Celeventus

Thermostable vaccines
using a new scalable & gentle process to dry sensitive biologically active substances in room temperature.

Stockholm, Sweden 2024-11-13
Fernando Acevedo, PhD (fernando@celventus.com)
Jonas Forsslund, PhD (jonas@celventus.com)

About this presentation

We are currently (2024-11-13) looking for:

1. Interested partners that want to do research with our technology, in particular those who have a difficult-to-dry “nich” vaccine or substance where conventional drying methods are too limited.

2. Investors or grant opportunities to fund verification studies and outreach

3. Opportunities to make this invention useful to humankind for profit or non-profit!

News

Recent milestones:

October 2024: Promising result from study of drying of real-world oral cholera vaccine (see slide 7b)

Soft funding 2023/2024:

Södertälje Science Park Infrastructure Grant 100 kSEK

ALMI Verification 100 kSEK

ALMI Innovationslån 300 kSEK

Thermostable vaccines tech

Opportunity	New scalable technology to dry vaccines & other biological substances with maintained activity
We have	Patented (2023) invention – a **mesh-nebulizer-based fast air flow spray dryer** for gentle drying solutions into a dry powder homogenous in particle size.
We're looking for	Pilot users and interested parties that need to **gently dry a sensitive vaccine** candidate or other substances while preserving their biological activity.
Relevant substances	We're targeting substances/structures sensitive to **shear stress** or **temperature** that would be difficult to dry in conventional spray dryers.

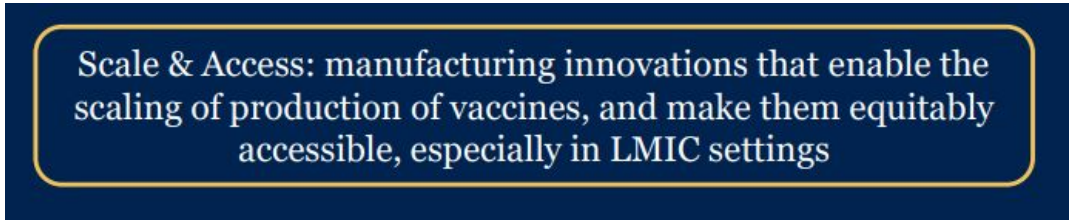
1. Background: why drying

Isolated biological components are important in medicine, biology, pharmacology or food industry, such as proteins, enzymes, nucleic acids, vaccines and subcellular/cellular structures. For these components to have any useful effect, they must retain their biological activity and not be damaged.

However, the biological activity decreases rapidly when separated from their original water-based environment. They become unstable, which makes it difficult to save or transport them, such as enzymes or vaccines.

Being able to dry the biological material with retained activity enables or facilitates handling, transport, and storage over time. Especially suitable for equitable access in Low- and Middle income countries.

Furthermore, dry powder homogenous in particle size has potential for direct delivery to the lungs or other novel administration routes.



Pictures from CEPI CFP *Innovative technologies to improve vaccine thermostability (2023)*

2. Ideal when drying sensitive substances & structures

When selecting a drying process for sensitive biologically active substances /structures, we believe the following attributes are of importance.

1. Low temperature: Almost all biologically active materials are temperature-sensitive. Many of the available spray drying processes involve heating of the material or air before drying, and freeze-drying obviously involve freezing.

2. Avoid shear stresses: the stress induced by e.g. nozzles when spraying are potentially very harmful to sensitive substances.

3. Fast liquid-to-powder transition: If the transition from solution/suspension of the material to dry powder is very fast (< 5sec) the drying induced structural changes in the biological material are minimized.

4. Ability to dry large molecules with preserved activity: Large molecules are often more sensitive to stress induced during the drying process. The larger the molecule, the more importance of a gentlge drying process.

5. Scalable process: The same principle should be able to be used in a laboratory setting as well as in production, the transition to production is faster.

6. Minimizing the requirement of protective substances during drying process: Mitigating stresses during drying process often require advanced formulations and extensive use of excipients.

3. Selection of Drying Methods in Litterature

The pros and cons of different drying methods has been discussed in the literature.

