The Washington Post
Democracy Dies in Darkness

Why grandparents can't find vaccines: Scarcity of niche biotech ingredients

Lipid nanoparticles for RNA vaccines were used in small quantities a year ago. Now Pfizer and Moderna can't get enough.

By **Christopher Rowland**

Feb. 18, 2021 at 3:59 p.m. CST

Acuitas Therapeutics, a tiny biotechnology firm in Vancouver, B.C., has just 30 employees and leases its labs from the University of British Columbia. The company doesn't even have a sign on its building. Until last year, it outsourced production of only small volumes of lipid nanoparticles, fat droplets used to deliver RNA into cells, for research and a single approved treatment for a rare disease.

But now, one of Acuitas's discoveries has become a precious commodity. A proprietary molecule called an ionizable cationic lipid is a crucial piece of the mRNA vaccine made by Pfizer and its German partner BioNTech, and it is in urgent demand for production of billions of vaccine doses worldwide.

Scaling up production of formerly niche substances such as lipid nanoparticles for a global vaccine drive has been among the most complex challenges facing the Biden administration as it aims to ramp up the frustratingly slow provision of shots across the country, according to interviews with company officials and outside scientists and government reports.

On Jan. 21, the new president's second day in office, the Biden administration issued a report that cited shortages of lipid nanoparticles among "urgent gaps" in the vaccine supply chain.

"It's on a scale that hasn't been done before," said Pieter Cullis, the Canadian scientist and Acuitas chairman who is considered a godfather of lipid nanoparticle technology.

Although companies are steadily increasing the flow of vaccine doses to states, deliveries have seriously lagged behind earlier government projections. The production problems — which the companies have declined to discuss in any detail — underlie the difficulty of the quest for vaccine shots by elderly U.S. residents in states that have prioritized this population for immunization.

The federal government has committed about $16 billion to vaccine development and manufacturing since last year. Operation Warp Speed, the government's vaccine effort launched under President Donald Trump, vowed last spring that 300 million doses of vaccine would be ready by the beginning of 2021.

That goal was downgraded by early December to a promise of 40 million doses by Jan. 1, enough for 20 million people to be immunized under the two-shot regimen. But by Dec. 30, only 12.4 million doses had been shipped, according to a recent report by the U.S. Government Accountability Office.

As of Thursday, according to data disclosed by the Centers for Disease Control and Prevention, Pfizer and Moderna had delivered 72.5 million doses combined. That represents only 36 percent of the 200 million doses that Moderna and Pfizer have pledged to deliver by March 31, just six weeks away.

Pfizer said in response to questions that it has made unspecified changes to its facilities and manufacturing that will allow it to double vaccine output. It said it will produce 2 billion doses by the end of the year. It makes its vaccine in Kalamazoo, Mich., and Belgium.

In late December, as part of a deal to obtain additional doses, the Trump administration agreed to use the Defense Production Act to help Pfizer gain access to more lipids, people familiar with the discussions have told The Washington Post.

And the federal government continues to use its authority under the rarely used Korean War-era law to direct domestic suppliers of lipids to prioritize Pfizer's orders, according to a senior administration official who spoke on the condition of anonymity to discuss sensitive policy matters.

"The scale-up of the raw material supply chain took longer than expected," Pfizer spokeswoman Amy Rose said in an emailed statement.

"Scaling up a vaccine at this pace is unprecedented, and we have made significant progress as we have ramped up the first-ever commercial scale production of an mRNA vaccine," she said, referring to messenger RNA technology.

Moderna did not respond to a request for comment. The company, which makes the only other mRNA vaccine authorized by the U.S. Food and Drug Administration, invented its own ionizable lipid and also has been racing to build production capacity.

Many other bottlenecks have plagued the manufacturing of vaccines for the novel coronavirus, which causes covid-19. Companies have had to build equipment from scratch, including machines that shoot two streams of solution — one containing mRNA and one containing lipids — into a high-speed collision to fuse the nanoparticles and encapsulate the genetic payload. The Biden administration said this month that it was using the DPA to help Pfizer procure more specialized industrial machines for the next step, filtering ethanol out of the lipid mixture.

The vaccine makers are also experiencing a lack of machine capacity to fill vaccine vials. The Pfizer-BioNTech team has struck agreements with two other drug giants, Sanofi and Novartis, in Europe for "fill-finish" services, the process of putting vaccine doses into vials and preparing them for shipment.

The idea of using lipid nanoparticles to cocoon a genetic payload for release into human cells had been pursued by researchers at the University of British Columbia since the mid-1990s.

Its first approved use was in 2018 for a drug called Onpattro, which is made by the biotech firm Alnylam. The drug is infused into people with transthyretin-mediated amyloidosis, a rare hereditary disease that affects 50,000 people worldwide.

For the coronavirus vaccine, the lipid nanoparticle releases messenger RNA into a human cell, instructing the cell to make a replica of the coronavirus spike protein. The spike protein then trains the immune system to fight the real virus.

Of the four lipids that make up the protective droplet, the ionizable cationic lipid is the one needed in the highest volume and is subject to restrictive patents held by Acuitas and a few other companies. Its electrical charge changes when it enters a cell, causing the mRNA payload to break free and deliver its instructions.

