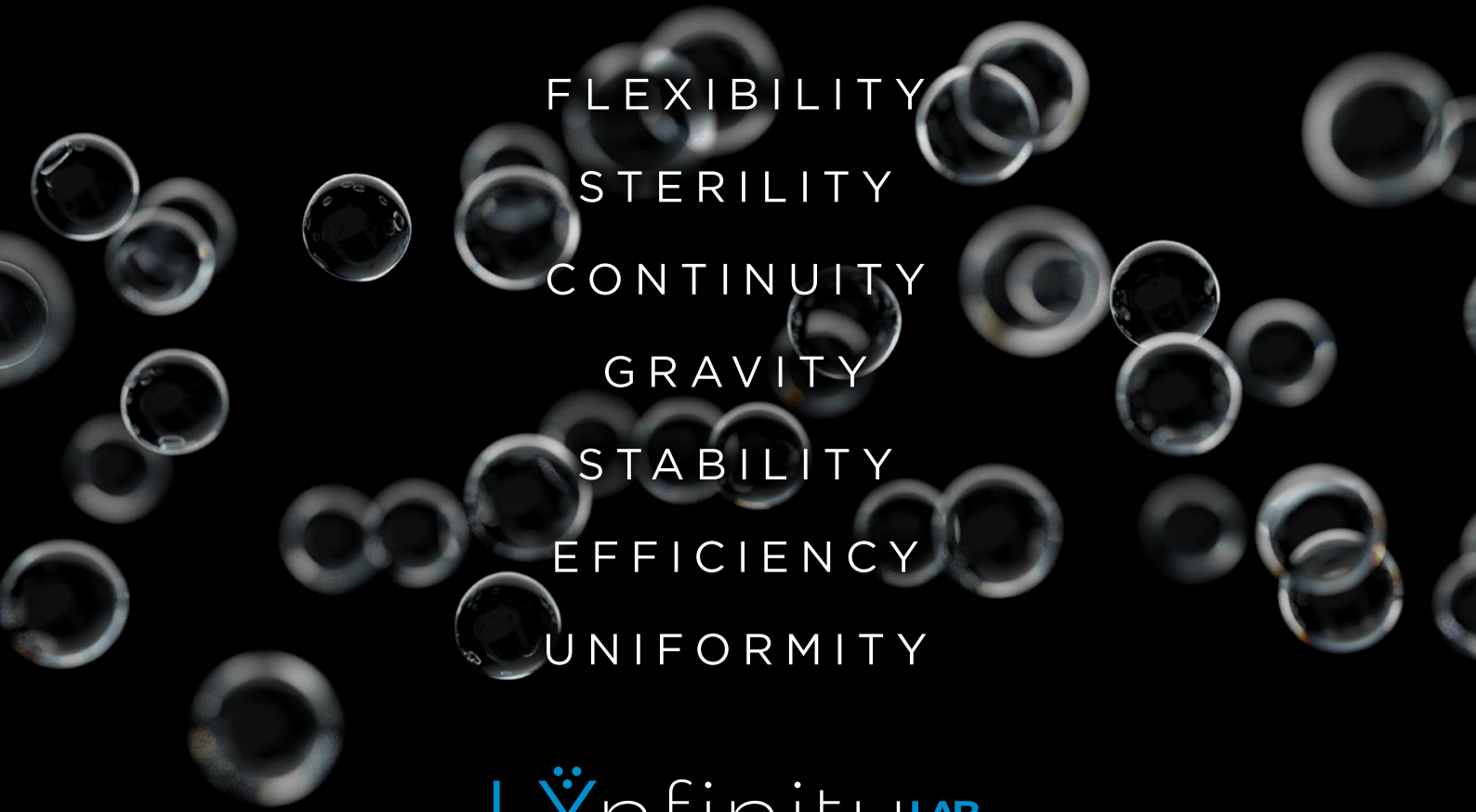
IMA LIFE

Aseptic Processing & Freeze Drying Solutions

LYnfinity

CONTINUOUS SPRAY FREEZE DRYING



FLEXIBILITY

STERILITY

CONTINUITY

GRAVITY

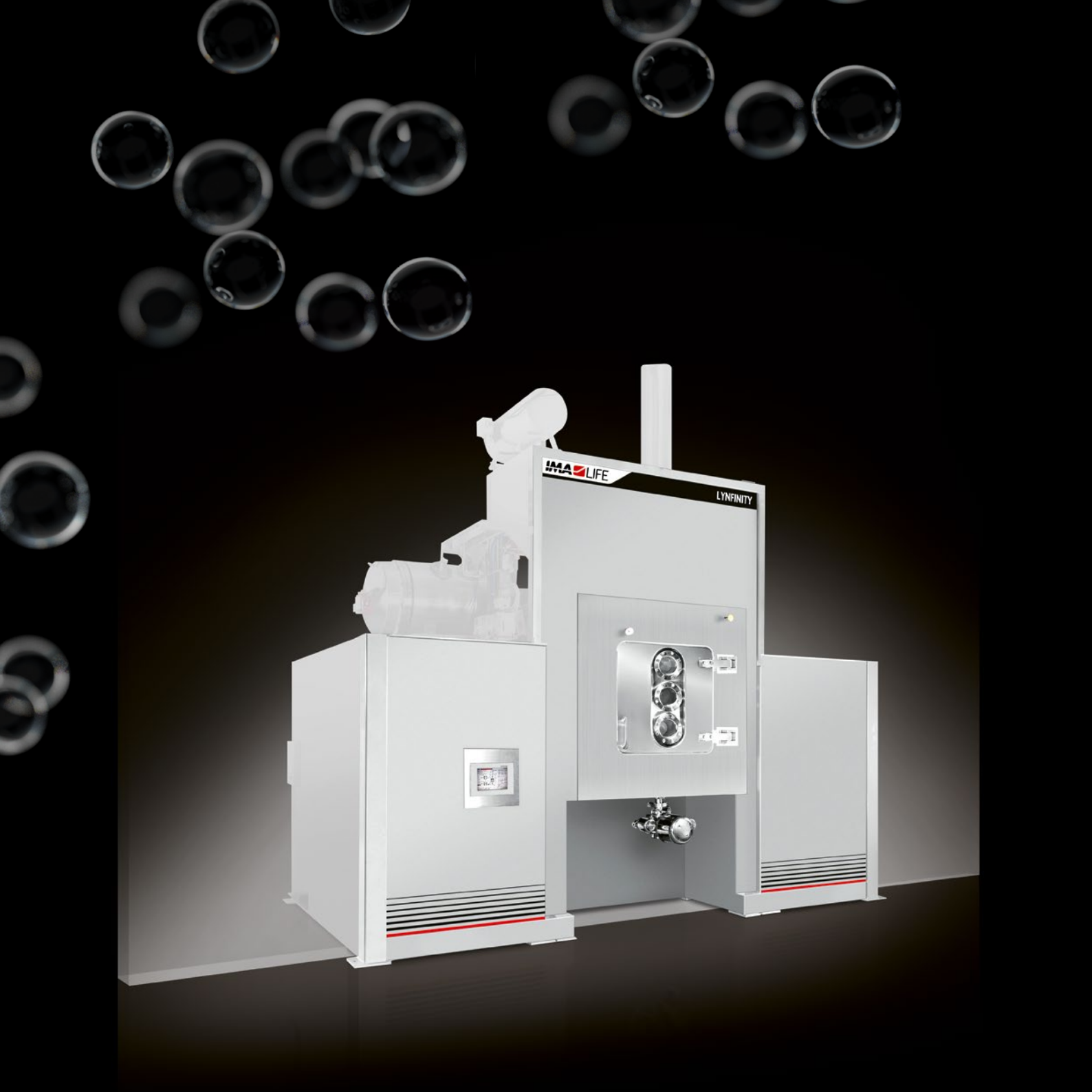
STABILITY

EFFICIENCY

UNIFORMITY

LYnfinity LAB

SPRAY FREEZING MODULE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LYNFINITY IS JUST A DROP AWAY

Conventional freeze-drying in aseptic conditions is typically designed for vials, or bulk product in trays, placed directly on the shelf of a freeze dryer. Traditionally, a batch process is both time consuming and energy intensive. The drying rate is controlled by setting the shelf temperature and chamber pressure in the product chamber. Poor thermal contact between the shelf and the containment is the rate-limiting resistance to heat transfer. Moreover, the drying rate in such a configuration is a function of the coldest front in the product volume, the sublimation front. With such findings, it becomes apparent that even though our process understanding has improved in leaps and bounds, its application to designing an efficient process-equipment configuration has not. Thus, there is a need to re-think the heat and mass transfer to improve process efficiency.

THE LYNFINITY TECHNOLOGY FOCUSES ON BRINGING TO MARKET A ROBUST YET GENTLE CONTINUOUS ASEPTIC PROCESS FOR SPRAY-FREEZE-DRYING WITH AN EYE TOWARD ACHIEVING HIGH THROUGHPUT AND HIGH CYCLE EFFICIENCY.