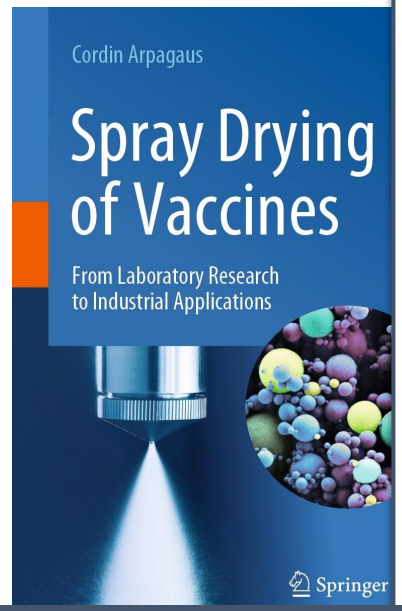


Table 3.16 Comparison of different drying methods for biopharmaceuticals and vaccines

Drying method	Benefits	Challenges
Freeze-drying	+ Low-temperature drying + Low moisture content (controlled) + Elegant cake appearance + No powder filling required (dosed in vials) + Aseptic processing + Industrial experience (established for vaccines)	– Long processing time – No particle engineering – Freezing stress and exposure to ice-water interface – Lower capacity (batch) – Equipment costs (vacuum pump) – Energy consumption (process efficiency)
Spray drying	+ Economic process + Fast drying process + High capacity + Particle design (e.g., free-flowing powder, good aerosolization properties, vaccine encapsulation) + Industrial experience with pharmaceuticals (no spray-dried vaccine commercial)	– Atomization stress (shear, air–liquid interface) – Thermal stress – Yield (50 to > 70% lab-scale, > 95% industrial scale) – Higher moisture content than freeze-drying – Special equipment required for aseptic processing – Aseptic powder filling

Arpagaus, C. (2023). Spray Drying of Vaccines: From Laboratory Research to Industrial Applications. Cham: Springer International Publishing. p. 165

4. Selection of Drying Methods, continued

		Main benefits	Main challenges
ESTABLISHED	**Freeze drying***	• Low-temperature • Cake appearance (no powder and low residual moisture) • Aseptic processing	• Long processing time and low capacity • Equipment and energy intensive • No particle engineering possibility and freezing stress
ESTABLISHED	**Spray drying***	• Fast processing time • Particle design possibility • High capacity and scalability	• Stress (shear stress, thermal stress, air-liquid interference) • Higher moisture content • Aseptic handling required
NOVEL	***Slow* low temperature mesh nebulizer-based drying (LaminarPace™)****	• No atomization (shear, air-liquid interface) or thermal stress • Market availability (albeit limited) • Suitable for small scale drying	• Not for high viscosity preparations • Not for concentrations > 25% • Slow and limited to small amounts
NOVEL	***Fast* low temperature mesh nebulizer-based drying (Celeventus)**	• No atomization (shear, air-liquid interface) or thermal stress • Short drying time • Scalable from small to large quantities	• Not for high viscosity preparations • Not for concentrations > 25% • New to market

*Arpagaus, C. (2023). Spray Drying of Vaccines: From Laboratory Research to Industrial Applications. Cham: Springer International Publishing. p. 165, **p. 176

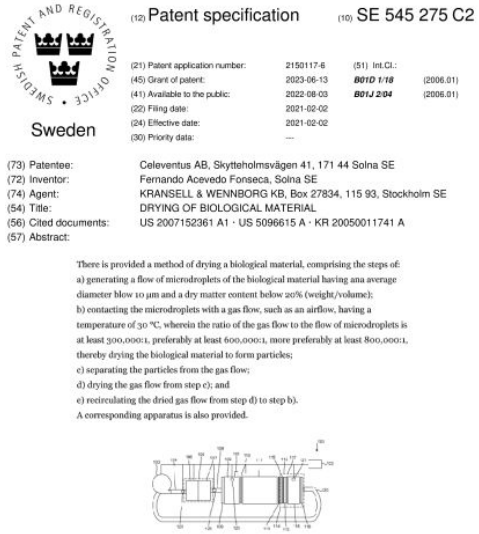
5. Celeventus Technology in Detail

1. The generation of micro droplets from solutions/suspensions is achieved by mesh ultrasonic nebulisers. Upon drying, the droplets of these nebulisers can generate particles with controllable and narrow size distributions with MMAD of around 5 microns or smaller.

2. The micro droplets generated by the mesh nebuliser are ejected perpendicularly to the flow direction of the drying media (air/nitrogen) , flowing in an horizontal path. This increases the efficiency of the drying chamber since the micro drops do not follow the drying media gravitationally.

3. The generation of micro droplets in mesh nebulisers is free of shear stress as compared to jet nebulisers. This prevents the possible damage on the native conformation, generally required for the activity in biologically active molecules/structures, by shear stress forces in jet nebulisers.

