Making the COVID-19 Oral Treatment: How 2,000+ Pfizer Team Members Made It Happen

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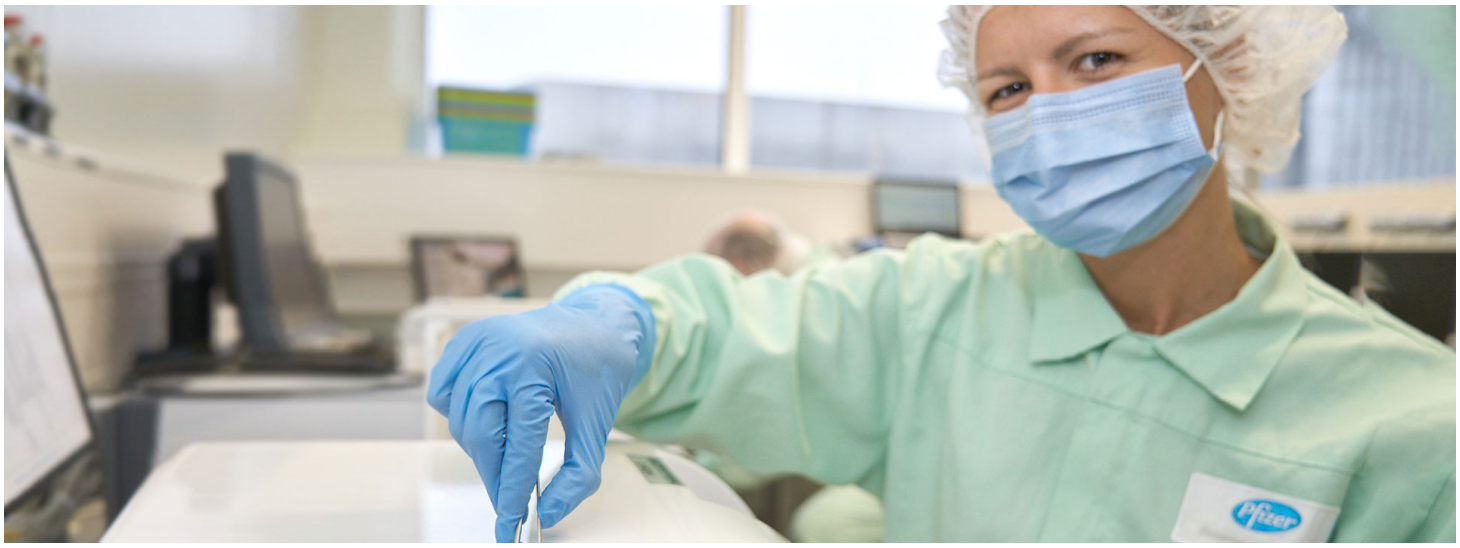

As the potential threat of COVID-19 became clear by early 2020, teams across Pfizer sprang into action. Together, they worked to better understand the novel virus. Hospitals were filling, and no one was sure how best to treat the people who were sick. While some infected people seemed to recover quickly, others were dying.

“We had started to think about how best we might be able to help address the pandemic,” recalls Annaliesa Anderson, who is Senior Vice President and Chief Scientific Officer Bacterial Vaccines and Hospital at Pfizer. “And the first, obviously was the vaccine. But the second was to be able to stop people from getting so sick that they had to go to a hospital.”

At that time, Pfizer had a relatively small team dedicated to supporting the development of antibacterial therapeutics within the company’s Hospital portfolio.1 But several long-

time colleagues had worked on prior in-house discovery and development programs focused on viruses such as HIV, Hepatitis C, Rhinovirus, and SARS-CoV-1—a virus that, in 2003, was spreading rapidly in Asia.2

One of those scientists is Jennifer Hammond, Vice President, Global Product Development at Pfizer. Hammond recalled pre-clinical work conducted within the Antiviral Discovery Group in 2003 on a SARS-CoV-1 main protease inhibitor, a small molecule which works by inhibiting viruses from making copies of themselves.2

While the SARS outbreak of 2003 resolved before the SARS-CoV-1 main protease inhibitor could be tested in humans,2 the similarity between the viruses causing both diseases suggested it could be a good place to start new research and development efforts. And data generated within Pfizer, as well as the broader scientific community, quickly emerged that confirmed the attractiveness of the main protease as a potential antiviral target.2

In parallel, other members from the team, together with colleagues from across Pfizer, were following the emerging data on the virus and exploring ideas to design a novel therapeutic agent. Within a week, this work came together, and a team was formed to explore the legacy compound, while another was tasked to design a novel, oral therapeutic agent.2

Deterring the COVID-19 virus from replicating

Over the next 24 months, more than 2,000 people came together from across the entire Pfizer organization to share their strengths and expertise to work toward the development of a therapeutic. The collective included experts in virology, oral small molecule design, synthesis, pharmacology, formulation, scale-up, clinical development, and more.3 All of this work began at a frightening time, when people around the world who were able to transition their work, schooling, and personal lives to be largely at home.

“In order to be respectful of colleagues' new obligations at home, we actually asked for volunteers who could come on site and help work on this program synthesizing novel molecules,” says Charlotte Allerton, Pfizer’s Head of Medicine Design. “We had more volunteers than we actually needed for the program. And they were exceptional. Around the clock, they worked different shifts, juggling some of these challenges at home as well as really moving the program forward.”