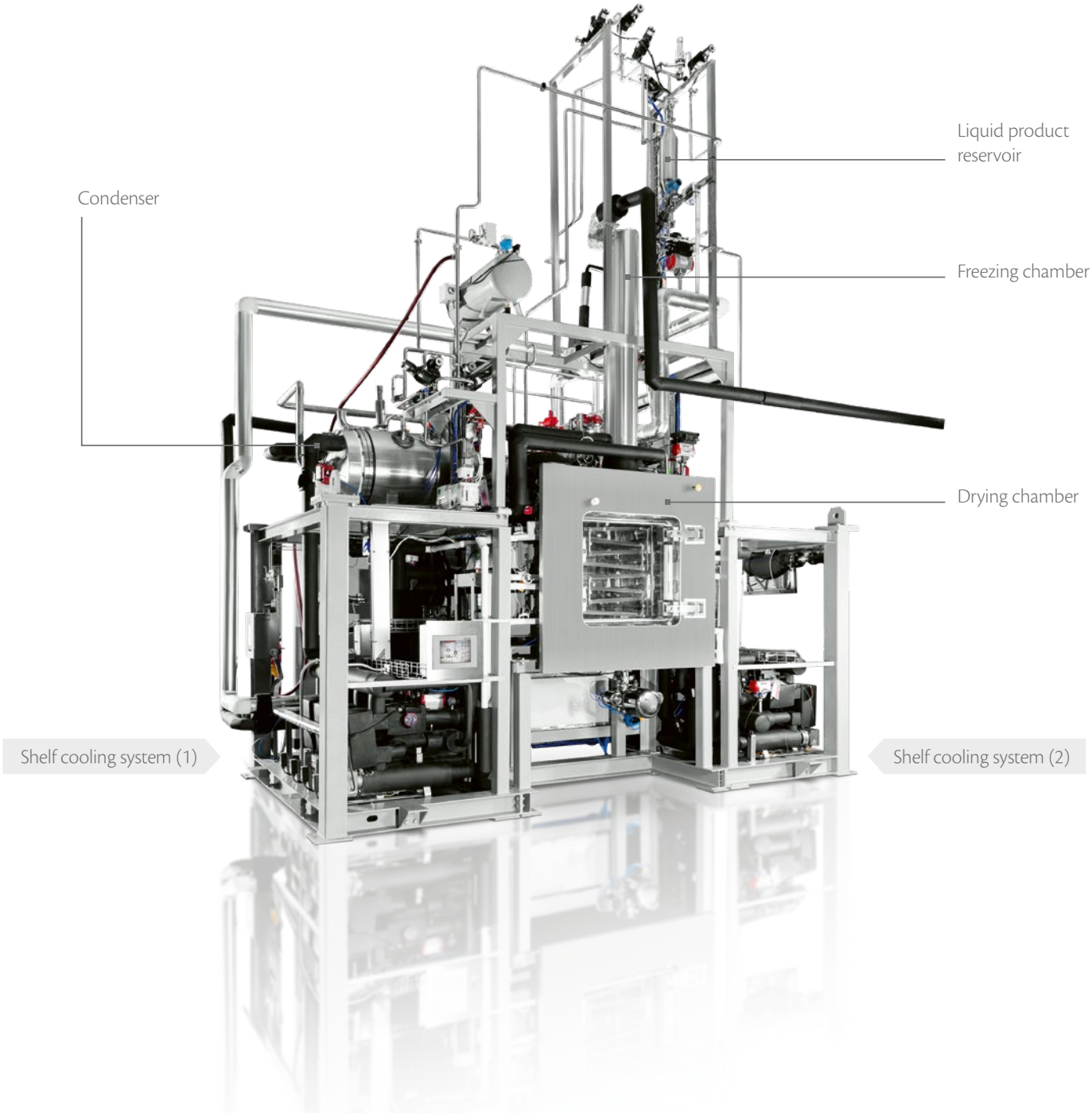
THE UNLIMITED BENEFITS OF LYNFINITY CONTINUOUS SPRAY-FREEZE-DRYING TECHNOLOGY

LYnfinity spray-freeze-drying process features a **controlled spray of liquid product into a cryogenically cooled freezing chamber**. The resultant frozen particles of the liquid product are freeze-dried in the drying module. The drying chamber contents are both transported and heated to promote rapid sublimation and prevent agglomeration.

The technology is designed to enable continuous lyophilisation, allowing processes with greater throughput flexibility. Direct thermal contact between the frozen product and the shelf provides better process control, as there is no requirement for vials or any containment, for increased heat transfer efficiency and minimized scale-up and scale-down challenges.

The continuous spray-freeze-drying process starts with bulk liquid product and ends with the discharge of dried particles, featuring total containment from formulation to powder filling. This enables higher sterility assurance levels, whereas traditional freeze-drying requires additional external material handling, for example during filling. Upon completion of drying, the uniform, dried product allows for the use of a variety of containers (vials, syringes, inhalation systems etc.).

Efficient and continuous operation leads to higher productivity and lower downtime, with potential for reduced CAPEX & OPEX.


Liquid product reservoir
Condenser
Freezing chamber
Drying chamber
Shelf cooling system (1)
Shelf cooling system (2)

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LYNFINITY TECHNICAL FEATURES

Freezing chamber

- The freezing chamber uses liquid nitrogen cooling to freeze the liquid product into frozen droplets.
- The product is sprayed into the chamber through a nozzle.

Intermediate chamber

- The intermediate chamber is an airlock between the freezing chamber and the drying chamber.
- A cooling jacket is used to keep product frozen during transfer through the chamber.

Drying chamber

- The freeze dryer chamber is a pressure vessel that houses the product shelves. The floor of the chamber is pitched to ensure drainage and product transfer.
- Horizontal nozzles within the chamber are also pitched to ensure drainage of liquids.

Product shelves

- The shelf stack consists of a series of cascading product shelves and one compensating baffle shelf that are all sloped to allow for product transfer through the drying chamber. Each shelf is designed with a serpentine path of channels through which a heat transfer fluid is passed for temperature control.
- Heat exchangers in series, through which heat transfer fluid is circulated by a pump for each shelf, allow for individual shelf temperature control.
- A system of vibratory drives is mounted from the outside of the chamber through the vacuum seals into the chamber and is fitted to pairs of shelves. The system is used to vibrate the shelves to move the product through the drying chamber in a gentle and controlled manner.

Dual ice condensers

- Dual ice condensers are located above the chamber and connected to the chamber via a vapour duct.
- The condensing surface within the condenser body comprises a number of polished stainless steel coils. Series of coils are manifolded in order to form a refrigeration circuit.

Refrigeration system

- The refrigeration system contains a low temperature liquid nitrogen CUMULUS® cooling unit. The CUMULUS® cooling system utilizes a liquid nitrogen supply as the refrigeration source.
- A heat transfer fluid heat exchanger is utilized to cool the main cooling heat transfer fluid.
- The refrigeration circuit is equipped with necessary cryogenic modulating control valves, heat exchangers, and condensers.