4. The drying process is carried out at room temperatures or lower. No heating is required. This is achieved by the high ratio between the volume of drying media (air or nitrogen) relative to the volume of liquid sample to be dried. As an example at room temperature (25C), the maximum amount of water that one cubic meter dry air (Rh = 0%) can take out from a nebulised sample to be dried (final relative humidity Rh =10%) is 2,5g which means that 1000L dry air are required to dry a 2,5 mL sample.



(12) Patent specification (10) SE 545 275 C2

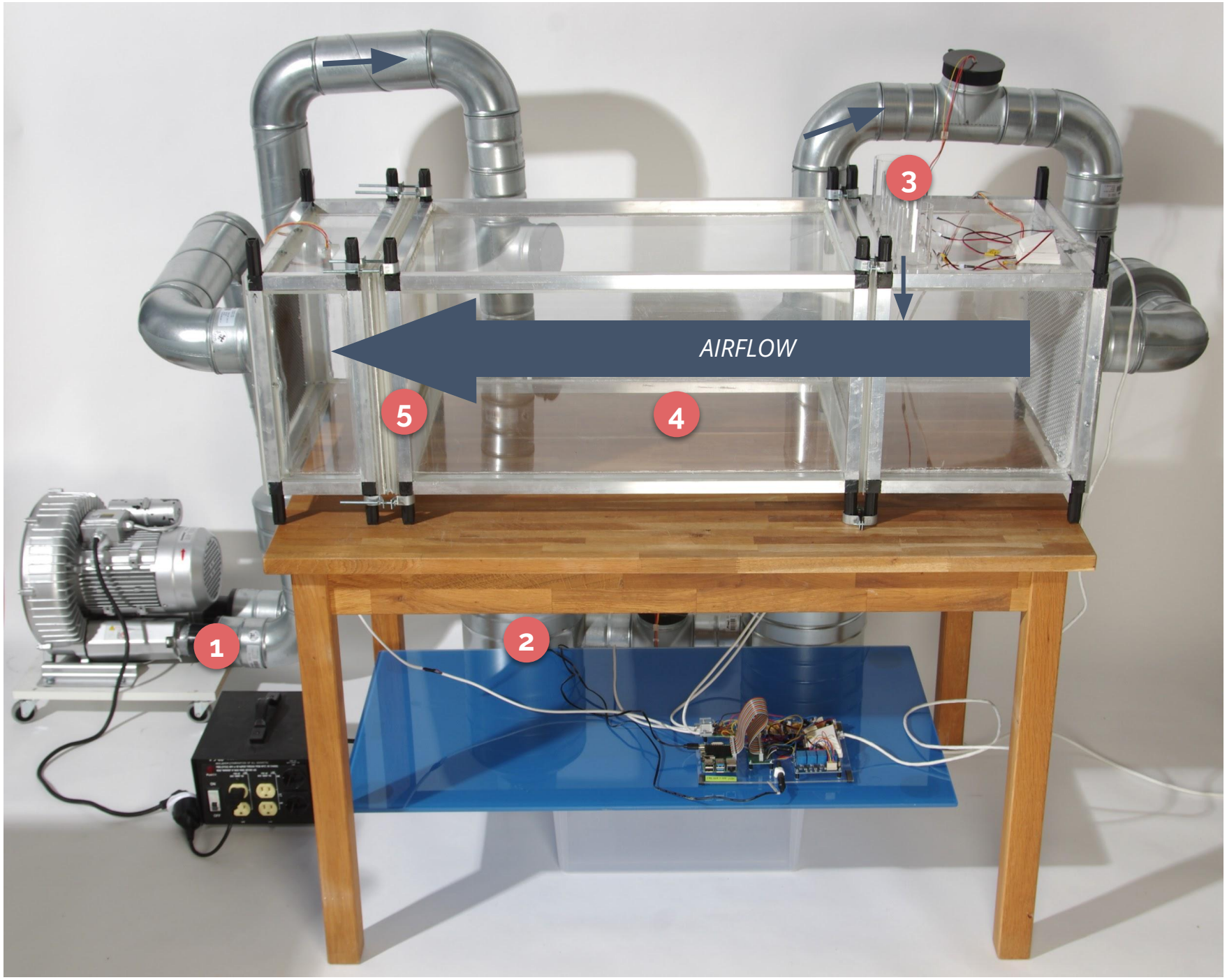
Sweden

(21) Patent application number:	2150117-6	(51) Int.Cl.:	
(45) Grant of patent:	2023-06-13	***B01D 1/18***	(2006.01)
(41) Available to the public:	2022-08-03	***B01J 2/04***	(2006.01)
(22) Filing date:	2021-02-02		
(24) Effective date:	2021-02-02		
(30) Priority data:	---		

