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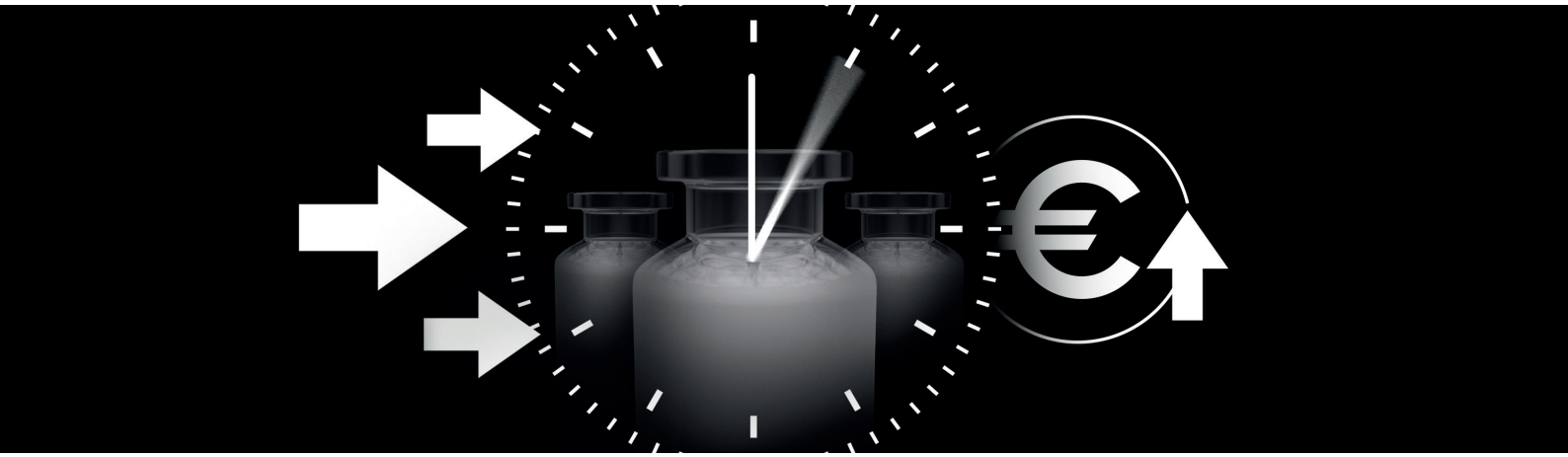
Faster time-to-market for lyophilized drugs and vaccines thanks to the RheaLyo™ Continuous Freeze-Drying Technology

White Paper



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Introduction

The pharmaceutical industry tries to make its drug development process more efficient for several reasons. The cost of drug development is increasing year-after-year. Also, the time needed to develop a drug generally gets longer. On top of that, the pharma industry sees increased competition from generic (biosimilar) drug manufacturers.

In such a tough economic environment it is no surprise that drug manufacturers are looking for ways to improve their profit margins.

In this White Paper, arguments are put forward to show how innovative technologies for thermostabilizing drugs and vaccines can help to get these medicinal products faster to the market. Getting drugs out in the market sooner means getting drugs out for more time under patent protection in the absence of generic competition. The extra revenue that can be generated in such way may significantly exceed the investments in the new technologies.

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The development of a new biopharmaceutical drug product is a long and costly process

McKinsey & company research has shown that the average time for taking a new medication from candidate nomination to launch is about 12 years.

