STEVANATO GROUP's *Ready To Use* nested vials – a high value solution for lyophilized pharmaceutical products

The biologics market is forecast to grow at a double-digit compound annual growth rate (CAGR) of more than 15 percent until 2027 and beyond.1 This growth will be driven by GLP-1, antibodies and proteins as well as mRNA applications.

The share of lyophilized drugs in the total number of injectable medicines in vials is estimated to be between 20 percent and 25 percent. A figure confirmed by the percentage of new biological drugs in lyophilized form approved by the FDA between 2017 and 2021 of 24 percent.

It is also expected that the demand for sterile small batch fillings will continue to rise in parallel.[1]

Ultra-low temperature storage was the only sensible solution for the Covid SARS-CoV-2 vaccines. The available capacities and, above all, the time pressure did not allow for any other options. However, ultra-low temperature storage is impractical in terms of handling and, in particular, supply chain costs. Alternative storage options, e.g. in the form of freeze-dried products, are therefore being considered for new developments to enable uniform storage conditions and times.

Ready-to-fill containers such as Stevanato Group's EZ-fill® vials have proven to be an excellent solution for filling small batches. Wouldn't it be perfect if these vials could be lyophilized in their nest without the need for additional handling steps?

Stevanato Group, in collaboration with the Politecnico di

Figure 1: Nested EZ-fill® Vials of Stevanato Group

In collaboration with the Politecnico di Torino University, STEVANATO GROUP has conducted a groundbreaking study to explore the freeze-drying of pharmaceuticals within nested vials. Recently published in two papers, the research delves into the potential of ready-to-use nested vials - demonstrating their potential as a high-quality solution for freeze-dried drug products.

Torino University (POLITO), has carried out an extensive series of tests to address this question of freeze-drying pharmaceuticals in nested vials. The results of these tests were published in two papers and are discussed and described in this article. [2,3]

INTRODUCING RTU NESTED VIAL – A HIGH VALUE SOLUTION FOR LYOPHILIZED PRODUCTS

The continued growth of biologics and biosimilars, whose complex characteristics require high-performance primary packaging, effective filling and finishing processes and therefore innovative solutions, poses significant challenges for pharmaceutical manufacturers. Manufacturers producing these typically high-value and low-volume drugs need to implement a flexible production strategy that provides control over the many variables potentially affecting the process, especially when freeze-drying is considered as an option.

The freeze-drying process consists of three sub-steps: firstly, freezing (ice formation), secondly, primary drying (sublimation) and thirdly, secondary drying (desorption). The current process with bulk vials is based on direct contact between the vials and the freeze dryer shelf. This ensures good heat transfer, which is considered essential.

The nested vials are placed in a suspended framework "nest" complying with ISO standard 21882. This avoids glass-to-glass contact during the filling phase and reduces the mechanical stress that can cause vial breakages and particle contamination. All this leads to a reduction of the risks of product wastage, productivity losses and, in the worst case, a costly product recall.

However, the suspended arrangement may raise doubts about the mechanism of heat transfer from the shelf to the vials. Doubts that turned out not to be critical thanks to the tests carried out.

TESTING CONDUCTED BY STEVANATO GROUP AND THE POLITECNICO DI TORINO

The test series included primarily the following aspects:

- Change of the ice nucleation temperature distribution due to the different loading configuration of the vials. Bulk vials directly placed on the temperature-controlled shelf and nested vials in a rack system - Stevanato Group EZ-fill® nested vials
- Influence of the loading configuration on the morphology of the lyophilized product
- Influence of the loading configuration on the residual biological activity of an enzyme (Lactate dehydrogenase (LDH) as selected model enzyme

-Freeze drying behaviour

Nested vials tended to nucleate at higher temperature compared to vials standing directly on the shelf. This can have an important practical effect. It is known from the literature that the higher the nucleation temperature (i.e., the lower the degree of supercooling), the bigger the ice crystals and the bigger the pores during the sublimation phase and thus the higher the sublimation rate. [4,5]

The different freezing profiles observed in the two groups of vials made it clear that the vials stored in a nest showed slower cooling dynamics than the vials in direct contact with the shelf. Since the two groups of vials were loaded together on the same shelf, they were exposed to the same freezing ramp of the shelf, apart from the intrinsic heat exchange heterogeneity of the shelf. This resulted in similar primary drying profiles of the nested and direct contact loaded vials. Thus, everything points to a noticeable influence of the nest on the heat transfer during the freezing step, resulting in a slower cooling of the solution in the vials.