Vacuum system

- During a freeze-drying cycle the vacuum system is used to evacuate the chambers and condensers utilizing two two-stage, oil-sealed, rotary vane vacuum pumps equipped with an oil mist filter and gas ballast.
- An additional two-stage, oil-sealed, rotary vane vacuum pump equipped with an oil mist filter and gas ballast is used for the intermediate transfer of product to and from the drying chamber.

Controls

- The eLyomaster modular control system is based on industry standard iFix SCADA. The PLC controls all machine functions, performs interlock checks, and generates process/device alarms.

Equipment size

- LYnfinity dryer occupies about 5m x 4.5m x h 4.2m, whereas a traditional freeze dryer with equivalent throughput occupies 12m x 9.5m x h 3.5m, including the stoppering piston.

LYnfinity Spheres

LYnfinity Spheres

LYO Cake


LYnfinity
SPRAYING
FREEZING
DRYING

SPRAYING

flexibility
sterility
continuity

FREEZING

gravity
homogeneity
efficiency

DRYING

uniformity
stability
productivity

KEY FEATURES OF LYNFINITY'S CONTINUOUS PROCESS

- Designed for **continuous process** from fermentation to final packaging;
- Greater throughput **flexibility**: minimization of scale up and scale down challenges;
- Better **quality attributes**: improved product uniformity through a gentle drying process;
- **Total containment** from formulation to powder filling: higher sterility assurance level (SAL);
- **Higher productivity and lower downtime**: allows increased formulation concentration, reduced drying time, reduced vapour flow limitation, direct heat transfer from shelf, minimal product resistance from cake thickness;
- **Reduced running OPEX** costs: reduced operating and utilities costs and reduced number of operators;
- **Reduced CAPEX** i.e. capital investments: equipment foot print reduction and no loading system requirements;
- **Faster reconstitution time**: increased Specific Surface Area (SSA) leading to faster reconstitution times;
- Suitable for **a variety of containers** (vials, syringes, inhalation systems, etc:).

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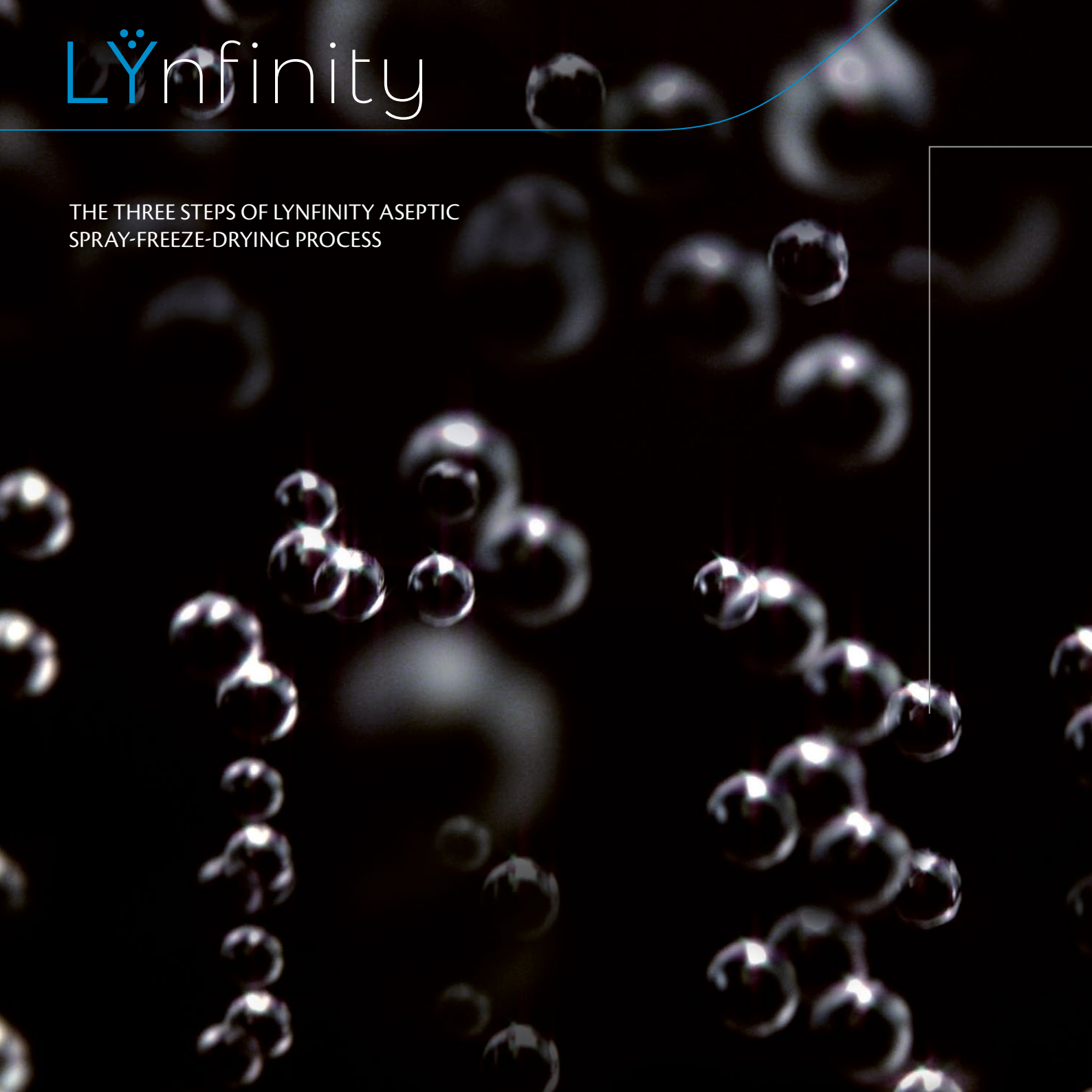
THE THREE STEPS OF LYNFINITY ASEPTIC SPRAY-FREEZE-DRYING PROCESS



SPRAYING

The product spray is initiated when a steady laminar product feed is broken into uniform droplets at the top of the freezing chamber. From the product reservoir, liquid product is fed to a temperature- controlled droplet zone through a specially designed nozzle mounted at the entrance of the freezing chamber.