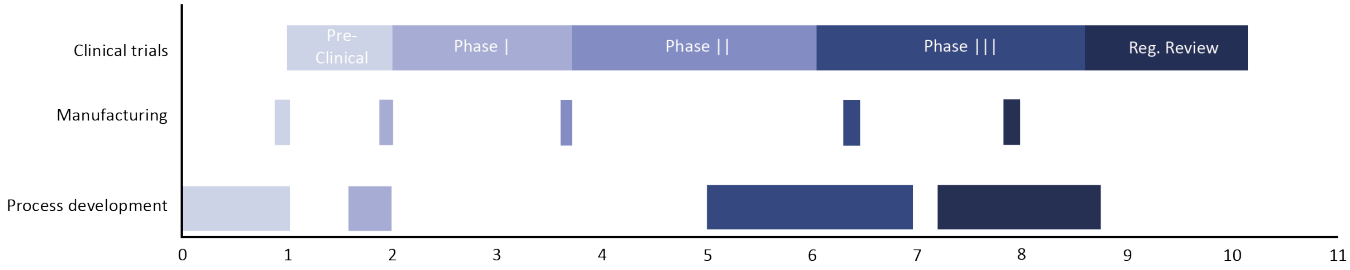

Figure 1: *Schematic overview of a drug development timeline with indications of the key workload for process development and manufacturing.*[1]

The past decade R&D time has increased by on average 3-5 years. This inevitably leads to patients not being treated optimally for a longer period. (Gelijns & Halm, 1991)

Pharmaceutical companies should always embrace technologies that could speed up the time to market as it benefits the patient population tremendously. Continuous manufacturing in general and continuous freeze-drying in particular could shorten the time to market by up to 1 year mainly because scaling-up trajectories from R&D to production scale can be avoided.

Biopharmaceutical companies only have a limited time frame to get a sufficient return on the development costs for new drug products. As soon as a potential lead compound has been identified, patent applications are filed at the very early discovery stage of the drug product development process. Once the patent is granted, the biopharmaceutical company generally benefits from 20 years of market exclusivity, before (generic) competitors can start selling the same drug leading to a decreased revenue upon patent expiration due to a combination of lower prices and decreased volumes. (Gupta et al.., 2010)

[1] https://www.mckinsey.com/industries/life-sciences/our-insights/fast-to-first-in-human-getting-new-medicines-to-patients-more-quickly

Therefore, the development time of new products should be kept to a minimum to get an as high as possible return during the patent protection period (see Fig. 1). In other words, from the moment a patent is issued, the clock starts ticking.

For many biopharmaceutical products, freeze-drying is an essential step in the formulation process to attain sufficient long-term stability at refrigerated or room temperature. Traditionally, freeze-drying of unit doses is operated as a batch-wise process, associated with several disadvantages (see below). RheaVita has developed a continuous and controlled freeze-drying concept for unit doses which resolves these issues and drawbacks. This continuous concept is based on spinning the vials during the freezing step while using cold gas for the cooling, resulting in a thin product layer spread over the inner vial wall. The spin frozen vials are subsequently dried under vacuum, where infrared heaters provide the energy for ice sublimation and desorption of residual moisture, until the final dried product is obtained. Thanks to the thin layer, the large surface area, and the efficient energy transfer, very short drying times can be obtained in the order of hours.

In the sections below, we explain how the RheaVita continuous and controlled freeze-drying technology can save precious time during the development process of biopharmaceutical products, compared to the conventional batch freeze-drying process.

Therefore, we will focus on the following aspects:

1. Gains during initial formulation development,
2. Gains during freeze-drying process development,
3. Gains during scale-up of manufacturing capacity, and
4. Regulatory gains.

Time gains during initial formulation development

Thanks to the unique controlled spin-freezing step and controlled radiation based drying, the RheaVita technology offers the possibility to lyophilize a typical vial in a matter of a few hours. This is in sharp contrast with traditional batch freeze-dryers which require multiple days to dry a formulation (For a comparison between batch freeze-drying and the RheaLyo processing, please consult table 1 on page 7). Consequently, the RheaVita technology offers a significant time saving for the Formulation Scientist. It is possible to produce several different formulations per day (i.e., immediately at optimal freeze-drying conditions for each formulation – see further), which can be analyzed the same or next day. This fast feedback loop gives the Formulation Scientist the option to perform multiple iterations in a matter of days. As such, a successful formulation can be developed in a fraction of the time needed for a traditional batch freeze-dryer.

