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Taking Lyophilization for a Spin

How technology developers at Ghent University developed a spin freeze drying process for continuous processing. With the help of CEPI, they plan to scale out.

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Thomas De Beer

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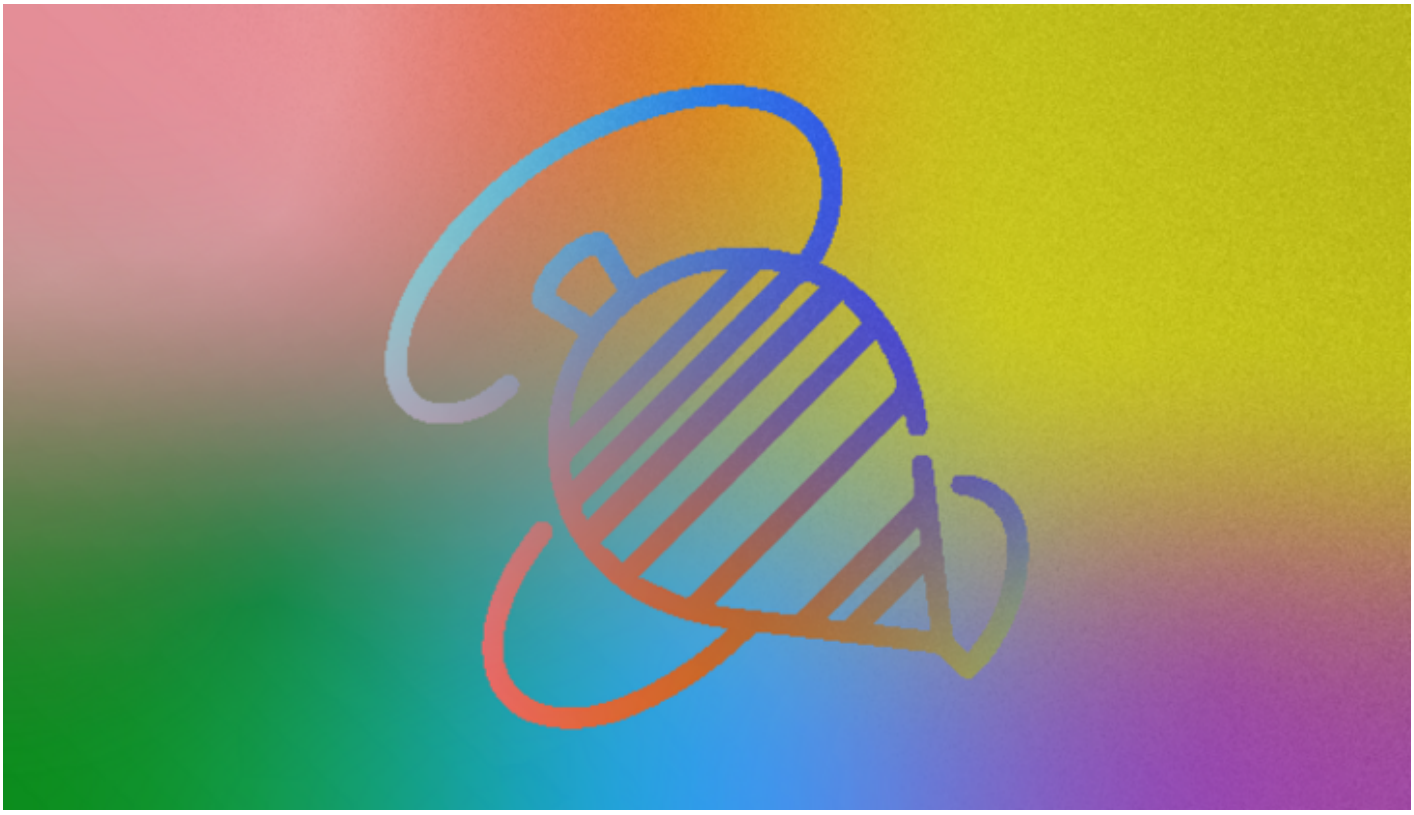
Especially post-COVID-19, the pharmaceutical industry is increasingly recognizing the need to speed up and improve the lyophilization process, specifically for mRNA LNP-based vaccines and in the event of any future pandemic preparedness requirements. Thus, Thomas De Beer, Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Belgium, helped pioneer a spin freeze drying stabilization technique that could bring about an end to frozen mRNA vaccine storage – with the additional benefit of moving away from batch to

continuous processing and manufacturing.

In the spin freeze-drying technique, vials are rapidly rotated along an axis during the freezing step as a cold gas solidifies the vaccines within, forming a thin frozen product film at the vial side wall to enable an accelerated drying process, greater manufacturing control, and improved vaccine quality.

Via Ghent University spin-off company RheaVita, Thomas De Beer sought a collaboration with pandemic preparedness organization CEPI to prepare the development, scale-up, and roll-out of pandemic-proof freeze-dried vaccines. With additional support from the Flanders Institute of Biotechnology, all the pieces are now in place to turn this project into a revolution, taking lyophilization to dizzy new heights – and taking much needed medicines where they are needed. Here, De Beer, alongside CEPI Innovations Director Renske Hesselink, discusses the potential of spin freeze-drying lyophilization.



What exactly is spin freeze-drying?

