Solving Freeze Drying Bottlenecks For Diagnostics and Vaccines Production In The 'New Normal'

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The Covid-19 pandemic has largely been characterised by speed; the speed at which the virus spread, the exponential increase in affected patients, the overload of healthcare systems and even the speed at which our adaptations to the virus became the 'new normal'.

From the onset of the outbreak, things were moving very quickly. The Chinese authorities announced a new cluster of pneumonia cases in a live food market in Wuhan on the 31st December 2019 and closed the market on the 1st January 2020. The Chinese CDC then confirmed the virus as Sars-CoV-2 on the 9th of January and the 1st genome sequence was published the next day in the GenBank database.

The speed at which the characterisation of the virus occurred prompted a massive work shift in the diagnostics and vaccine industries, who turned their not inconsiderable resources to producing one of the following:

1. An antigen test to diagnose patients with symptoms
2. An antibody test to understand which patients have had the disease and may be immune
3. A vaccine that would protect from the virus itself

Almost overnight, an industry that relies on methodical processes to produce safe and effective products, threw everything into trying to research, manufacture and distribute these products, encouraged by both government subsidy and a desire to do the right thing, but also the prospect of being first to market and the commercial gains that would ensue. 'Time to market', quite often measured in years, became a metric measured in weeks with pressures that were felt throughout the parent organisations along with their R&D and production partners.

What quickly became apparent was that one area, freeze drying, would be a significant bottleneck in terms of both research and manufacture.

Freeze drying is used to remove water from a liquid, leaving a dry product or a 'cake' as it is known. Everyone is familiar with freeze dried coffee, which starts as a liquid product, has the water removed to leave a dried residue and can then be restored by the simple process of adding water back to the product. Diagnostic reagents and vaccines that have a short shelf life window of days or hours can have that shelf life extended to years by using freeze drying, whilst also increasing the ability to transport and store in ambient conditions, vital if vaccines and diagnostics are going to reach populations that are isolated or have less well developed infrastructures.

Addressing the Bottlenecks

Freeze drying capacity is a limited resource that would normally be expanded by adding additional machines, but in a time of crisis when many manufacturing units are closed and their reopening uncertain, the lead times for new freeze dryers can run into months or even years in some cases. It is a timescale that doesn't really work for the immediacy of a pandemic.

With an increasing demand for R&D work to finalise diagnostic kits and a consequential increase in production volumes of those kits, we were faced with just this scenario at Biopharma Group.

The 3 key areas identified that would allow us to fulfil the demand that COVID had generated were:

1. Cycle Development and product formulation

Freeze Drying cycles can range from hours to days and are a complicated interaction of chemistry and volume. Generally, the more water that a product contains the longer it will take to freeze dry but freeze-drying time is also affected by the chemical constituents of the products and excipients that are added to it. By changing the freeze-drying cycle and the product formulation, it is possible to increase activity of an active ingredient whilst reducing the cycle length considerably. An example was a diagnostic reagent with a 5-day drying cycle and a visibly poor finished product. Using Biopharma Group's own specialist pre-lyophilisation analytical instruments, the Lyostat & Lyotherm, the R&D team were able to understand the critical temperatures of the product and identify the weaknesses in the formulation. A range of excipients were identified that would:

- aid the bulking of the lyophilisate and improve the visible quality of the finished product
- thermally stabilise the solution, increasing its critical temperatures
- provide protection to the active ingredient during lyophilisation, increasing product activity considerably

These changes allowed the team to dramatically reduce the freeze-drying cycle time from 5 days to 1.5 days allowing 3 production cycles to be run on one machine where previously only 1 could be run. Coupled with an improvement in cake quality and an increase in activity of the finished product, these changes worked to increase capacity within the facility without the need to add additional freeze dryers. Many established freeze-dried products have never had full cycle and product formulation development performed on them and the improvement in lead times and costs can be significant.

2. Novel Packaging Formats

Cycle development and product formulation improve the efficiency of the freeze drying process, but improving the physical packaging of product in the freeze dryer can have a large impact on throughput. Freeze dried products are processed in a wide range of packaging, from bulk processing which is generally the most space efficient, through vials to tubes and finally to blister packs, which are inefficient in terms of freeze dryer space. For instance, processing PCR plates is around 16x less efficient per test than processing vials and processing blister pack are 8x less efficient than PCR plates. These large variants in space efficiency greatly alter the throughput and consequently the economics of production, and packaging format should be at the top of the list for new-product development teams.

R&D teams work closely with customers to identify the best way to package freeze dried products; sometimes this is a simple as increasing the size of the standard freeze drying tray by 4mm, a tiny increase that allows freeze drying scientists to process 50% more product on an individual tray. Other solutions are more complex and involve custom formats which increase shelf capacity whilst simplifying the secondary packaging of the finished kit. Space efficiency is an important part of improving capacity and throughput, with significant increases being realised without the need for further freeze dryers whilst reducing the unit cost and reducing manpower in kitting and assembly.

3. Increasing Capacity

The easiest option is to just buy further freeze dryers but the worldwide demand for the freeze drying of COVID related products has seen lead times rise dramatically since the start of the year, sometimes increasing from several weeks to several months on some of the more specialist models. How then to reduce the purchase time of a freeze dryer in the current market?

Biopharma Group is in the enviable position of being the largest global distributor of freeze dryers for SP Scientific and support the installation and servicing of those freeze dryers throughout Europe with our own team of engineers, based in our UK office. This puts us

in a priority position for new freeze dryers on a reduced lead time whilst also having access to the refurbished/ pre-used market in Europe and beyond. The upsurge in both R&D and production work since the start of the year combined with our strong strategic position in the supply chain has allowed us to increase freeze drying capacity by 120% since the start of the year - a combination of new freeze dryers and refurbished equipment that has been installed, serviced and IQ/OQ'd by our own specialist technical engineers. Our mean response time to a freeze-dryer fault is in the region of 5 minutes - an industry leading figure that is hard to beat.

The challenges of overcoming capacity issues in freeze drying have been a focus for Biopharma for the past 6 months and our desire to meet and exceed the requirements of our customers has led us to change some of the ways we work fundamentally, whilst still providing the benefit of over 30 years' experience in the freeze drying market. This refocusing in response to the changing requirements of our customers and of the pharma industry in particular, has allowed us to dispense, freeze dry and package millions of COVID test this year and with the 2nd and 3rd generation kits nearing market readiness, increasing capacity in both freeze drying and production will be Biopharma's 'new normal'.

To discover more on freeze drying or about increased production capacity, please contact us https://biopharma.co.uk/intelligent-freeze-drying/about-us/contact/ or visit www.biopharma.co.uk