In traditional batch freeze-drying, different formulations are freeze-dried simultaneously during one cycle. However, each formulation has specific characteristics regarding glass transition temperature of the maximally freeze-concentrate (Tg'), collapse temperature, dried product mass transfer resistance (Rp) and glass transition temperature of the dried product (Tg). Therefore, conservative drying settings are applied to avoid cake collapse for any of the formulations that are included in the screening. Consequently, the resulting freeze-drying cycle takes very long, even up to 1 week, and suboptimal drying conditions are used for each of the formulations. As a result, there will be differences in for instance residual moisture content for the samples and there is a risk to reject formulations and to make wrong formulation screening conclusions due to the application of suboptimal drying conditions leading to non-optimal end product quality attributes.

The RheaVita continuous and controlled freeze-drying technology allows for most efficient and thorough screening of different formulations, even with only a limited amount of material available. Using the RheaLyo Mono freeze-dryer (also called "Single Vial Unit"), the continuous freeze-drying R&D tool for formulation and process optimization, each formulation can be immediately freeze-dried applying optimal freezing and drying conditions for each formulation. For instance, with the Tg' value of the formulation as an input parameter, the feedback controls integrated into the software of the equipment allow automated drying of the product as efficiently as possible without exceeding this critical temperature. One vial can be

dried within 1.5-3 hours, with the possibility to immediately analyze the Critical Quality Attributes (CQAs). The conclusions based upon previous experiments can be considered for subsequent experiments allowing efficient and flexible screening of several formulations with minimal consumption of precious material.

Method	Traditional batch processing	RheaLyo processing
Cycling	All formulations in same conservative cycle	1 vial = 1 cycle
Process	Different formulations = different Rp and Tc	Each formulation is optimally dried Remain 2/3 K below Tg' thanks to feedback control
Total time	1 week	3 hours
Result	Suboptimal drying • Different residual moisture levels • Risk of rejecting promising formulations	Testing CQA • Efficient formulation screening

Table 1: *Comparison between traditional freeze-drying and the RheaLyo freeze-drying method. The latter is faster and more economical.*

Time gains during freeze-drying process development

When using RheaVita's spin freeze-drying technology, an optimized freezing, primary drying and secondary drying trajectory can be quickly obtained based on the determination of just a few parameters. For freezing, desired cooling and ice crystallization rates can be accurately set. For primary and secondary drying, only the critical product temperatures (Tg' and Tg) need to be known. For primary drying, there is no need for vial heat transfer coefficient values (Kv) or mass transfer resistance values (Rp) determinations since the controls of the system automatically keep the product temperature below the critical temperature. This results in a significant process optimization time saving, since determining these parameters is associated with labour intensive experimental campaigns.

The feedback control algorithms for the different stages of RheaVita's continuous spin freeze-drying process are highly effective to regulate the freezing and drying process of medicinal products. Combined with the very thin layer of product to be dried, the overall lyophilization recipe development can be done in a

fraction of the time typical for conventional batch freeze-dryers. All the time savings combined result in a meaningful acceleration of the drug development in this early stage (figure 2).