When the laminar liquid jet is mechanically disturbed at a set frequency, droplets of uniform size are formed. Generation of uniform droplets is not only important for consistent drying operation, but also for downstream powder filling.

Figure 1 shows the imaging of the droplet formation process for a range of upstream parameters as seen using a monochromatic high-speed camera shot at a 2 ms frame rate.

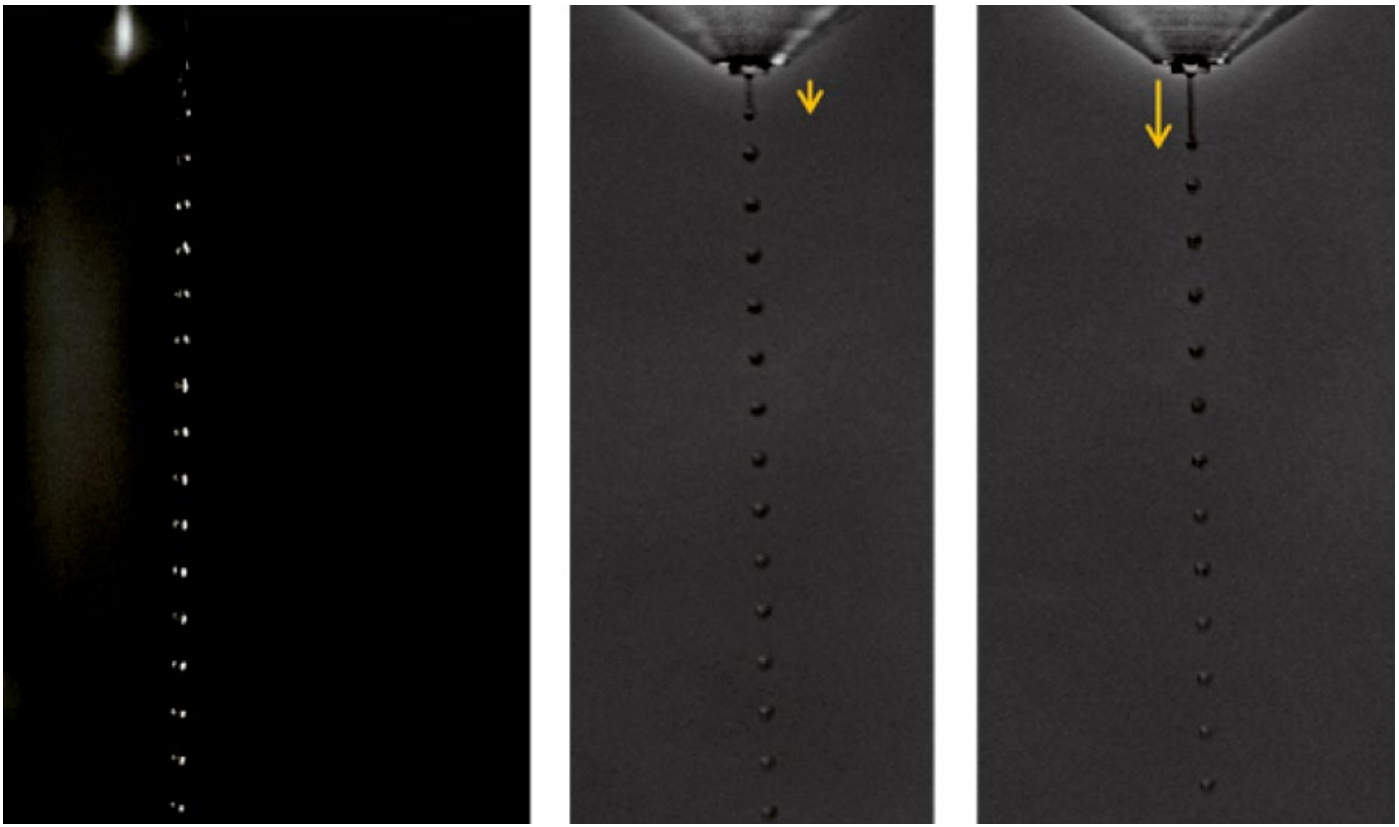


Figure 1: droplet formulation process

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FREEZING

The stream of liquid droplets is frozen in the freezing column, cooled using a double walled jacket. Liquid nitrogen and silicone oil cooling jackets are utilized around segments of the freezing chamber for temperature control. The gas inside the cylindrical stainless steel cooling chamber is maintained below -130 °C.
The liquid product nozzles are mounted directly above the freezing chamber and the freezing column itself is situated above the drying chamber.

After conditioning the freezing chamber, the product is sprayed into the chamber through the nozzle mounted at the top of the freezing column. The liquid product freezes as the stream of droplets falls vertically through the column of cooled gas. Rapid freezing allows maintaining the spherical shapes obtained from the spraying process. For example, it is estimated that at a gas temperature of -150 °C and a mean volumetric drop diameter of 500 microns, the drop freezes in less than 5 feet from the point of injection into the cooling chamber. Finally, individual frozen droplets collect at the base of the freezing chamber, awaiting transfer to the chamber below.

