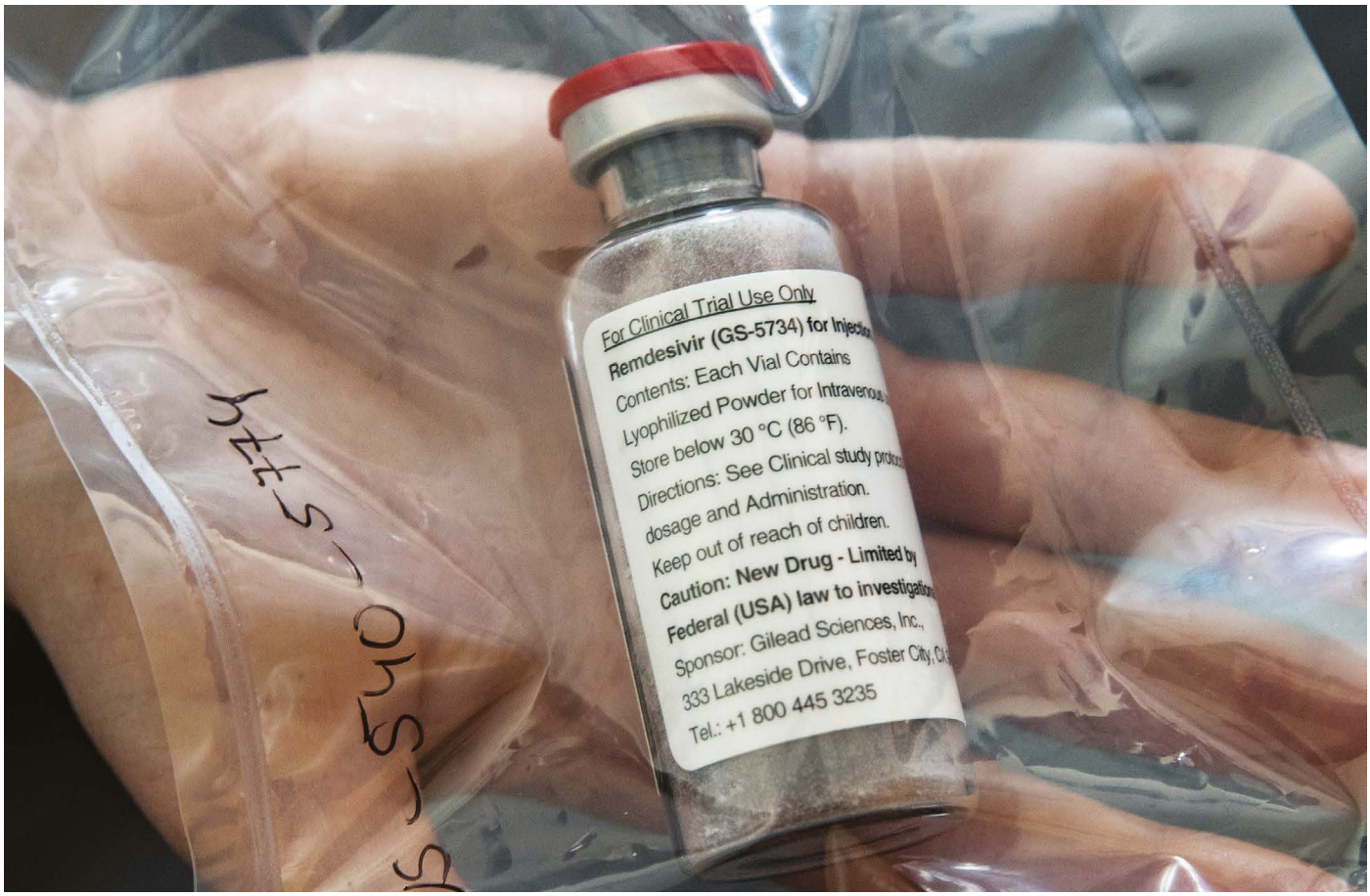
News in focus



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Production of remdesivir, an antiviral drug approved to treat COVID-19, is ramping up.