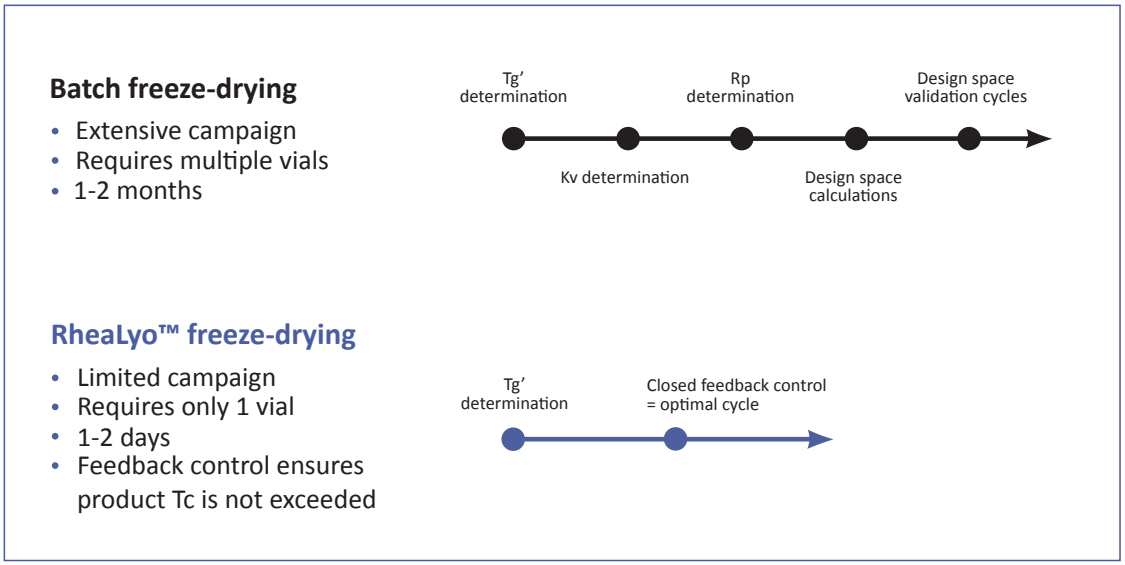

Figure 2: *Comparison between traditional freeze-drying and the RheaLyo freeze-drying method. The latter requires less work and material and time.*

The design of a suitable freeze-drying cycle is essential to obtain the dried end-product with the desired critical quality attributes such as residual moisture content, solid state, etc. within an acceptable cycle timing and without inducing any cake defects. The optimization of freeze-drying cycles increases the process efficiency and helps to reduce manufacturing OPEX costs. As indicated in the previous section, the RheaLyo Mono freeze-dryer allows freeze-drying of each drug formulation immediately by realizing optimized settings via the closed feedback controls which are integrated in the equipment. Based upon the critical parameters of the formulation such as Tg' and Tg, the desired product temperature during processing can be set and is controlled via in-line non-contact temperature measurements. The energy input from the radiators during drying is automatically adapted to dry the product as efficiently as possible without the risk of exceeding the set temperature value. Hence, one freeze-drying cycle is sufficient to attain the optimal drying settings, while only consuming one vial. This approach saves a lot of precious material and time, at a crucial moment in the drug product development process regarding both material availability and timing.

The development and optimization of batch freeze-drying cycles can be conducted via the use of

mechanistic models, via the application of data-driven models (i.e., Design of Experiments) or, lastly, via trial-and-error. These approaches are ranked according to an increasing experimental load, each of them requiring an increased consumption of material and time. To make a fair comparison with the continuous freeze-drying technology, we will focus on the application of mechanistic models in the optimization of the primary drying step of the batch freeze-drying cycles, which is the most ideal way for development and optimization. Mechanistic primary drying models are a mathematical approximation of the sublimation process, allowing the calculation of the optimal combination of shelf temperature and chamber pressure in the batch freeze-dryer to dry as fast as possible without exceeding the critical temperature and taking the constraints and limitations of the freeze-drier itself into account. To compute the optimal cycle settings, multiple model input parameters need to be determined, of which the vial heat transfer coefficient (Kv) and the dried product layer resistance (Rp) are the most labor-intensive and time-consuming. The methods to determine both coefficients are described in strict protocols. (Jameel et al., 2021) In brief, the Kv coefficient is quantified as a function of the chamber pressure and is specific for each freeze-dryer, vial type, and the number of vials loaded upon the shelves of the freeze-dryer. In addition, within the vials grouped upon the shelves in the drying chamber, there are also inter-vial differences in heat transfer (e.g., edge vial effect) which should be considered. The Rp coefficient is different for each formulation and is to be quantified in function of the dried layer thickness, is impacted by the degree of supercooling, the physical nature of the solids, and the solid content of the drug formulation. Moreover, the Kv and Rp parameter need to be determined each time the product is transferred to another equipment scale, hence, often three to four times in total (see next section). The time needed to determine these parameters can easily take up a few weeks, for one formulation and for each equipment scale. While the determination of the Kv parameter does not require any material, the Rp determination does require a full load of the actual product to be processed. Lastly, for each freeze-dryer, the equipment capability needs to be characterized, given by the minimal achievable pressure as a function of sublimation rate, i.e., choked flow limit.

Compared to the straightforward procedure for cycle optimization using the RheaVita technology, cycle development in batch freeze-drying is time-intensive, consumes much more expensive material, and requires specific expert knowledge.

