Vaccine production on mathematical formula

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The coronavirus pandemic has made vaccine production a hot topic covered daily in the Danish media. How much can be produced and when can the coveted vials be delivered? The Danish vaccine producer Bavarian Nordic asks itself the same questions when they are to produce their vaccine against the highly contagious smallpox virus at the company's new vaccine factory in Kvistgård just outside Elsinore.

To answer these questions, Bavarian Nordic resorts to mathematical modeling to enable them to produce as many vaccine doses as possible, limit wastage, and inform customers as accurately as possible about the time of delivery. The mathematical model tool has been developed in collaboration with DTU Management and was taken into use at the end of 2020.

Vaccine against eradicated disease

The last registered outbreak of smallpox was in Somalia in 1977, and the same year Denmark stopped its smallpox vaccine program. Three years later, the World Health Organization (WHO) declared that the disease had been eradicated globally. So why does Bavarian Nordic continue to produce smallpox vaccine? This is due to the fear of bioterrorism, where smallpox virus is used as a biological weapon. Soldiers, nurses, and other frontline personnel therefore still receive the vaccine when operating in war and conflict zones where such terrorist attacks are a realistic threat. In addition, some countries are still building up stocks of smallpox vaccine as emergency preparedness.

Complex production planning

The production of smallpox vaccine is a complicated process. It all starts with the production of a raw product with a high concentration of the active substance. The active substance is Bavarian Nordic's own patented virus, which has been modified so that it cannot multiply in human cells.

The concentration of the active substance varies, depending on which production batch it originates from, one reason being that— like other drugs—it is degraded gradually. To arrive at the exact strength of the finished vaccine, the production planner must therefore choose the right mix of production batches from the warehouse and also add the correct

amount of diluting fluid. And this must be done in a way that ensures that as many vials as possible are produced. In addition, Bavarian Nordic must take into account the production capacity of the filling factory where the finished vaccine is made. These are just some of the parameters that the production planner must deal with.

"It used to be insanely time consuming to make a production plan. It was done manually, and you could almost tear a week out of the calendar to prepare the plan—it was heavy going," says Michael Væver Jørgensen, Supply Chain Planner at Bavarian Nordic.

When Bavarian Nordic had then prepared a production plan, they could not even know for sure that it was the optimal way of doing things, and there was often undesirable large wastage. Therefore, the company approached DTU Management a couple of years ago, because there had to be a way to do this better and easier. Associate Professor Richard Martin Lusby was given the assignment of helping Bavarian Nordic.

Richard Martin Lusby elaborates on the problem: "If you were to prepare the optimal production plan manually, you would need to make hundreds of thousands of active choices. It's quite simply not possible to do this systematically. You need to have a mathematical model to help you."

Mathematical model

Over the past few years, Richard Martin Lusby has therefore developed a mathematical model that is based on so-called integer programming. The model is written in a spreadsheet, where Michael Væver Jørgensen can enter all relevant data. When he then presses the calculate button, the complex calculations are made in the cloud. "It typically takes no more than five to ten minutes before a usable result is available.

The result is a production plan, and the plan generates a value for how good it is," explains Richard Martin Lusby, who continues:

"Our model allows us to estimate the theoretically optimal solution, and if you allow the model to make calculations for ten minutes, you will typically be within one percent of what is theoretically optimal."

The short calculation time provides Bavarian Nordic with completely new opportunities.

"It's an easy way to test different input parameters, so we can see whether it can be done more optimally," says Lasse Bengtson, who is a Tech Transfer Scientist with detailed knowledge of the physical-chemical properties which the vaccine ingredients possess.

Michael Væver Jørgensen supplements: "It has also become a decision-making tool. I think this is a huge advantage." We can test a number of different scenarios and present them to the management, who can then say what is a good or bad idea. Mind you, without us having to spend a whole month preparing it."

Current and future needs

In the spring, there was a special need to plan production using the new tool, explains Michael Væver Jørgensen:

"Our filling factory was brand-new. We had accumulated a certain amount of stocks of the active substance before the factory was ready, and we were to come up with the best possible plan for using and getting as much as possible out of these stocks.

These were batches of the raw product which had been produced over a long period of time and which therefore had very different strength due

to the degradation that occurs over time. This made the calculation particularly difficult, because the individual batches could be mixed in more than one billion different ways—with widely differing results.

Once Bavarian Nordic had overcome this backlog, the situation was different. The filling factory would then continuously take delivery of the batches from the raw production.

"There will be less material for us to combine on an ongoing basis. So we're not quite on top of how precisely we will 'play' with the model tool in the future," says Michael Væver Jørgensen.

But one thing is certain: Bavarian Nordic will use the tool for much more than the smallpox vaccine.

"We also need to produce rabies vaccine and vaccine against tick-borne encephalitis, and it may well be that we will need to use the modeling tool for these," ascertains Lasse Bengtson, who also sees opportunities for some of the other vaccines currently in the pipeline—including a COVID-19 vaccine.

Bavarian Nordic thus sees great opportunities in the mathematical planning tool, and—in reply to the question about how satisfied they are with the new tool in their toolbox, the answer is clear:

"On a scale from one to 10, this is a 10," states Lasse Bengtson.

Michael Væver Jørgensen says "Definitely."

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