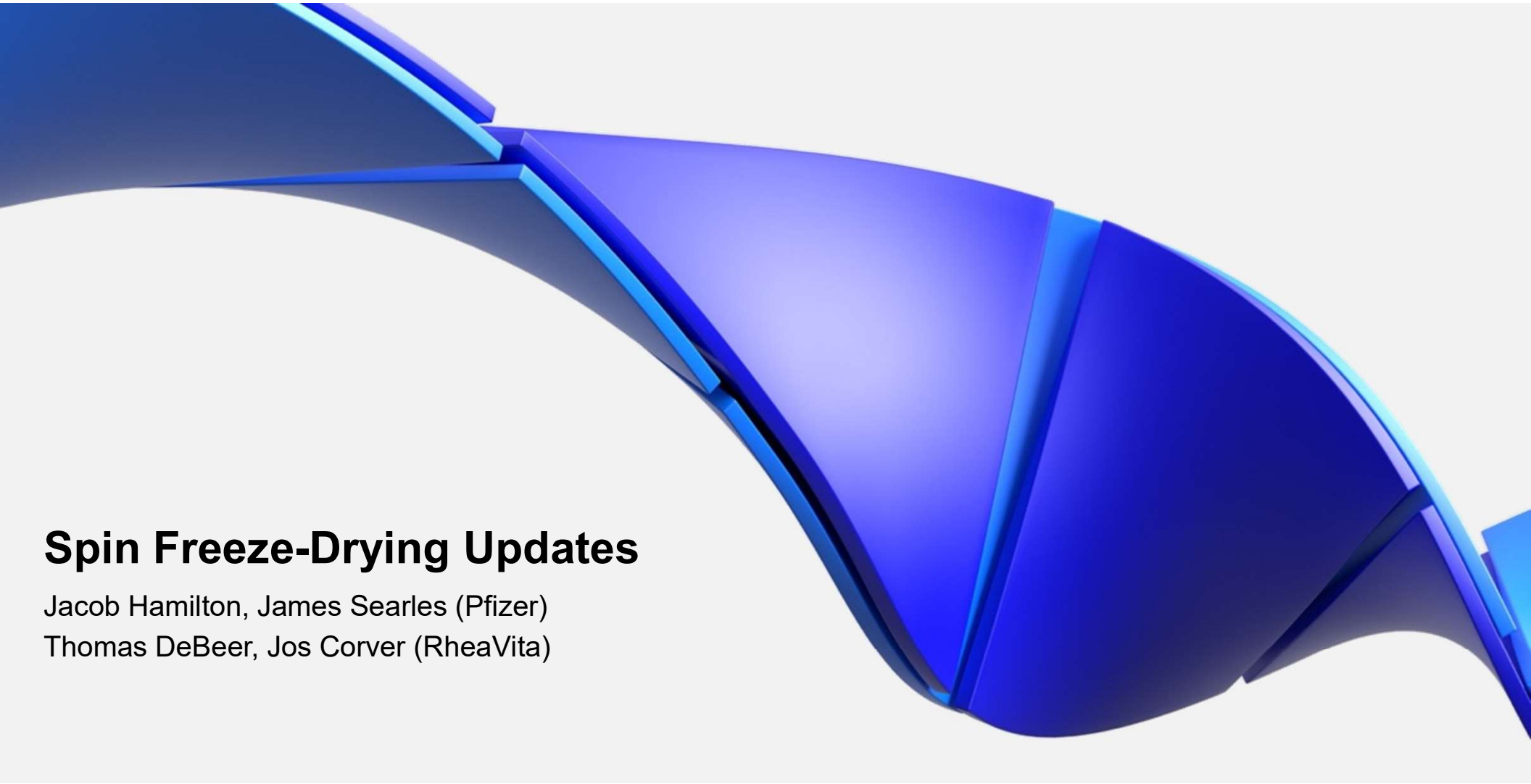
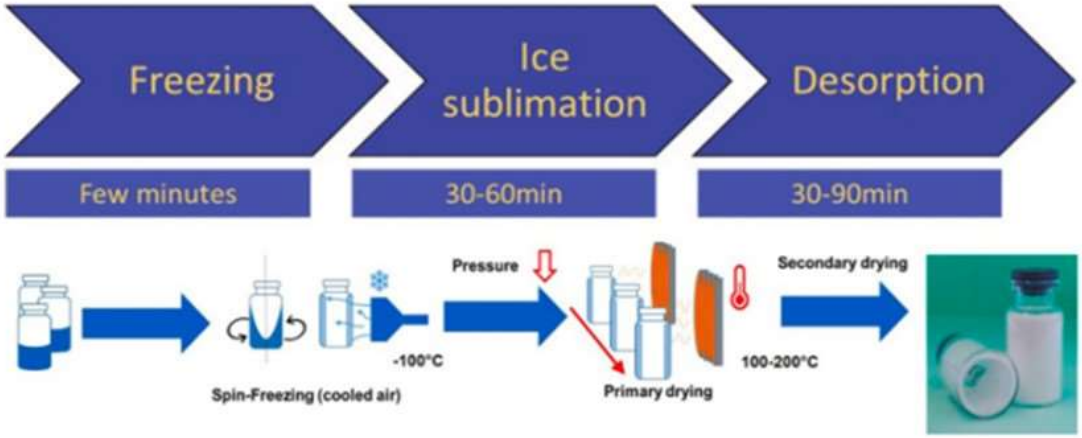