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The time gains during scale-up of manufacturing capacity

Due to inherent design characteristics, there are important differences in heat and mass transfer between laboratory-scale, pilot, and production freeze dryers. “Hot” and “cold” spots are very common on the shelf surface of different freeze dryers and impacts the total drying time. It is demonstrated that a front vial in the laboratory lyophilizer may receive 1.8 times more heat than a front vial in a manufacturing freeze dryer operating. (Rambhatla et al., 2006)

With edge vials, scales-up adjustments are complex. Differences in wall temperatures impact the edge vial effect and scale-up, and estimates for wall temperatures are needed for both laboratory and manufacturing dryers. (Pikal et al., 2016)

To compensate for these effects, it is necessary to revalidate the freeze-drying protocol every time a scale-up step is made. This is not only time-consuming, but also leads to the consumption of significant amounts of drug product. When using RheaVita’s continuous freeze-drying methodology, there is no scale-up impact. The advanced process control systems guiding the product through the process in an automated way are implemented on all RheaVita’s continuous freeze-dryers from R&D to production scale. The production capacity can be increased by scaling out. Additional production lines are deployed, or the length of existing production lines is extended, or you simply run the production line for a longer period. The individual vials will continue to go through an identical process and have an identical process signature, regardless of the through-put of the production line. Hence, no laborious revalidation of processes is needed at all.

A further advantage of this continuous manufacturing principle is the ability to choose the appropriate scale for accelerated and stress tests and stability batches for registration purposes. There is no need to produce at full scale as for a batch freeze-dryer. This also leads to a significant cost saving in terms of raw materials.

Scientific literature clearly describes the benefits of continuous manufacturing in the pharmaceutical industry. Most of the evidence relates to decreases in development and production/operating costs and improvements in product quality and reliability. Perhaps most importantly for patients,

continuous manufacturing has the potential to expedite patient access through improved manufacturing agility and easier scale-up to commercial production.

In summary, the huge size of industrial batches is impractical for process development in batch freeze-drying. The initial development of freeze-drying cycles is conducted with lab-scale equipment. Subsequent steps in the development process demand scale-up from lab-scale to pilot-scale and, finally, to industrial-scale freeze-dryers. The difficulties associated with process scale-up and tech transfer for batch freeze-drying are well-known and extensively documented. (Tchessalov et al., 2022) These challenges include the occurrence of vial breakage during freezing at commercial scale, differences in degree of supercooling and Rp for the same product processed using different equipment scales, and the impact of differences in refrigeration capacities and geometry on the performance of dryers, i.e., Kv and choked flow limit. All these factors need to be considered during scale-up and tech transfer as they all impact the final product quality.

Regulatory gains

The United States Food and Drug Administration (FDA) champions the development and implementation of advanced manufacturing technologies like continuous manufacturing for drug substances and finished drug products. Continuous manufacturing offers the potential to improve product quality and reliability, lower manufacturing costs, reduce waste, decrease inventory, and increase manufacturing flexibility and agility in response to fluctuations in product demand. The cumulative effects of continuous manufacturing adoption could reduce or mitigate drug shortages. Continuous manufacturing can be applied to all classes of products, including biotechnology products filed in Biologics License Applications (BLAs). The industry is expected to follow the ICH guideline Q13 on continuous manufacturing of drug substances and drug products. This guideline describes scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing (CM).

The FDA's Center for Drug Evaluation and Research (CDER) has several visible commitments to facilitate the adoption of continuous manufacturing. CDER's Emerging Technology Program seeks to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing, such as continuous manufacturing, through direct engagement with industry representatives. Under this program, FDA staff and participants discuss, identify, and resolve potential technical and regulatory issues regarding

the development and implementation of a novel technology prior to the filing of a regulatory submission. FDA approved the first application employing continuous manufacturing in 2015 following extensive engagement between the applicant and the CDER's Emerging Technology Program. Recognizing that global regulatory harmonization can be significant barrier to CM adoption, the FDA leads international regulators in developing a harmonized international guideline on continuous manufacturing (ICH Q13) to further lower regulatory uncertainty regarding implementation across multiple regulatory regions.