DRYING

The drying module is designed for continuous operation by utilizing intermediate vacuum chambers, cascading temperature-controlled vibratory shelves, and a dual ice condenser setup.
Following uniform droplet generation and freezing, the frozen product particles are transferred from the freezing chamber to the drying chamber. An intermediate chamber, utilizing a dedicated vacuum pump and jacket cooling, allows for transfer between the freezing chamber at atmospheric pressure and the drying chamber under vacuum without impeding continuous operation.

The freeze dryer chamber is a pressure vessel that houses the product shelves. Continuous operation dictates controlled movement that allows sufficient resident time for drying. However, it is imperative that the transport be gentle on the product. Thus, here the product is moved at a controlled rate through a cascading shelf stack, shown in **figure 2**, using vibratory agitation for transport. A system of vibratory drives is mounted from the outside of the vessel through vacuum seals into the chamber and is mounted to each pair of shelves. The system is used to vibrate the shelves to move the product through the drying chamber in a gentle, controlled manner.

The drying chamber contents are both agitated and heated to promote rapid sublimation and prevent agglomeration. Each shelf is designed with a serpentine path of channels through which a heat transfer fluid is passed for temperature control. Heat exchangers, in series, through which heat transfer fluid is circulated by a pump for each shelf allow for individual shelf temperature control.

In traditional freeze dryers, a single ice condenser is defrosted and drained before it can be used again, a process which requires down time. Lynfinity features a dual ice condenser setup allowing continuous operation with condenser change-over during drying, where a condenser can be defrosted, while the other condenser is in use.

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LYNFINITY TECHNOLOGY: CONTINUOUS MANUFACTURING

Uniform particle generation

A steady liquid product feed is atomized into uniform particles at the top of the freezing column. Uniform particle sizing allows for controlled and rapid drying.

Product transfer with continuous movement

Continuous generation and collection of frozen product particles occurs within the freezing column. An intermediate chamber, utilizing a dedicated vacuum pump and jacket cooling, allows for transfer between the freezing column and drying chamber, without interfering with continuous operation.

Continuous product transport

Continuous operation dictates controlled movement that allows sufficient resident time for drying. However, it is imperative that the transport be gentle on the product. Thus, here the product is moved at a controlled rate through a cascading shelf stack while drying, using vibratory agitation for transport. An intermediate chamber below the drying chamber serves as an airlock for the discharge of dried product.

Aseptic environment

The system has been designed to be cleaned in place and steamed in place (CIP/SIP) up to the same high standards as any of the other freeze dryers from IMA Life.

Smart engineering

- Unique nozzle design for controlled product droplet delivery.
- LN2 cooled compact refrigeration system.
- Independent shelf temperature control for each shelf.
- Split condenser for continuous condensing capability.
- Minimal footprint at production scale.
- Split valve to allow simultaneous drying/product loading/discharge.
- Overhead duct with a baffle upstream of the entrance to the condenser to prevent product loss to condenser.

Figure 2: LYnfinity Spheres

Applications of the technology:

- Of the total of 200 mAb in various stages of clinical development of biologics, 65% are freeze-dried.
- Most Biologic drug substance (DS) are often stored and transported in cryogen vessels before being converted to drugs, making it extremely expensive.
- Antibiotics are often bulk dried, milled and powder filled now.
- Self-administration through the use of pre-filled syringe/cartridge system with improved process efficiency and better control within minimal human intervention.
- For reducing reconstitution time of hard-to-reconstitute products.