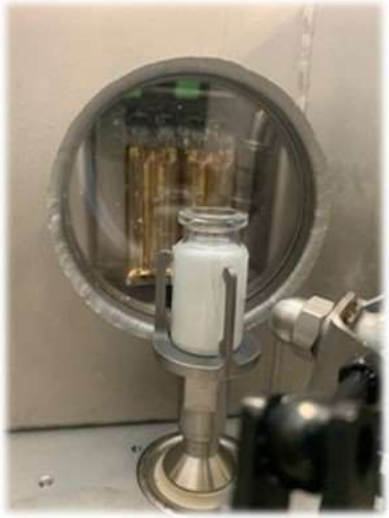
Spin Freeze-Drying Updates

Jacob Hamilton, James Searles (Pfizer)
Thomas DeBeer, Jos Corver (RheaVita)

What We Are Investigating…

- We currently operate a Single-Vial Unit (SVU) prototype for Continuous Spin Lyophilization in the lab
- Fast formulation, process development, and optimization with limited material usage





- Spin freeze and dry vials with controlled cooling and heating-same for every vial
- Freezing profiles and rates that are not the same as with shelf lyophilization
- Process monitoring and control uses IR imaging
- Faster process due to higher surface area of ice interface and well controlled energy delivery

Potential applications of Spin Freeze-Drying

- Low-throughput / high-value products

Pros

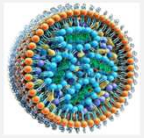
- Continuous process
- Individual vial feedback control to improve product quality
- Faster freezing and drying
- Improved visual inspection
- 40x faster drying

Cons

- Low-throughput at full scale compared to shelf lyo
- Complex mechanical parts, instruments, and controls
- Vacuum load-locks
- Separate chambers for freezing, primary drying, and secondary drying

Summary of Work – Experiment and Formulations

- **Study 1: Lipid Nanoparticles**
  - Formulation: LNP in sucrose-buffer matrix, pH 7.4
  - Objective: To investigate the effect of conventional FD vs. Spin FD on product attributes
  - Does fast freezing translate to a less decrease in %Encapsulation efficiency typically associated with LNPs post freeze-drying and reconstitution?