(73) Patentee: Celeventus AB, Skytteholmsvägen 41, 171 44 Solna SE
(72) Inventor: Fernando Acevedo Fonseca, Solna SE
(74) Agent: KRANSELL & WENNBORG KB, Box 27834, 115 93, Stockholm SE
(54) Title: DRYING OF BIOLOGICAL MATERIAL
(56) Cited documents: US 2007152361 A1 · US 5096615 A · KR 20050011741 A
(57) Abstract:

There is provided a method of drying a biological material, comprising the steps of:
a) generating a flow of microdroplets of the biological material having ana average diameter blow 10 µm and a dry matter content below 20% (weight/volume);
b) contacting the microdroplets with a gas flow, such as an airflow, having a temperature of 30 °C, wherein the ratio of the gas flow to the flow of microdroplets is at least 300,000:1, preferably at least 600,000:1, more preferably at least 800,000:1, thereby drying the biological material to form particles;
c) separating the particles from the gas flow;
d) drying the gas flow from step c); and
e) recirculating the dried gas flow from step d) to step b).
A corresponding apparatus is also provided.

Acevedo, F. (2023) Drying of biological material. Patent no. SE 545275



6. Celeventus Technology in Detail: Working Prototype

1. Compressor / air flow generation
2. Air cooling / drying chamber (behind table)
3. Liquid substance input, atomization
4. Aerosol fast drying chamber
5. Collection of dry matter

A 1200 cm^2 cross section area with a maximum capacity of **240 mL/hour**.

Concepts for **large scale production** (e.g. for 10 million doses of vaccine) has been considered and is deemed feasible.

7. Results & Early Verification

Multiple tests have verified the technology by drying enzymes at 5 to 30 gram/h, >80% yield of substance & preserved activity

Two enzymes, Alpha Amylase and Lactase tested

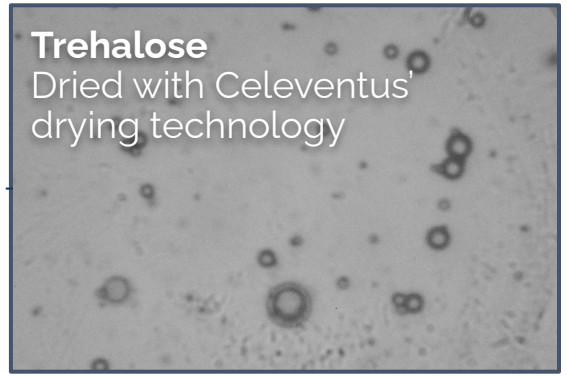
5 g each diluted in 150 mL Phosphate Saline Buffer containing 15 g Trehaloset

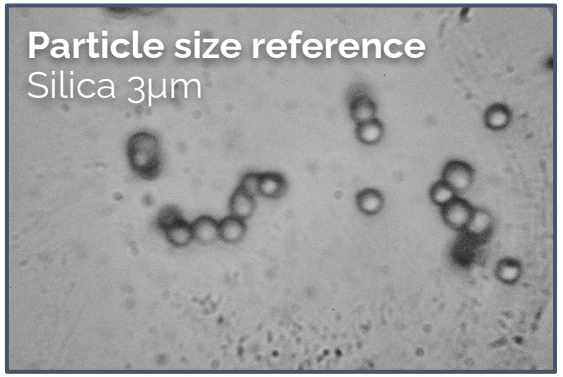
Dried ~1hr through Celeventus' technology