The two freezing profiles delivered in a clearly different morphology of the freeze-dried cakes, as shown by SEM

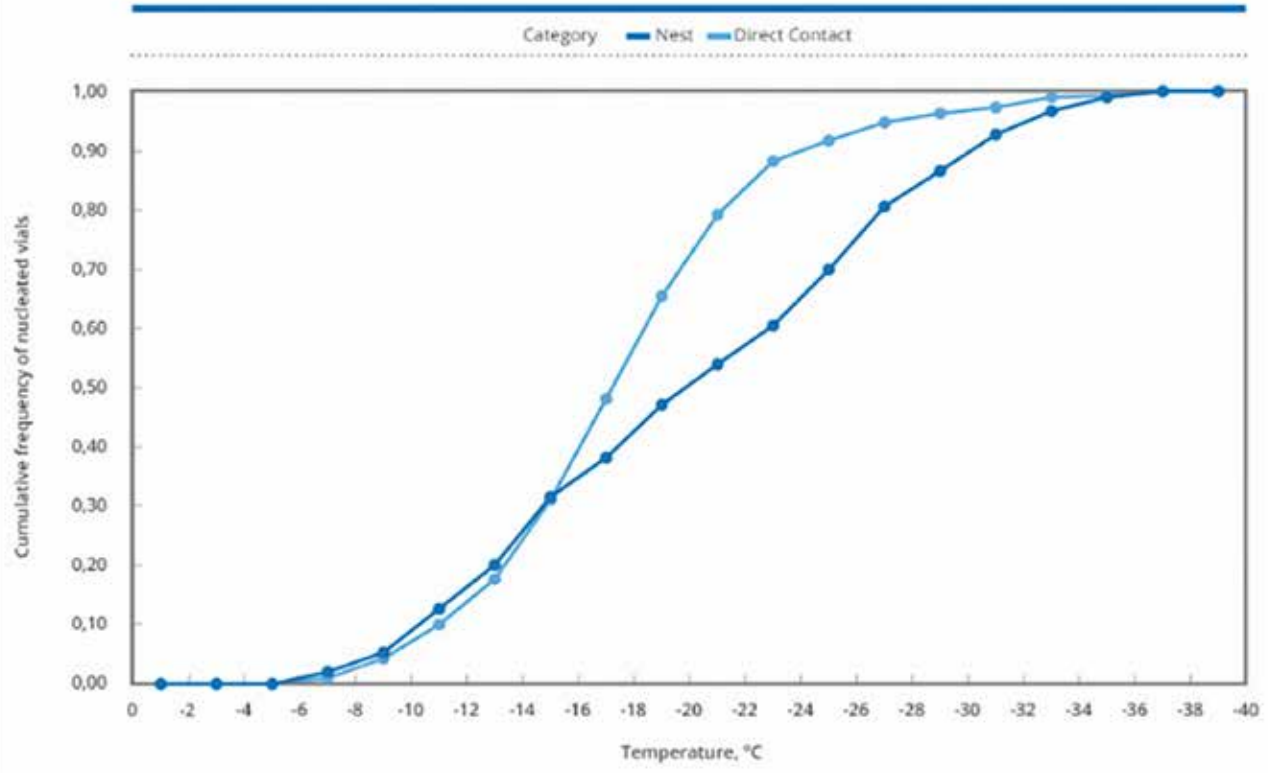


Figure 2: Comparison between cumulative nucleation temperature distributions for nested vials and in direct contact with the shelf applying a 1.0 °C/min freezing ramp

(Scanning Electron Microscopy) (Figure 3). The product freeze-dried in the nest exhibits a more open structure characterized by larger pores, which is consistent with the higher nucleation temperature. In contrast, the product freeze-dried in vials in direct contact with the shelf had a more compact structure with smaller pores. More specifically, the average pore size of the sample in the nested vials was 170 µm compared to 75 µm for the vials placed directly on the shelf.