Unfortunately, there is still a misconception in the pharmaceutical industry of regulatory barriers that reduce the attractiveness of continuous manufacturing. Since regulators had not yet described the regulatory outcomes of products made using continuous manufacturing, the FDA carried out a self-audit of pharmaceutical continuous manufacturing regulatory submissions. (Fisher et al., 2022)

There were no substantial regulatory barriers identified for continuous manufacturing applications related to manufacturing process changes or pre-approval inspections. Continuous manufacturing applicants had relatively shorter times to approval and market as compared to similar batch applications, based on the mean or median times to approval (8 or 3 months faster) and marketing (12 or 4 months faster) from submission. It is estimated this corresponds to about $171-537M in early revenue benefit.

Calculation model

We built a simulation model to assess the impact of several months of development time gain in the launch of a biopharmaceutical. We modeled the simulation from development on the RheaLyo Mono freeze-dryer to production on the RheaLyo GMP-Flex™ Model "4/120" with a yearly output around 100,000 vials. We assumed an average selling price per vial of €8,000 (based on Cablivi® data from Sanofi) and a 31% price erosion after the introduction of a biosimilar (based on a real case regarding the entry of the biosimilars Imraldi® and Amgevita® in the market, in 2019 in Belgium). We used the conservative estimate of 3 months for the time gained to marketing of the drug. Our simulation suggests an incremental revenue per asset of more than €18 million in year 10 of the drug development timeline. The corresponding net present value, using a 10% discount rate, is more than €12 million.

The calculation model and the economics of the RheaVita technology are a subject of another White Paper.

The controlled freeze-drying methodology marketed by RheaVita avoids time-consuming and costly revalidation steps during scaling up. The net present value of a very conservatively estimated 3 months acceleration to the market exceeds significantly the CAPEX of the corresponding freeze-dryer.

Key Takeaways

Using the RheaLyo lyophilization technology, a successful formulation can be developed in a fraction of the time needed for a traditional batch freeze-dryer, and which much less material consumption (which is scarce and very expensive at the early R&D phase).

The RheaLyo feedback control algorithms do not need vial heat transfer coefficient (Kv) or mass transfer resistance value (Rp) determinations to regulate the freeze-drying process of medicinal products. This fact, combined with the very thin layer of product to be dried, results in a very fast lyophilization recipe development of weeks, not months.

It is not necessary to revalidate the freeze-drying protocol every time an increase in manufacturing capacity is made. This time-consuming, and wasteful step is completely absent from the RheaLyo continuous freeze-drying methodology.

Furthermore, this continuous manufacturing principle allows one to choose the appropriate production scale for clinical and commercial batches. There is no need to produce at full scale as for a batch freeze-dryer. Again, this leads to a significant time and cost saving.

Finally, the FDA concluded from a self-audit that continuous manufacturing applicants had relatively shorter times to market as compared to similar batch applications. This represents a potential early revenue benefit of hundreds of millions of dollars.

The time gains above start right at the beginning of drug development with the RheaLyo Mono and RheaLyo Multi freeze-dryers, tailored for drug discovery and preclinical phases, followed by the RheaLyo GMP-Flex models, a key asset during clinical trials and compatible with commercial scale productions (see Figure 3).