- **Study 2: Adeno Associated Virus (AAV)**
  - *Formulation*: AAV in sucrose-buffer-surfactant matrix, pH 7.4
  - Objective: Investigate the effect of conventional vial FD vs. spin lyo (fast freezing) AAV
  - Critical to evaluate the benefits of fast freezing for low volume, high value products (viral vectors)

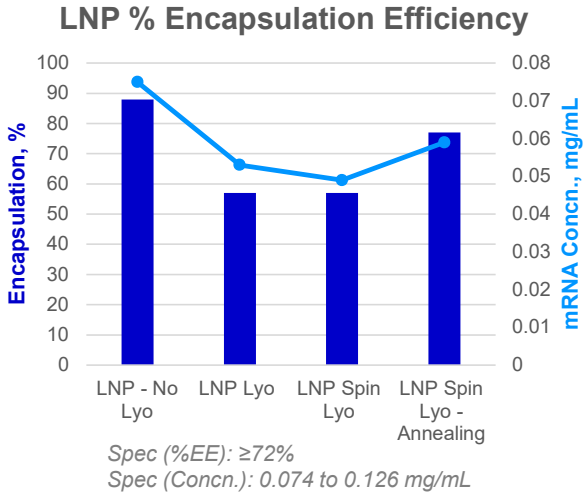
- **Study 3: Spin Lyo Protein**
  - Formulation: Low concentration protein in mannitol-sucrose-isotonicity agent matrix, pH 7.4
  - Objective: Test a Mannitol-Sucrose-Protein formulation with Spin FD and assess mannitol hemihydrate.
  - Assessing claim that annealing may not be needed for formulations containing mannitol.

- **Business case evaluation in progress**
  - Commercial - Ability to process 250 vials/day GMP grade DP

Summary of Work – Results

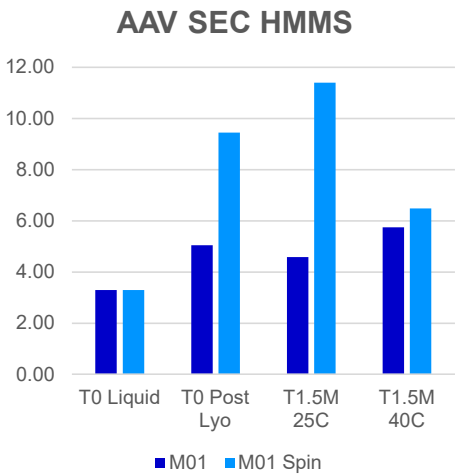
- **Study 1: Lipid Nanoparticles**

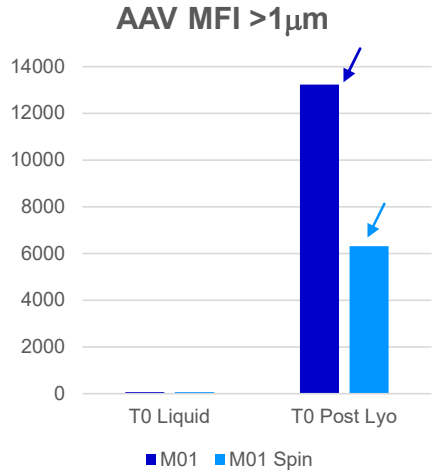
  LNP %encapsulation better on samples with spin freeze + annealing



- **Study 2: Adeno Associated Virus (AAV)**

  AAV link between SEC and MFI
  Higher aggregation in spin lyo samples





- **Study 3: Spin Lyo Protein**

  High moisture cakes, mannitol hemihydrate present. Will need to further optimize cycle - most likely annealing needs to be implemented or high secondary drying temperature needs to be used

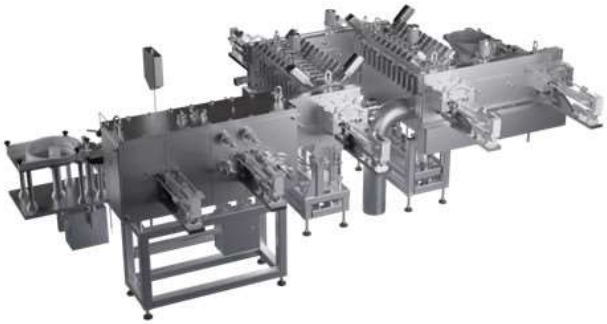
- In summary: Further evaluation of Spin freeze-drying needs to be performed. Modifications to software allowing annealing, slow ramps and wall temperature controls are needed