at normal room temperature and pressure

80% yield with biological activity preserved

collected, weighed and measured for biological activity





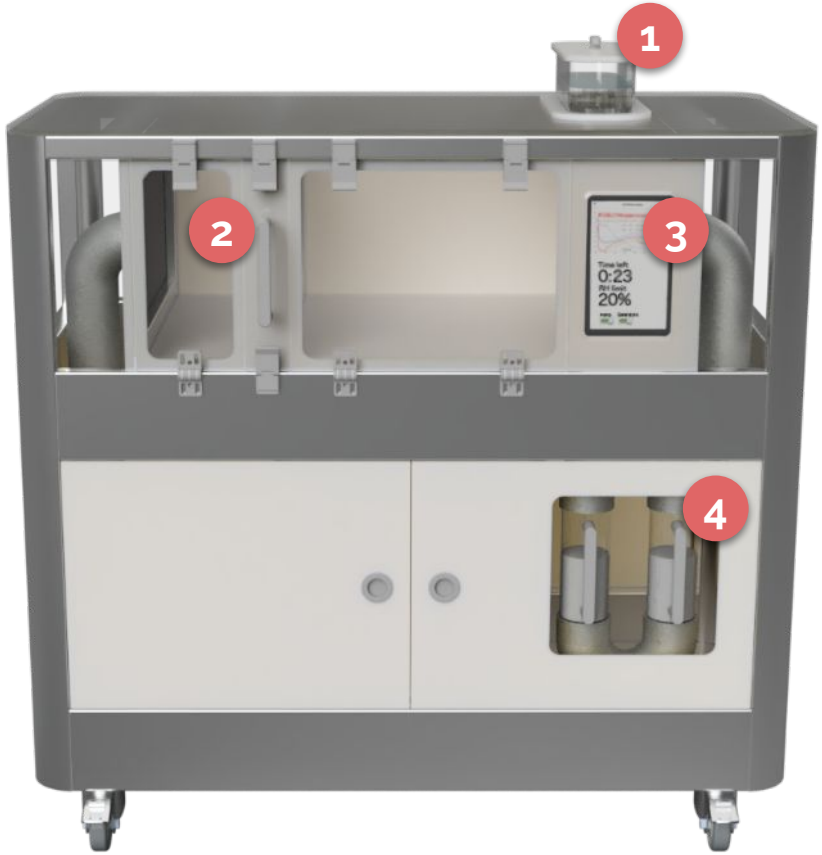
7b. Results Cholera Vaccine

News 2024-10-21
First real-world vaccine being dried with Celeventus technology!

Celeventus has been invited to collaborate with world-renowned vaccine researcher professor Jan Holmgren and his research group at University of Gothenburg to evaluate its drying technique for dry vaccine production.

Professor Jan Holmgren, recently recognized for the development of the first cholera vaccine, leads a research group where they are actively working on producing a thermostable variant of the dried oral cholera vaccine in capsule form, currently using freeze-drying. The first experiment using Celeventus fast-air nebulizer-based spray-drying technology has now been completed where the vaccine has been dried and evaluated for maintained activity in a set of tests, with promising results. To verify the long-term ability of the powder to resist a heated environment it will now be stored at 40’C and tested again.

8. Commercial Prototype for R&D under development



Key Benefits

- Technology based on drying in large and very fast air flow.
- Stand-alone all-in-one equipment, easy to use and maintain in a laboratory setting
- Supports large quantities > 200ml already in prototype. A variant for small quantities are in the making.
- Fast batches (200 ml/h)
- 100x larger quantities enables new research and production.
- Opens for larger markets than mRNA
- Modular - possible to use with existing high pressure vortex fan system if preferred.

1. Input of liquid substance
2. Collection of dry material
3. Control panel and live statistics
4. Replacement of drying material

9. Next Steps

We are looking for partners to validate the technology with pilot studies **at lab scale** to investigate wheter there are substances that we can dry for which alternative methods fall short.

Subsequently we will look at how to scale production for that particular candidate once identified. We believe that the technology is scalable due to the ability to increase air flow, number of nebulizers working in parallel and the overall technical simplicity and low cost of components.

So far our technology is validated internally: drying enzymes: alfa-amylas and lactase with repeated success in terms of preserved activity.

We have also done experiments with subcellular structures that are

- Sensitive to temperature and shear stress
- Easy to obtain
- Easy to validate

We have successful preliminary results but not yet published.

We are happy to collaborate and joint publications if desired.

10. References

- **Acevedo, F**. (2023) Drying of biological material. Patent no. SE 545275
- Arpagaus, C. (2023) Spray Drying of Vaccines: From Laboratory Research to Industrial Applications. Cham: Springer International Publishing. p. 165, p. 176
- Gerde, P., Sjöberg, C. O., & **Acevedo, F**. (2010). The laminarpace spray dryer: producing small portions of fine powders at ambient temperatures in high yields. In Respiratory Drug Delivery (Vol. 2, pp. 605-608).
- Soltani, S., Gerde, P., **Acevedo, F**., & Rasmuson, A. (2015). Counter-current spray drying with stream separation: Computational modeling of a novel dryer design. Chemical Engineering Research and Design, 93, 163-173.

Thanks for your consideration

Celeventus

Thermostable vaccines
using new gentle process to dry biologics

Fernando Acevedo, PhD (fernando@celventus.com)
Jonas Forsslund, PhD (jonas@celventus.com)