Case Study

Creating a New Dosage Form from an Approved Drug for a New Rare Disease Indication

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Background

Armed with a promising idea and an urgency to help patients with Hereditary Hemorrhagic Telangiectasia, Cure HHT contacted Pii for assistance in developing a formulation and filing an Investigational New Drug (IND) application with FDA.

Cure HHT is a foundation representing a group of patients, and their families, suffering from a genetic blood vessel disorder that causes bleeding in multiple organs of the body. This disease affects males and females of all ages and from all ethnic and racial backgrounds. The genetic mutation causes blood vessels to form abnormally and lack normal capillaries between arteries and veins. Patients with this disorder experience arterial blood under high pressure flowing directly into low-pressure veins without first having to move through small capillaries. The area where the artery connects directly to the vein tends to be a fragile site that can rupture and bleed, and tissue in the areas receive a decreased amount of oxygen as well. Symptoms can appear as re-occurring nosebleeds or as serious strokes and heart attacks. There is currently no treatment for this disease, and therapies focus on treating the symptoms only.

A pharmaceutical company, developing a molecule for another indication, discovered side effects during clinical trials that might mitigate or even cure the rare hereditary blood disorder. The initial clinical work began for the rare blood disorder, but due to a variety of unexpected circumstances, the program was never completed. However, a clinician that had worked on the original project began working with Cure HHT to reestablish the project.

Led by a passionate clinician who had experience with the molecule, Cure HHT believed they had the ability to pursue a cure. The project was re-started, an Investigational New Drug (IND) application was filed, but the FDA rejected it, placing the project on a clinical hold, because it lacked adequate testing and controls. The foundation was disappointed by the set-back but remained stalwart in their intent to find a solution.

Cure HHT possessed a wealth of information on the rare disease and direct clinical experience yet lacked a feasible formulation with adequate testing and controls. Pii was confident they could help.

The Challenge

The molecule, a BCS Class II, had originally been developed as 200mg and 400mg tablet formulations for a different indication. The client believed that a 25mg dose was needed for the rare disease, but they required a fully developed, tested, and properly documented formulation and regulatory support to properly file an IND application with the FDA. The most significant challenge was they needed the work done in an extremely short timeframe. The Pii team felt their development, analytical and CMC experience and ability to work collaboratively for rapid solutions could overcome the challenges.

Confidence, Experience and Collaboration

The formulation, analytical and regulatory teams at Pii worked with a unity of effort and filed the IND fourteen days after starting the project. Here are the eight key factors that led to success.

- Early gap analysis: first step, the Pii team conducted a gap analysis of the client's initial work so they could focus appropriate resources on the biggest challenges and solve problems before they occur.
- Keeping it simple: the team sought a stable, simple formulation solution that would be easily understood and communicated to FDA for approval: a 25mg dose in a re-sized hard gelatin capsule comprised of two ingredients in addition to the API.
- Using materials on hand: to eliminate the time and costs associated with finding and contracting partners for materials, Pii focused on using what they had on hand, microcrystalline cellulose, magnesium stearate and gelatin capsules, backed by a rigorous quality risk analysis.
- CMC expertise: the team relied on their deep Chemistry and Manufacturing Controls (CMC) experience to select the right excipients and establish the testing and controls that were inadequate in the first IND application.
- PPQ expertise: the team's extensive experience in process performance qualification (PPQ) created a solution after only one blend uniformity test, saving significant time.
- Parallel supporting work: formulation development work, analytical testing, and regulatory filing preparation was done simultaneously, again saving time.

- Collaboration: the process was rigorous and systematic involving a team of formulation developers, analytical specialists, and regulatory experts in which collaborative communications is a well-established routine.

- Success as the end-state: due diligence was incorporated into each step of the process so that upon having initial clinical trial success, Pii could rapidly scale-up manufacturing to support further clinical studies.

Results

IND application was filed in 14 days and FDA reviewed it in 45 days allowing clinical studies to proceed.

Pii manufactured a GMP batch of the formulation in a capsulated 25mg dose to supply clinical pharmacokinetics (PK) studies. Based on the results of the initial clinical trials, Pii stands ready to quickly manufacture larger batches for further studies for efficacy.

At Pharmaceutics International, Inc. (Pii), our motto is “challenges frame opportunities.” We are a contract development and manufacturing organization (CDMO) that has “walked in your shoes” and has a passion for problem-solving. Emphasizing collaboration, our experts complete projects on time with the highest quality standards, all from our Hunt Valley, Maryland campus.

Pii’s campus includes four cGMP and FDA certified facilities, 70 manufacturing suites with all the necessary analytical testing capabilities on site, and four integrated aseptic filling suites delivering quality, safety, and efficiency. Experienced with small and large molecule compounds, we have special expertise in developing and manufacturing complex parenteral drugs, extended-release formulations, and non-aqueous injectable drug products. We can also overcome stability challenges with precision lyophilization cycle development and production.

Pii’s Pharmaceuticals Know How™ can quickly and safely advance your drug from discovery through clinical testing to commercialization. Find out more at https://www.pharm-int.com/

Since its establishment in 1991, Cure HHT has consistently been at the center of the national and global effort to advocate for patients and families, raise awareness of HHT, guide and fund critical research, create lasting collaborations and encourage scientists to work on new treatments. Cure HHT has the perseverance and experience to integrate and drive vital progress across the patient, medical and scientific communities. https://curehht.org/

Cure HHT Goals: Find, Treat, Cure

Find. Dramatically reduce the number of undiagnosed cases of HHT through focused awareness to the public and medical community. Cure HHT provides a supportive environment for those who are diagnosed and provide opportunities for people to connect to others who share similar experiences and concerns.

Treat. Significantly expand the availability and accessibility to consistent, quality care. We seek to educate physicians and healthcare professionals to recognize HHT and refer for diagnosis and screening. Through creation of a comprehensive The HHT Center of Excellence model featuring multi-discipline specialists working together to treat patients and families has been emulated throughout the world. We strive to accelerate advances in clinical care.

Cure. Through our collaborations with physicians and scientists, we look to set the global agenda for finding more effective HHT treatments. Cure HHT invests in breakthrough research and supports the best science worldwide to uncover the mechanisms underlying HHT, improve treatments and ultimately, to find a cure. Dedicated and unrelenting, Cure HHT is constantly working to ensure HHT patients and families can live long and productive lives full of joy and spontaneity.

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