From single vial to production scale: maturity state

Single and multi-vial lab scale units are available, pilot scale in development

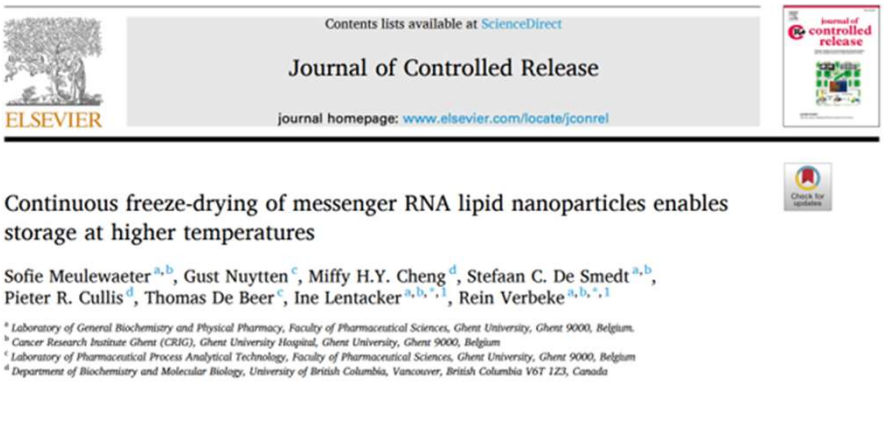
Single-Vial Unit (SVU)
R&D equipment including software & digital twin for fast product & process development with very low product consumption

Multi-Vial Unit (MVU)
Available for evaluation studies by pharmaceutical companies for stability analysis and formulation optimization



GMP-FLEX
GMP production scale continuous freeze-dryer: custom made assembly

Application of Continuous Spin Freeze-Drying for Preservation of LNPs (RheaVita)



Contents lists available at ScienceDirect

Journal of Controlled Release

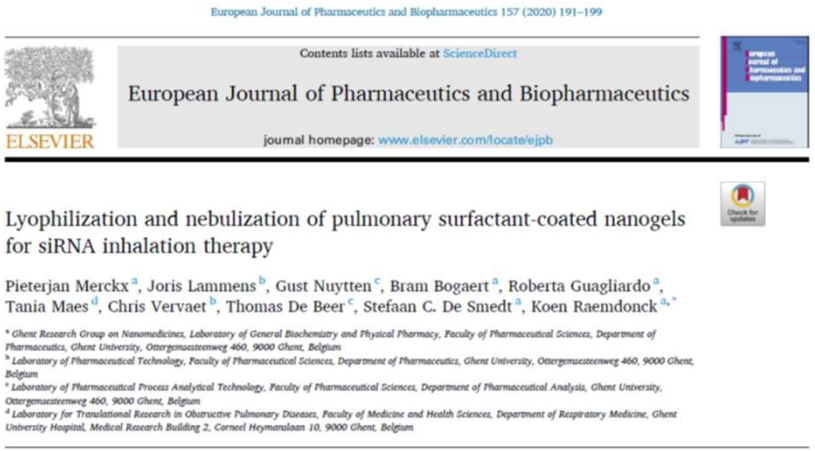
journal homepage: www.elsevier.com/locate/jconrel

ELSEVIER

Continuous freeze-drying of messenger RNA lipid nanoparticles enables storage at higher temperatures

Sofie Meulewaeter[a,b], Gust Nuytten[c], Miffy H.Y. Cheng[d], Stefaan C. De Smedt[a,b], Pieter R. Cullis[d], Thomas De Beer[c], Ine Lentacker[a,b,*,1], Rein Verbeke[a,b,*,1]

[a] Laboratory of General Biochemistry and Physical Pharmacy, Faculty of Pharmaceutical Sciences, Ghent University, Ghent 9000, Belgium.
[b] Cancer Research Institute Ghent (CRIG), Ghent University Hospital, Ghent University, Ghent 9000, Belgium
[c] Laboratory of Pharmaceutical Process Analytical Technology, Faculty of Pharmaceutical Sciences, Ghent University, Ghent 9000, Belgium
[d] Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, British Columbia V6T 1Z3, Canada