De Beer: Our continuous lyophilization technology is based on spin-freezing followed by drying, including the process control at an individual vial level. The main goal was to move away from conventional lyophilization to a continuous process that is faster, and allows faster product development and shorter time to market. Conventional lyophilization, even for an individual product, takes several days. Usually, many individual products are lyophilized together so, after a few days, you have a lot of vials available, but for continuous lyophilization we needed to find a method to do things faster. And that's where spinning during freezing came in. There are two steps to the process: freezing, during which we rapidly rotate the vial around its axis and jet, adding cold sterile gas to create a frozen layer at the sidewall; and drying. The spin freeze-drying was a trick, really, to make continuous lyophilization possible.

How was the process developed – from concept to GMP manufacturing?

TDB: The development of the concept itself was not too difficult. In an academic environment, an idea can be transformed quickly. The next step was translating that conceptual proof into GMP-ready pharmaceutical production equipment – especially for parenterals. We first developed a non-GMP continuous processing demonstrator at Ghent University, and then it was time to bring in a spinoff company called RheaVita to work on the GMP-ready equipment, which we've now finalized for smaller volumes. The next step is to further scale out.

There is a willingness and intention in the pharma industry to move away from batch processing towards continuous, but it requires greater monitoring and control. We have therefore adapted the sensors that measure the critical quality attributes for every individual vial and product processed. The information is used for monitoring and for feedback control for the process settings.

Hesselink: CEPI's aim is to make RNA-based vaccines more equitable and accessible, especially in low- and middle-income regions. One big challenge for RNA vaccines, however, is that they're not very stable and have to be frozen at

ultra cold temperatures of -60 °C or below. Lyophilization is a traditional way of making biologics more stable. By removing the water, you slow down degradation processes, but it takes a long time and you need very large batches. It's also expensive. Spin lyophilization technology solves those issues through the benefits of stability and the avoidance of traditional lyophilization challenges. Ideally, we want to make an RNA-based vaccine product that is stable at 2–8 degrees celsius.

What is also interesting for us is the flexibility and scalability that comes with continuous processing. When it comes to vaccine manufacturing, you don't always know in advance how big an outbreak is going to be; how many vials you'll need; or at which location.

How else is the system designed for flexibility?

TDB: We've also developed single-vial R&D equipment in case a manufacturer needs to develop a new product with very small amounts of material. This can be done quickly – between one and two hours – on a single vial R&D unit with inherent process monitoring and control systems. By performing monitoring and control at the vial level, once the first formulation and process development is done, it's possible to transfer production-scale equipment on a one-to-one basis.

Production-scale spin freeze drying is automated, so we don't have the typical scale-up issues seen in batch lyophilization. Conventional batch lyophilization is performed at the R&D scale batch level, before using a pilot-scale GMP batch freeze dryer for clinical batches, and then moving up to larger volumes. This is not a linear process; it requires reformulation, redevelopment, and revalidation of everything. It also consumes a lot of material – and if you have to run it several times, it costs time and money too. A continuous solution will avoid these problems.

What are the benefits and challenges of scaling out over scaling up?

TDB: As I alluded to above, scaling out, for me, means an increase in production

capacity without redeveloping, reoptimizing, or revalidating the process. With our technology, we can generate identical process conditions at an individual vial level, but we don't set process settings – we set product settings. In conventional pharmaceutical manufacturing, you typically work with a process recipe where you set identical process settings and assume all products are the same.

We work with a product recipe, with feedback control over the process settings. The product will have certain conditions during the process, and the process settings should automatically adapt towards the progress of the product. The recipe should be good for all the products at any production capacity. I think it's very future proof – and in line with the latest regulatory guidelines.

RH: The speed component is not just the speed of manufacturing but the speed of development and scaling out. Spin freezing technology offers benefits in both areas, as well as ease of tech transfer.

However, one challenge is that specific equipment will need to be installed at manufacturing sites. We'll need more investment in this area and more people using the technology so that it can be fine-tuned.

Have you tested spin freeze drying with mRNA products?

TDB: We are currently investigating the use of the technology with mRNA LNP-based products. We've demonstrated that it can lyophilize these products. The combination of controlled cooling and freezing rates should help create the optimal quality.

RH: mRNA LNP products are sensitive. They can degrade rapidly and in multiple ways. Controlled freezing means we can ensure that every vial contains a product that will be effective for the patient. It's quality guaranteed on every individual product.

We're working with Ghent to develop the technology as a platform for mRNA-

based vaccines so that when a new pandemic occurs, we can rapidly switch the technology to focus on the emerging viral pathogen.

How has CEPI been involved in the project?

RH: CEPI brings much more to the table than funding. We're a connector working with technology developers, such as in this project, vaccine developers, vaccine platform developers, and stakeholders in the global health ecosystem. We enable connections between technologies and vaccines, between manufacturing facilities where this technology could be installed, and between the decision makers who can use technologies such as this. The "C" in CEPI stands for "coalition".

Through our funding, expertise, and partners, our goal is to accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats so they can be accessible to all people in need.

What are your hopes for the future of spin freeze-drying?

RH: I would like to see this technology installed in some of our facilities in the global south, where it could help manufacture vaccines locally for both rapid responses and routine vaccinations for people who need them in low- and middle-income regions.

TDB: As a technology developer, reaching the first milestones is really important. The ability to create the first clinical batch and then make sure that the products are administered to patients through our technology is what we are really working towards. We want to make sure that we can contribute to global healthcare in the future.