The surface area of the cakes was also determined. As expected, the surface area of the freeze-dried product in the nest was smaller than in the direct contact configuration (0.45 and 0.61m2/g, respectively).

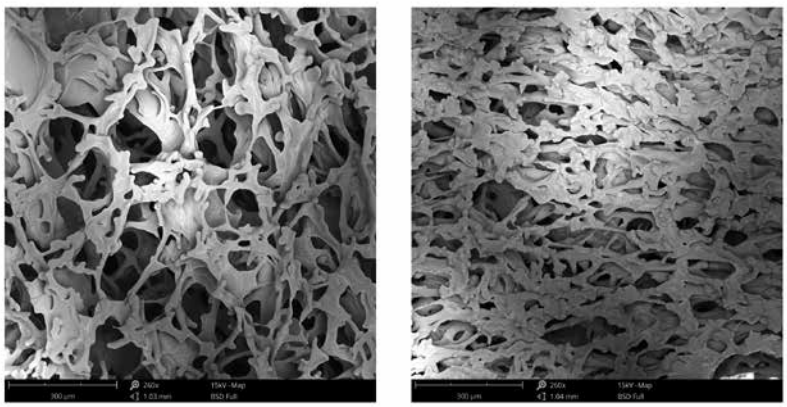


Figure 3: SEM images of the dried center of the cake - in the case of (left) nested vials and (right) in direct contact with the shelf

A freeze-drying cycle using a 5 percent Mannitol solution was performed to compare the thermal behaviour of the product during primary drying. During the ice sublimation phase, the product temperature in nested vials was about 2°C lower compared to the direct contact configuration. Overall, the differences in temperature and time were very minimal.

The distribution of the heat transfer coefficient (Kv) within the batch showed less variability for nested vials compared to the vials in direct contact with the shelf, suggesting a more uniform heat transfer from the freeze dryer to the product within the batch. Such a feature is particularly interesting as it reduces the variability between the vials and increases the homogeneity of the batch.

The biological activity of the enzyme LDH (lactate dehydrogenase) was almost 40 percent higher in the nested vials after