DOZENS OF CORONAVIRUS DRUGS ARE IN DEVELOPMENT — WHAT HAPPENS NEXT?

Drug-makers face supply-chain weaknesses and sourcing issues as they ramp up complex production processes to meet global demand.

By Heidi Ledford

The world was waiting for any sign of hope in countering the COVID-19 pandemic when researchers released the first encouraging data from a large clinical trial of the antiviral drug remdesivir last month. The drug, they said, reduced the time to recovery from COVID-19 by a few days — not enough to be branded a 'cure', but enough, it's hoped, to relieve some pressure on overwhelmed health systems.

The discovery of remdesivir's potential focused attention on the next problem facing the development of COVID-19 therapeutics: ramping up complex manufacturing processes to address a global pandemic. It is likely to be one of the biggest drug-making challenges the world has ever faced. Some of the therapies being tested against COVID-19 are new and difficult to produce. Others — even if they are relatively simple compounds that have been in use for decades — face complications such as supply-chain weaknesses as drug-makers try to scale up production.

"A major rate-limiting step is going to be manufacturing," says Ezekiel Emanuel, a bioethicist at the University of Pennsylvania in Philadelphia. "Getting up to hundreds of millions of doses is hard."

Spectrum of drugs

Researchers are working furiously to test a wide variety of potential COVID-19 treatments. Those therapies run the gamut of complexity, from familiar generic medications, such as the malaria drug hydroxychloroquine, to experimental small molecules such as remdesivir, which was previously trialled against

the Ebola virus. Scientists are also exploring antibody treatments that tamp down the body's immune response when it becomes destructive, which happens in some people critically ill with the coronavirus. And if the history of infectious disease is any guide, it will take a combination of drugs — each with a distinct, even if relatively minor, impact on the disease — to tame the new coronavirus.

Each treatment will face different challenges when scaling up production, says Stephen Chick, who studies health-care management at the business school INSEAD in Fontainebleau, France. "If it's successful and the technology is then adopted, you need to be prepared to deliver," he says. "And if you're not, you're in trouble."

Remdesivir's maker, Gilead Sciences in Foster City, California, has been working for months to scale up production of the compound, even before the latest data release. After the US Food and Drug Administration authorized use of the drug for COVID-19 under emergency rules on 1 May, the company announced that it had reached out to drug manufacturers around the world to find ways of boosting production.

By then, Gilead had already been streamlining its manufacturing process — reducing the time needed to produce large batches of the drug from 9–12 months to 6–8 months — and searching for alternative sources for the rare chemicals needed to make it. The company has projected that it could make enough remdesivir to treat one million people by the end of the year, and potentially twice as many if it finds that lower doses of the drug are sufficient to reduce recovery time from COVID-19.

But it also warned that production of remdesivir relies on a complex chemical synthesis — with individual steps that can take weeks to perform — and could be derailed by shortages of key ingredients. Remdesivir's structure is similar to the nucleotide building blocks the virus uses to copy its RNA genome. By imitating those building blocks, remdesivir blocks the enzyme that the coronavirus uses to replicate itself.

Bargain search

Gilead faces a particular challenge because it was not making large amounts of the drug when the pandemic started. But even for compounds that are already produced in bulk — such as hydroxychloroquine and its chemical cousin chloroquine — scaling up presents a problem, says David Simchi-Levi, an operations researcher at the Massachusetts Institute of Technology in Cambridge.

Over the past two decades, manufacturers in many industries have been shifting to a 'lean' manufacturing model that reduces the amount of raw materials and finished product they keep in stock. "This was successful in terms of reducing costs," Simchi-Levi says. "But it increased exposure to risk."