European Journal of Pharmaceutics and Biopharmaceutics 157 (2020) 191–199

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

ELSEVIER

Lyophilization and nebulization of pulmonary surfactant-coated nanogels for siRNA inhalation therapy

Pieterjan Merckx[a], Joris Lammens[b], Gust Nuytten[c], Bram Bogaert[a], Roberta Guagliardo[a], Tania Maes[d], Chris Vervaet[b], Thomas De Beer[c], Stefaan C. De Smedt[a], Koen Raemdonck[a,*]

[a] Ghent Research Group on Nanomedicines, Laboratory of General Biochemistry and Physical Pharmacy, Faculty of Pharmaceutical Sciences, Department of Pharmaceutics, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[b] Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Department of Pharmaceutics, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[c] Laboratory of Pharmaceutical Process Analytical Technology, Faculty of Pharmaceutical Sciences, Department of Pharmaceutical Analysis, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[d] Laboratory for Translational Research in Obstructive Pulmonary Diseases, Faculty of Medicine and Health Sciences, Department of Respiratory Medicine, Ghent University Hospital, Medical Research Building 2, Corneel Heymanslaan 10, 9000 Ghent, Belgium

"*We demonstrated that lyophilization of mRNA LNPs is an attractive strategy to enhance the stability of mRNA vaccines at higher temperatures, as lyophilized mRNA LNPs preserved their functionality when stored at 4°C, 22°C and even at 37°C for a period of 12 weeks*"

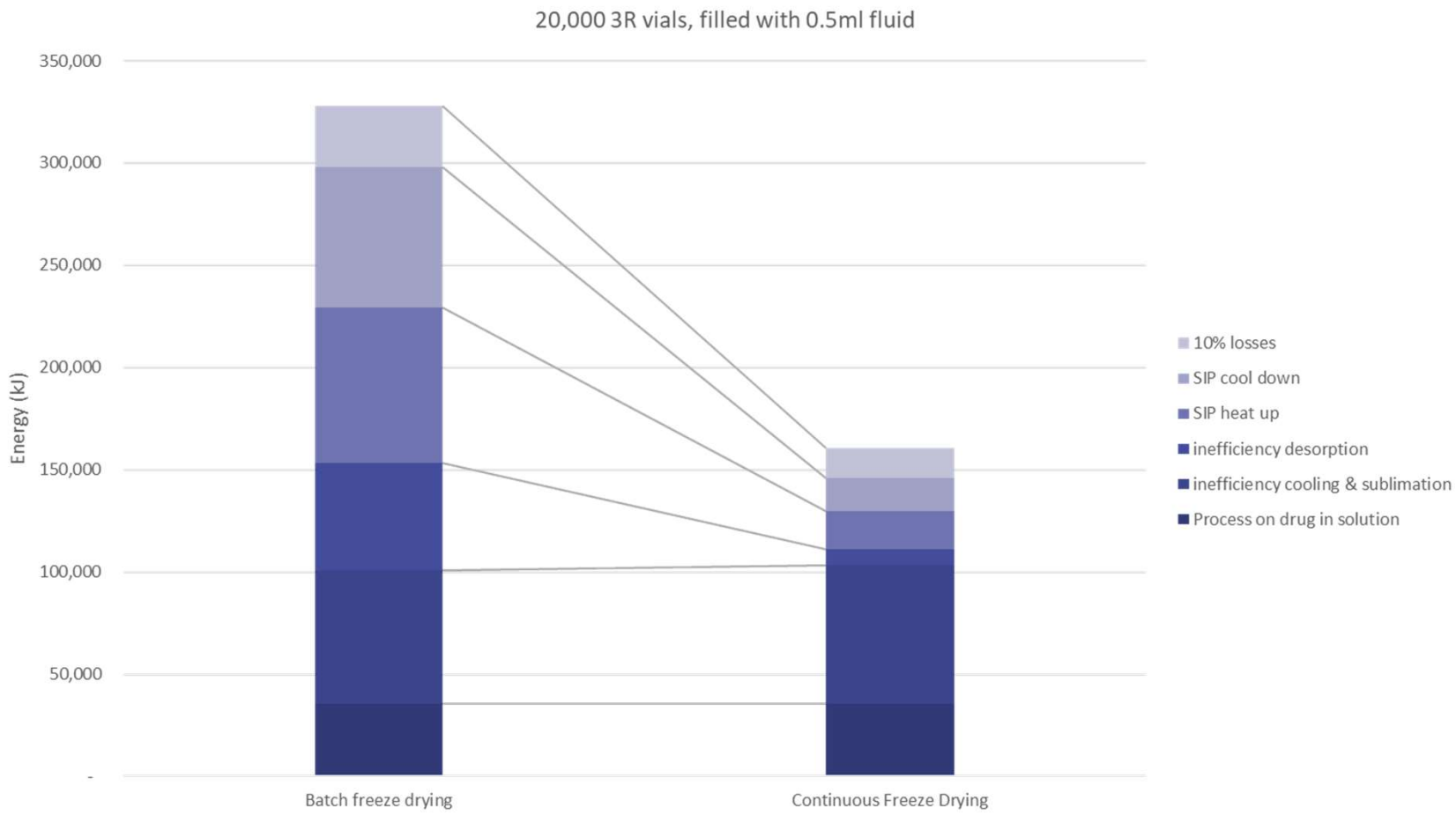
Case study RheaVita technology > batch freeze-drying (higher encapsulation efficiency)