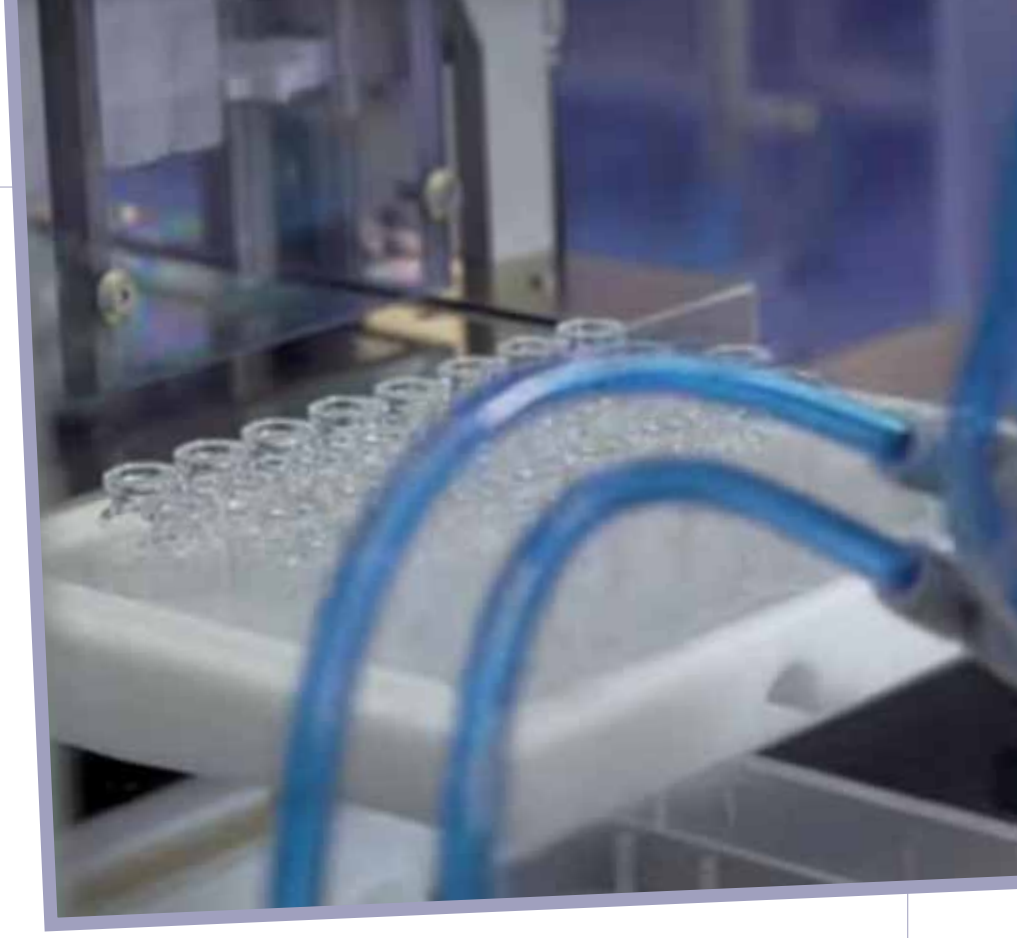
	Freeze-thawing (0.25°C/min)	Freeze-thawing (1.00°C/min)
Nest	36.9 (± 12.0) %	33.9 (± 12.4) %
Direct contact	17.1 (± 7.2) %	21.8 (± 6.8) %
	After lyophilization	
Nest	27.1%	
Direct contact	19.4%	

Figure 4: LDH residual activity obtained after the freeze-thawing and lyophilization for vials loaded in the nest and direct contact with the shelf.

freeze-thawing and after lyophilization. This is consistent with the different morphology of the ice crystals obtained for the two loading configurations: Vials loaded in nests were characterized by larger crystals and consequently a smaller interface between the ice and the cryo-concentrated solution. Since this interface is the trigger for the denaturation of LDH, the recovery of LDH bioactivity was always significantly higher for nested vials.

CONCLUSIONS AND ADVANTAGES OF EZ-FILL® NESTED VIALS

The main advantages of the EZ-fill® nest configuration highlighted from these tests are:



- Easier scale-up of the cycle and safer transfer to the final industrial site
- No significant impact on the duration of the freeze-drying cycle
- Reduction of interfacial stresses to which a biopharmaceutical product is exposed during the freezing and drying phases
- Considerably better recovery of LDH bioactivity
- Reduction of variability within and between batches

These advantages are key for both setting the lyophilization cycle conditions during the freezing and drying phases as well as for transferring a cycle from one freeze dryer to another.

The overall results of the study confirm the usability of nested vials for lyophilization and, most importantly, demonstrate their potential as a high-quality solution for freeze-dried drug products.

This in addition to the unique and proven benefits of nested vials:

- Lower Time-to-Market from the clinical stage to industrialization: resulting in faster revenue gain, a reduced risk of entry of new competitors and a reduced risk of failures during tests/clinical phases
- Higher Flexibility: A flexible aseptic process - providing the nest & tub format for all sterilized containers (vials, cartridges, syringes), EZ-fill® allows pharmaceutical companies maximum flexibility in aseptic filling with a common filling platform (combi-line)
- Increased Quality and Patient Safety: No glass-to-glass contact increases container performance resulting in less breakage, less cosmetic issues, less particles, less rejections and waste
- Reduced Total Cost of Ownership: reduced complexity, less implementation (lower investments) and operating costs, less validation costs, less quality costs, less utilities costs (e.g. energy, WFI), less labor costs and overall and an overall lower footprint

The significantly higher residual bioactivity together with the virtually non-existent impact on freeze-drying cycle time and the above-mentioned advantages of EZ-fill® containers represent a truly high value solution for lyophilized pharmaceutical products.

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