After working on lipid-based drug delivery systems for so many years, Cullis said in an interview that he has been awed by their sudden success in vaccines that will save countless people from the ravages of the coronavirus pandemic.

“It was a bit of a fringe field as things were starting off,” said Cullis, who is one of the founders of Acuitas. “To see it come into the mainstream like this is completely mind-boggling.”

Problems with the manufacture and delivery of doses were inevitable after the vaccines were developed in record time, he added.

“Some of the hiccups are probably to be expected,” he said. “You can argue that the manufacturing efforts have been largely quite successful.”

Growing pains for the lipid nanoparticle technology have intensified as the government has increased orders for mRNA vaccines. Pfizer and Moderna have now committed to producing 300 million vaccine doses each for the United States by the end of July, in addition to hundreds of millions more for Europe and elsewhere.

The core problem, say executives and scientists, is the accelerated global demand for a technology that had barely reached commercialization as of early last year, a demand surge that has caught suppliers of raw materials unprepared. Explosive demand that began last summer has only intensified as other vaccines in the pipeline that use other methods have hit delays or faltered.

“The biggest difficulty is the lipids to make the lipid nanoparticles,” said Drew Weissman, who pioneered mRNA vaccines at the University of Pennsylvania and is seeing the fruit of his work being used to save millions of lives. He said it is difficult to know the extent of any shortfalls because companies typically do not make such details public.

Kinks in the supply chain could have been foreseen, Weissman said. In retrospect, the government also should have funded the suppliers of raw materials needed to make vaccines — just as it did by providing billions of dollars in advance contracts for the big drug companies that would make the vaccines.

“The pharmaceutical companies should have known that this was going to be a problem, and they should have started last year talking to the lipid companies, talking to the mRNA raw material companies, that they needed to scale up,” Weissman said.

Vaccine companies have released minimal information publicly about how they have used their money to support vaccine manufacturing. The raw materials supply chain also has been shrouded in secrecy relating to proprietary licensing deals and contract manufacturing arrangements.

Acuitas licenses its technology to others and farms out production of its lipids to contract manufacturers.

“The challenge obviously is they needed to ramp up from manufacturing hundreds of grams or kilograms to tons of lipids, so we have worked with them to support that process,” said Acuitas chief executive Thomas Madden, who also is a founder of the company. “There’s never going to be enough.”

Acuitas also is supplying its technology to CureVac, a German company that is developing an mRNA coronavirus vaccine.

The company producing the Acuitas lipids used in the Pfizer-BioNTech vaccine, Avanti Polar Lipids, of Alabaster, Ala., declined to comment. Avanti was bought last summer by a British company, Croda, for $185 million.

CordenPharma, which has plants in Europe and Boulder, Colo., and is supplying Moderna with lipids, also declined to comment. A CordenPharma executive in Switzerland told a trade publication this month that making ionizable cationic lipids requires 10 manufacturing steps and takes months.

“Put yourself in the shoes of one of these manufacturers. Most of them had a full set of orders for pharmaceuticals and other raw materials they were producing” before the pandemic hit, said Patrick Boyle, an executive at Ginkgo Bioworks, a genetics platform company in Boston. “To expand, they have to build new equipment or they move another paying customer aside, and that has been one of the challenges.”

Pfizer-BioNTech made agreements this month for more supply from two German companies, but that new capacity will not come online for months.

One of those German suppliers, Merck KGaA (which is not related to the American pharmaceutical manufacturer Merck & Co.), said in a Feb. 5 news release that it would "significantly accelerate the supply of urgently needed lipids," with delivery "toward the end of 2021." A second German company, Evonik, said last week it was ramping up lipid supply that would be available in the second half of this year.

"They have multiple dependencies on third parties for supply of the materials," said Andrey Zarur, chief executive of GreenLight Biosciences, a biotechnology company that is working on its own mRNA vaccine.

Executives in the industry also pointed to potential bottlenecks in the production of certain nucleotides and DNA plasmids (which provide the blueprint for the mRNA in vaccine), as well as synthetic capping agents that attach to the end of a string of mRNA. The synthetic capping molecules are produced under patent by a single company, TriLink, in San Diego.

TriLink's list price for capping agent is $197 for just 0.0012 grams, according to its website, although it says it offers bulk pricing. TriLink's parent company, Maravai, went public in November as the frenzy for its products grew. It raised $1.6 billion. TriLink, through the parent company, declined to comment. It said in a news release in August that it would expand capacity at its San Diego facilities to make more mRNA raw ingredients.

Increasing production of TriLink's RNA capping agent is not difficult, requiring only more space and equipment, said Anton McCaffrey, a co-inventor of the capping agent who recently left TriLink.

"I think this is surmountable, easily," he said. "From the perspective of making this chemical, you put resources behind it and it's not going to hold things up."

The success of the vaccines for the novel coronavirus is adding momentum to drug projects that will rely on lipid nanoparticles to deliver RNA to human cells.

Research is underway to use lipid nanoparticles for delivery mechanisms in a variety of vaccines and gene therapies, including in cancer immunotherapy. New production capacity for coronavirus vaccines ultimately will benefit those new therapies, scientists said.

“This is going to totally change the pharmaceutical industry for years to come,” said Michael Mitchell, a principal investigator who leads a University of Pennsylvania bioengineering lab working on cancer immunotherapy and vaccine projects.

Isaac Stanley-Becker contributed to this report.