but it was also the year of several "firsts": first drug to be approved with the pivotal clinical trial using a morbidity and mortality endpoint with macitanten; first therapy to utilize the soluble guanylate cyclase (sGC) stimulator pathway with riociguat; first oral prostanoid treatment with oral treprostinil; and first treatment to be approved for a condition outside of Group 1 PH with riociguat in chronic thromboembolic pulmonary hypertension (CTEPH).

It is my sincere pleasure to present this issue which focuses on the new treatments in pulmonary hypertension. I really appreciate all the efforts of our Guest Editor, Dr. Lynn Brown, for inviting a distinguished group of experts to share with us not only the details of the pivotal clinical trials but also the subtleties among different regimens, as well as including an article that discusses the financial aspect of prescribing new therapies. Also, I am pleased to announce the debut of PH Grand Rounds in *Advances,* with sincere thanks to Dr. Deborah Levine for all her efforts in launching this terrific feature.

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References

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GUEST EDITOR'S MEMO

As a former chemist, I spent years making a series of drugs that I hoped would be effective in treating breast cancer, only to learn when they were tested in cultured cells that they did not have a substantial effect. The disappointment was palpable; yet continuing with more advanced testing should be limited to those drugs that hold the most promise by demonstrating early, successful results in the setting of rigorous testing. It is estimated that up to 12 years or more can be spent performing preclinical and clinical testing to bring an effective drug from the laboratory to patients. It sometimes seems impossible that this extensive process is ever successfully completed with positive results. In the special situation of a rare disease such as pulmonary hypertension (PH), it also requires that there be a high level of commitment to treating an orphan disease for the development process to proceed in the first place. In the last year, the PH community has seen the culmination of a great deal of effort as 3 new treatments for PH became available to patients. In this issue of *Advances*, we are delighted to discuss these new options in PH care.

Drs Caccamo and Lahm introduce us to 3 new agents: riociguat, macitentan, and oral treprostinil. In a competitive market, many "me too" medications are developed where a simple change is made to a molecular structure and a "new" drug is created. Riociguat excitingly has both a novel design and a novel mechanism of action. It provides a therapeutic option for patients with pulmonary arterial hypertension (PAH) but the soluble guanylate cyclase stimulator has also gained approval for treatment of patients with chronic thromboembolic pulmonary hypertension (CTEPH), which to date has lacked an approved pharmacologic treatment after appropriate consideration/performance of a pulmonary thromboendarterectomy. Also finding itself on the forefront of PAH treatment is the endothelin-receptor antagonist, macitentan. The clinical trial of the medication produced exciting results, but macitentan will likely remain most notable for performing well in a study design driven by events and not changes in 6 minute walk distances. Finally, oral treprostinil with its unique extended release osmotic tablet will provide an option for prostanoid therapy that is not dependent on parenteral administration. Overall, these 3 new medications add to the field because of unique characteristics and they will undoubtedly each find a position on the PH treatment algorithm.

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I have been tasked with ensuring that the committee provides a standardized approach to evaluating applications upon receipt, and adheres to the process for conducting site visits and voting provided by the PHCC Oversight Committee and the PHCC Implementation Task Force. I am extremely proud of the team that has been assembled and the intense level of behind-the-scenes work already completed. The PHCC Review Committee is well prepared and eager for the official launch of the PHCC program.

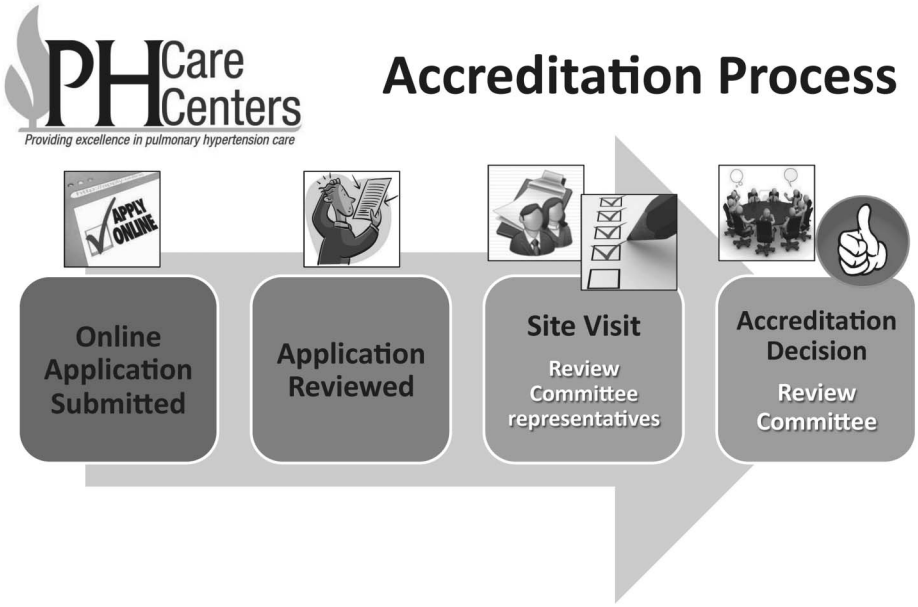

Figure 1. Diagram of accreditation process.

GUEST EDITOR'S MEMO

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Pulmonary hypertension is a complicated disease with multi-pathway dysfunction such that the successful introduction of several medications in a relatively short period of time does not mean that research and development can be totally eclipsed by the enthusiasm behind the new agents. Additional novel molecules and treatment pathways are under study and Dr Preston provides a glimpse in this issue of *Advances* as to where the field of PH research is headed in the future.

Finally, as the PH community is welcoming new medications, the complexity that is caused by the availability of these same agents cannot be overlooked. How is a particular medication selected? Who should be involved in the decision making? Is the drug worth the cost? How do we monitor response to therapy? These are all questions that are discussed by the roundtable participants, Dr Studer in the "Ask the Expert" column, and by Drs Raina and Benza in their article.

Although my first foray into drug development was less than successful, it taught me the importance of tenacity. Study the pathway, find the molecule, make the medication, treat the patient, and cure the disease.

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