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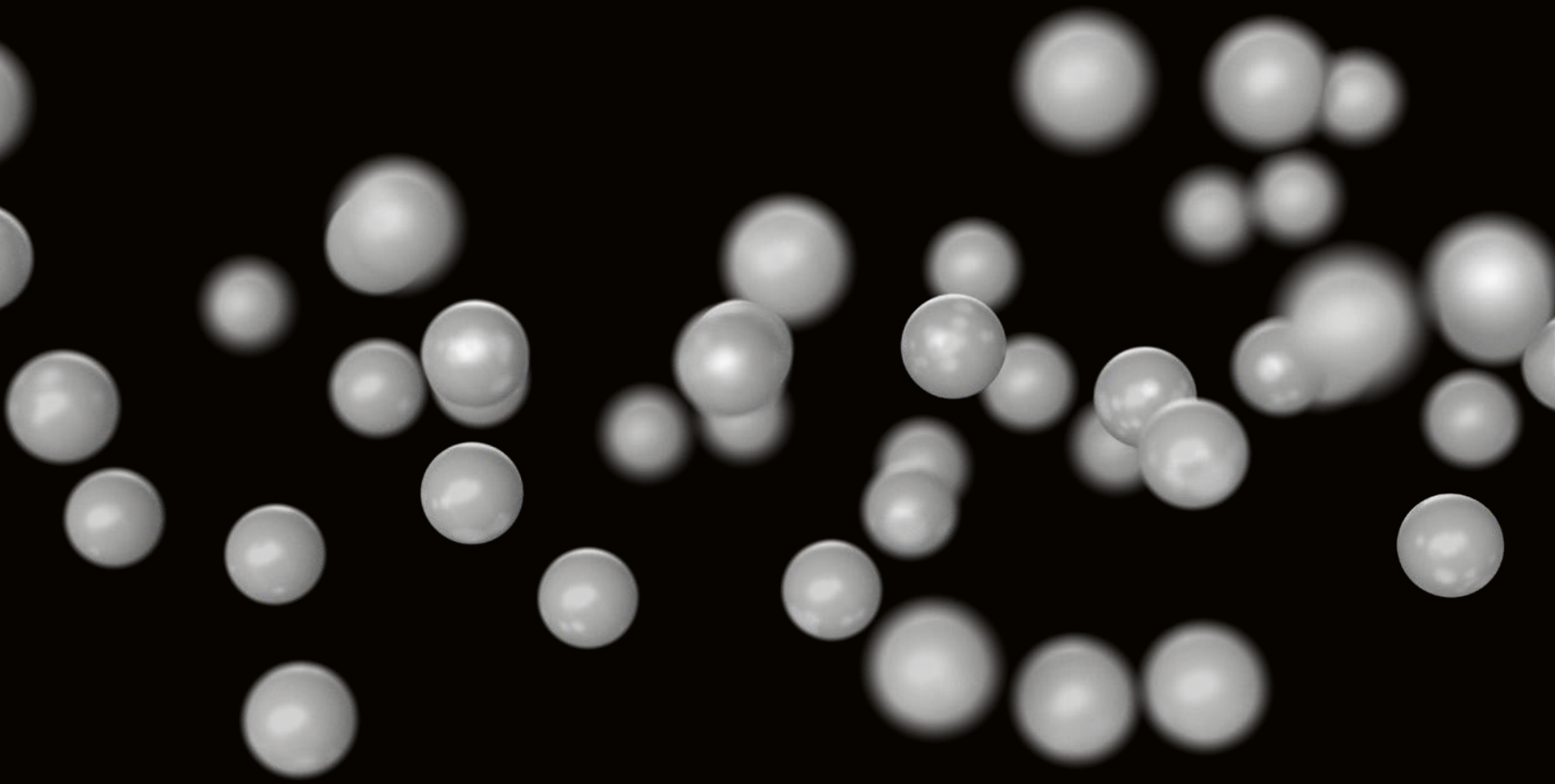
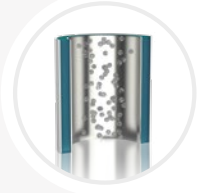
LYNFINITY SPHERES



1 LIQUID SOLUTION

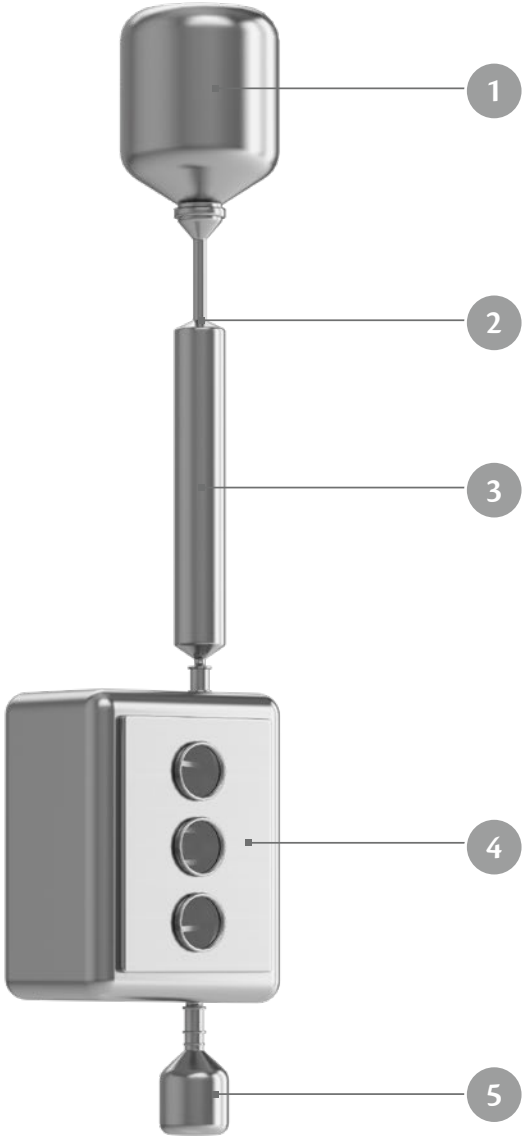
2 DROPLET GENERATION

3 FREEZING COLUMN



4 DRYING CHAMBER

5 LYNFINITY SPHERES



LYnfinity LAB

THE COOLEST LABORATORY SPRAY FREEZING MODULE

Designed for the lab environment, **LYnfinity LAB** features the freezing process identical to that of the production LYnfinity, generating uniform frozen droplets from liquid formulation. The resulting frozen particles are stored in a cooled canister to transfer manually for drying in a traditional lab freeze dryer.

LYnfinity LAB offers access to the emerging technology of spray-freeze-drying allowing for process development, technology evaluation, model building, product characterization with limited formulation, in a small footprint in the lab environment.

LYnfinity LAB allows scientists and lab technicians to test a formulation and collect vital data before switching to a production environment.

THE DESIGN

LYnfinity LAB features a stainless steel and molded polyurethane enclosure with optimal ergonomics and aesthetics in mind. An intuitive LED panel provides machine and process status information and a 19" multi-touch display (HMI) integrated into the design making it easy to use. Complete operation is possible through the HMI.