- Wider range of process settings possible with RheaVita technology
- e.g., wider range of very controlled cooling and freezing rates
- Better control of residual moisture content
- Much shorter time under vacuum

Benefits of Continuous Process (RheaVita)

- **Continuous and controlled** freeze-drying technology for **unit doses** with unique features addressing all challenges associated with batch freeze-drying
- **Very fast** process & throughput – hours instead of days
- **Improved Quality Assurance** – decreased defect levels – approaching zero
  - Identical process conditions for each vial
  - Process visualization methods **(PAT)** provide 100% unit monitoring, control, inspection
  - Same **quality** from pre-clinical to production – no scale-up issues
- **Inherent high potential for RTR from process understanding, control and 100% inspection**
- Equivalent **efficacy and safety**
- No large batch rejections
- Proven **process understanding** via validated mechanistic models and **digital twins (model-based design)**
- **Fast** formulation and process **development** with limited material needs
- **Flexibility/production efficiency:** rapid change-over, short CIP/SIP times, flexible volumes
- **Faster time-to-market** for biopharmaceuticals (reduction > 1 year estimated)
- Reduced **ecological footprint** and **operational costs**
- **Enabler for products**
  - Wide controlled cooling & freezing rate
  - Low Tg' & Tc products
  - Speeds up reconstitution

Energy Consumption: Batch vs Continuous (RheaVita Assessment)



Maturity State of Technology

Activity	Spray Freeze-Drying	Spin Freeze-Drying	Foam Drying
POC at laboratory scale for different types of products	Shown for multiple products	Shown for multiple products	
Stability of dried products	Shown for multiple products	In evaluation	
Pilot/commercial scale equipment availability for aseptic manufacture	Yes	In development	
Process understanding at commercial scale (reliable models)	Reliable model for spray freezing exists, drying model is in development	Model was developed and validated at laboratory scale	
Successful tests at pilot/commercial scales	Performed	Not available	
Infrastructure readiness	LN2 lines available at some commercial sites	LN2 lines available at some commercial sites	
Regulatory bodies awareness	Some regulatory agencies are aware of technology, aseptic manufacturing must be shown at scale	Some regulatory agencies are aware of technology, aseptic manufacturing must be shown at scale	

- Proven at commercial scale
- Proven at laboratory scale
- In development