By March, Pfizer scientists had confirmed that the protease inhibitors from the original SARS program also blocked the SARS-CoV-2 main protease, meaning they had the potential to be used for treating COVID-19.3 However, because these inhibitors were only suited to be given intravenously, they were likely only going to be useful for treating patients who were ill enough to be in the hospital. To potentially benefit the most people and prevent them from going to the hospital, the team wanted to develop a novel oral treatment.3 “We decided that we needed to design and develop a novel medicine that could be taken as a pill soon after infection to hopefully help prevent progression to severe disease,” says Anderson.

Developing a COVID-19 oral treatment

Introducing a new drug (from discovery to approval) in the U.S. takes an average of 12 years.4 As COVID-19 surged around the world, the clock was ticking. The discovery team moved urgently, using structure-based design and state-of-the-art computational and synthetic technologies to identify a highly promising molecule to move into the clinic. With encouraging preclinical data in hand, they started to scale up activities and toxicology studies to enable the start of a Phase 1 study, just 12 months after the program had launched.1

In order to work quickly while still making safety the top priority, the team conducted some of the processes in parallel instead of taking a traditional stepwise approach, where one set of experiments is completed before the next one begins.1 What that meant to Pfizer was making an enormous financial investment in this treatment—including designing clinical trials in parallel, as well as making the medicine and packaging so it was ready to be sent immediately if the clinical trials were successful—while still not knowing whether it would be authorized or approved.1

Arthur Bergman, who is Group Head of Clinical Pharmacology in Pfizer’s Anti-Infectives Early Clinical Development, says that, in order to expedite the process, they designed a clinical study protocol that could be flexible and amended as needed along the way. That was valuable when it came to figuring out dosage, for example. He says that going into the Phase 1 part of the trial—when they’re testing for safety, dosage, and potential side effects in healthy volunteers—the team wanted to safely maximize the concentration of the medicine in the body to be confident of achieving efficacy and minimizing resistance mutations. So they evaluated the molecule alone and co-administered with a pharmacokinetic booster, which helps the compound stay in the body longer, allowing for higher concentrations.5

Bergman says the U.S. Food and Drug Administration (FDA) and other regulatory agencies were critical in the effort to keep up this fast pace. Tasks that might traditionally take regulators a month—like protocol review—were prioritized by the agencies and completed in a matter of days. And in many cases, the FDA would supply early feedback to help move things along quickly.2

In order to save time, another Pfizer team used technology to model and simulate clinical trial outcomes, in place of a traditional Phase 2 trial.2 They did that using something called a “viral kinetics model,” which simulates virus replication in humans and also simulates the way the drug would inhibit that replication in people with COVID-19.2 That modeling data, along with the data from the trial that used healthy volunteers, informed the dose that would be focused on in the subsequent Phase 2/3 studies.2

With safety always a paramount priority, Pfizer enrolled an initial cohort of just 60 COVID-19-positive patients, who were at increased risk of progressing to severe disease, in the first of these studies (called a pivotal trial). All had experienced symptoms for no more than five days.2 Shortly thereafter, an external safety committee consisting of experts in critical care, infectious disease, cardiology, and other therapeutic areas, reviewed the data from that cohort for any potential health concerns.2 When that panel reported back no concerns, a flurry of activities began to launch the trial on a broader scale.

All told, 2,246 people participated in the Phase 2/3 EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) trial; 41% came from the US and 59% came from around the world, with representation in South Africa, Western Europe, Eastern Europe, Thailand, Malaysia, Japan, Argentina, Mexico, and beyond.6 The results were striking: in non-hospitalized adults with COVID-19 and at least one risk factor for progression to severe disease, the oral therapy was found to reduce the risk of hospitalization or death by 89% compared to a placebo when treated within three days of symptom onset.6

Bergman gets emotional when he reflects on the moment he learned the results. “It still brings a tear to my eye today, thinking about how all the hard work from this team came together to create something with such potential to impact patients' lives,” he says. “You know, that’s something that I'll never forget.”

Continuing to evolve the research

In December of 2021, the FDA granted emergency use authorization for the treatment of COVID-19 patients at high risk of progressing to severe disease—the first oral treatment

to be authorized to fight COVID-19. “It was an exhilarating experience to be part of something that has such important potential for mankind,” says Anderson.

But everyone who contributed to the endeavor knows the work isn’t done yet. COVID-19 is still here, after all. Rhonda Cardin, Ph.D., who is Executive Director, Anti-Infectives at Pfizer, says scientists are continuing to watch the virus as it evolves. “At our Pearl River, NY site, for example, we are monitoring the development of emerging variants in the GISAID (Global Initiative on Sharing Avian Influenza Data) database, which tracks virus sequences from around the world,” she says. “And we’re not only tracking the variants; we’re actively testing them against nirmatrelvir to understand whether our oral treatment will be able to treat the emerging variants.”

For now, they’re cautiously optimistic. Hammond says that even as the virus mutates, research is finding that the protease inhibitor still seems to interfere with the ability of the virus to replicate, in part due to its ability to bind tightly to its target.2 But, as always, they’ll be keeping a careful eye out for any changes and responding to them accordingly. “We are definitely remaining vigilant because viruses surprise us all the time,” she says.

Pfizer's oral treatment for COVID-19 has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. The emergency use of Pfizer's oral treatment for COVID-19 is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner. See EUA Fact Sheet: www.COVID19oralRx.com

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