In addition, companies have been seeking low-cost suppliers of raw materials in countries including China and India. When a crisis such as a pandemic strikes, those countries might clamp down on exports of pharmaceutical ingredients to ensure availability to their own people.

Simchi-Levi and his colleagues' research in the automotive industry showed that the riskiest links in the supply chain were providers of crucial components that cost as little as 10 cents. The same could be true of other industries, he says, including pharmaceuticals, where there are already concerns about having enough glass vials to produce and distribute a vaccine, once one becomes available.

"If supply of these components is disrupted you have to stop the production line," Simchi-Levi says. "And many companies don't have a good enough understanding of their own supply chains to know who are the suppliers of their suppliers."

Three stages

For small-molecule drugs such as remdesivir or hydroxychloroquine, production broadly involves three stages. The first yields the active ingredient in the drug; the second modifies the drug to make it stable and readily absorbed by the body; and the third packages the drugs, for example into tablets or vials. This takes place under the watchful eye of regulators, who periodically inspect facilities to ensure that quality and safety standards are maintained.

Relatively few sites are approved by regulators to make drugs, meaning that when one site fails an inspection — or when more facilities are needed to crank out higher volumes of a particular drug — it can be difficult to find a replacement. "That can be pretty significant," says Simchi-Levi. "There's high dependency on only a few sites for manufacturing."

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Production can be even more troublesome for more complex therapies, such as proteins or antibodies. Researchers are hopeful that antibodies that block certain immune-system processes will help against COVID-19, by restraining the out-of-control immune responses. Genentech in South San Francisco, California, makes one such antibody, called tocilizumab (Actemra), which blocks the activity of an immune-system regulator called IL-6. Tocilizumab is already approved for use against some forms of arthritis, but if it is found to be useful against COVID-19, production would need to be vastly scaled up.

Antibody treatments such as tocilizumab are made in cells grown in culture, most often in Chinese hamster ovary cells. Antibodies are increasingly used to treat a range of diseases, from various forms of cancer to arthritis, and research has boosted production yields. About ten years ago, a manufacturer might expect to get less than 1 gram of antibody per litre of cell culture; now they typically extract 5 grams or more from the same volume, says Charles Christy, head of commercial solutions at the chemicals firm Lonza in Visp, Switzerland.

A 2,000-litre culture might produce enough antibody to fuel an early clinical trial, but drug-makers can scale up to as much as 20,000 litres of culture grown in giant steel vats to handle larger trials and commercialization.

Because antibody drugs are now such a large part of the pharmaceutical industry, there tend to be multiple suppliers for key reagents, Christy says. But you can always be blindsided, he says. "We and others are looking very hard at our supply chain."

Tocilizumab has not yet been shown to help people with COVID-19, but Genentech says that it has already increased supply by 50% and is working to raise capacity further.

Massive demand

But even when companies work proactively to build supply, demand will almost certainly outstrip initial supplies of any compound found to be effective against COVID-19. That raises the spectre of determining who will be first to receive the treatments. Complaints have already surfaced about the allotment of remdesivir. Gilead has donated its stocks of the drug to treat COVID-19, with about 40% — enough to treat 78,000 people — going to the United States. The US government has been distributing those vials to individual states, but some hospitals have complained about lack of access.

Gilead also announced this week that it had entered into agreements with five makers of generic drugs. Those manufacturers can produce remdesivir for distribution in 127 countries that have limited access to health care, without paying royalties to Gilead. The agreement will remain in place until the global health emergency ends, or another treatment or a vaccine is found for COVID-19.

Concerns about access to pandemic medicines have arisen before, for example during the H1N1 influenza outbreak in 2009, says Emanuel, when countries raced to stockpile the influenza drug Tamiflu. "It was a free-for-all," he says. Those issues have never been fully addressed because the outbreak ended quickly. "People move on and no one stays around long enough to solve the problem," Emanuel says. "That will not happen here. We will be in this problem for a number of years."