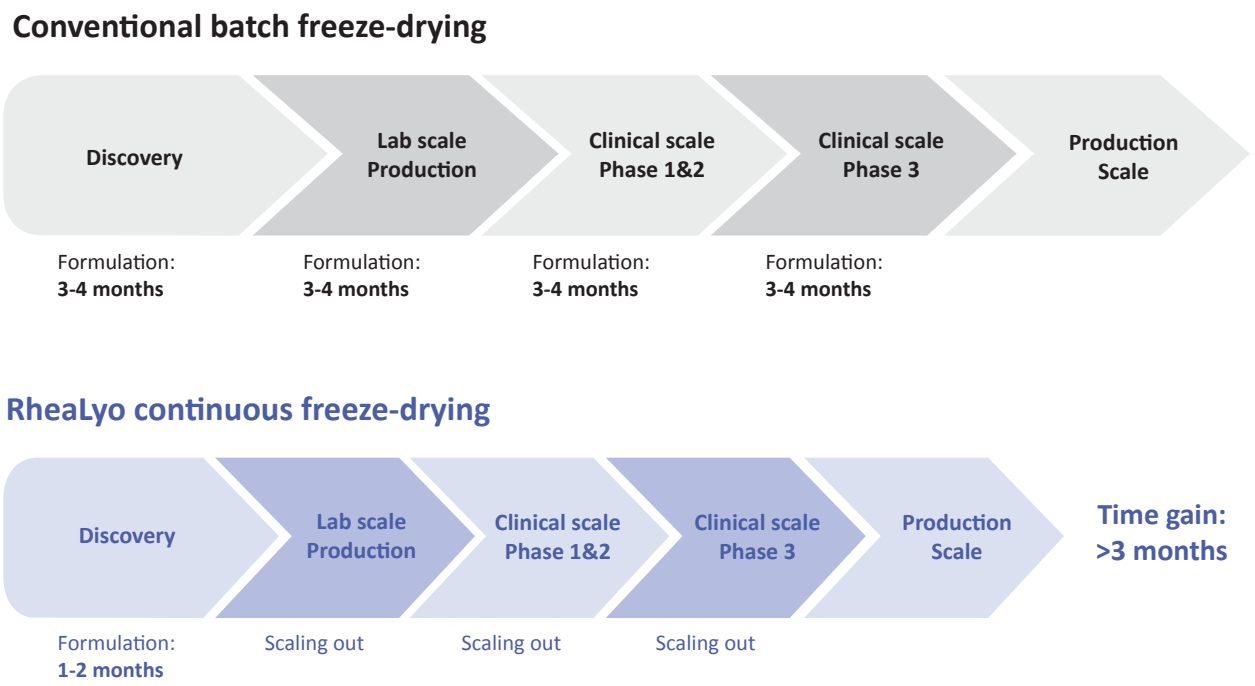

Figure 3: *Comparison between traditional freeze-drying and the RheaLyo freeze-drying method. The RheaVita approach leads to a faster time to market thanks to time gains during the formulation, process development and scale-up work.*

Each of the aspects discussed above contributes to the time gained via the RheaVita continuous freeze-drying technology compared to the batch freeze-drying process. In total, the time gained during the drug product development trajectory is estimated to be at least 3 months but can be a multiple depending on the specific situation.

This faster time-to-market benefits to the patients and provides a significant economic incentive by prolonging the market exclusivity during the patent protection period. Also, a much lower amount of drug product is required in a phase where the active component is still relatively scarce and expensive to produce.

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CEPI

The RheaLyo freeze-dryers present a revolutionary solution to expedite pandemic preparedness. Even with accelerated efforts during the COVID-19 pandemic, which reduced the timeline to around 20 months by parallelizing clinical trials and initiating risk-associated commercial production, there's still a pressing need to further shorten this duration in alignment with the CEPI 100 days program. The primary goal of the CEPI 100 days program is to achieve a remarkable reduction in vaccine development time to just 100 days. In this pursuit, the RheaLyo freeze-drying technology emerges as an ideal component by offering a range of unparalleled benefits. First and foremost, it ensures a seamless scale-out, reducing the challenges of transitioning from research to large-scale production. Ghent University in Belgium has received funding from CEPI to explore whether the RheaLyo vaccine stabilization technique could end the need for frozen storage of mRNA vaccines and support a fast and scaled-up response to future outbreaks.

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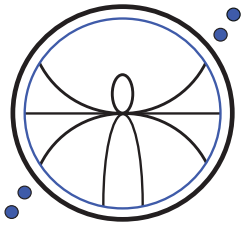
Disclaimer

The values displayed in this document reflect the current status of our knowledge in respect of the performance of the device and the production process. They are based on average values in production data observed with various inputs. The actual performance in a particular case can deviate from the values shown, as a function of the type of material and other aspects affecting the output. As a result, these outputs cannot be warranted as absolute or typical values.



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