Inside the enclosure, a vibratory nozzle is mounted directly on top of the freezing chamber, identical to the one used on the continuous spray freeze-drying process. In fact, the design of the freezing column is identical to allow easy cycle development and scale up. The freezing chamber is a stainless steel vessel with a liquid nitrogen jacket. A cryogenic butterfly valve isolates the freezing chamber from the stainless steel vacuum-jacketed collection canister.

A series of temperature probes and pressure transducers are used to control and monitor the process from vacuum to atmospheric pressure.

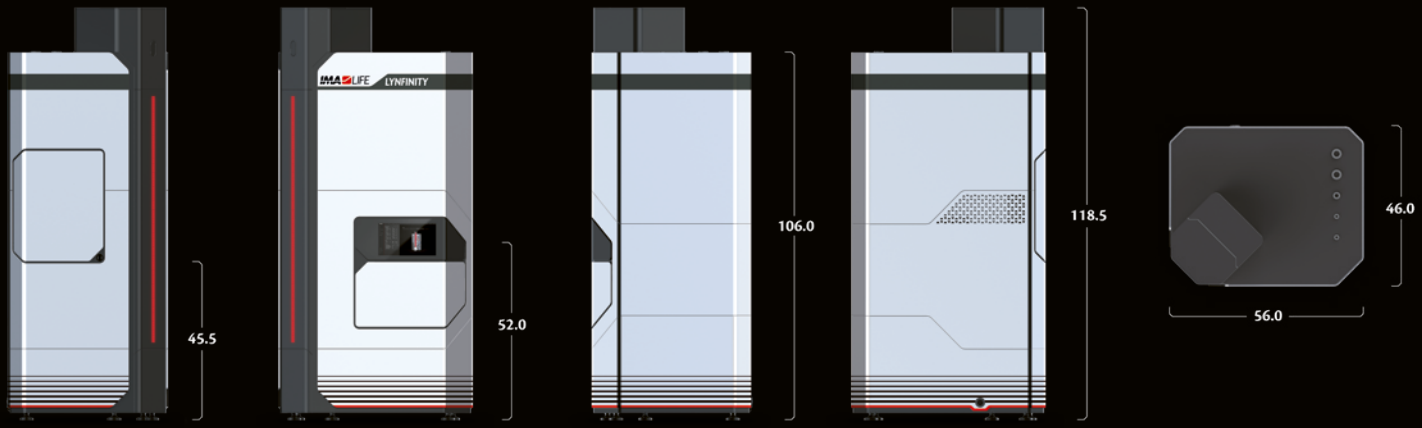


Figure 3: LYnfinity LAB dimensions (inches)

LYNFINITY STARTS HERE

LYnfinity LAB offers access to the emerging technology of spray freeze-drying:

- Easy to use
- Small footprint for setup in the lab
- Low barrier to entry prior to moving product towards continuous freeze drying
- Model building
- Technology evaluation
- Process development with limited formulation (down to 200 ml)
- Generate uniform frozen droplets of mean volumetric diameter 600 microns
- Dried product characterization
- Stability testing

THE EXPERIENCE

LYnfinity LAB represents a unique, low barrier to entry into the technology of spray freeze-drying. With the knowledge that the module will be used in the laboratory environment, it has been designed to be user-friendly not only in terms of the hardware interaction for first time users, but also thanks to its multi-touch HMI and integrated LED messaging board on the front panel. Built-in connectivity features allow for remote support from IMA's global service team.

This will give scientists and lab technicians around the world an opportunity to test formulations of interest to them, characterize the frozen or freeze-dried pellets and develop/model cycles prior to switching to a production operation for continuous manufacturing.

Figure 4: HMI controls

Figure 5: Detail of the LED strip

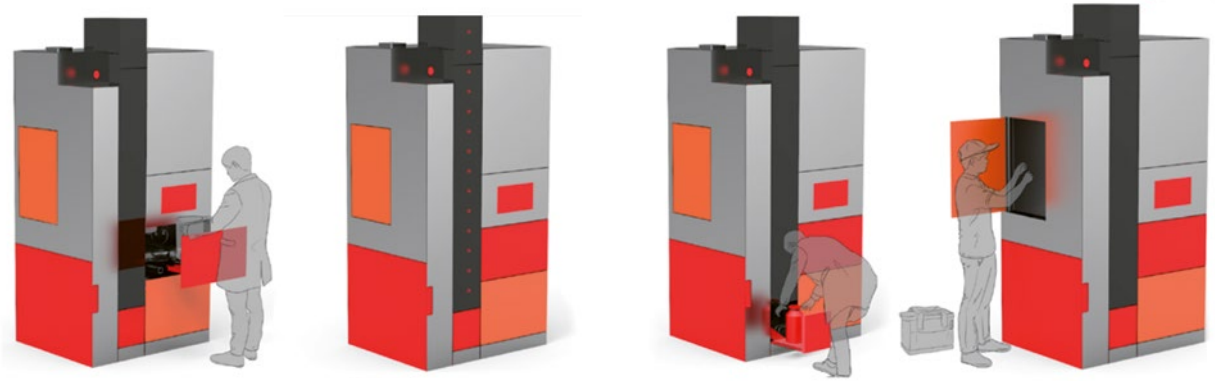
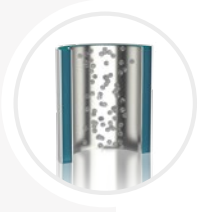


Figure 6: (From left to right) Loading of liquid product reservoir, LED messaging during process, collection of frozen pellets, maintenance on electrical cabinet

1 LIQUID FORMULATION

2 DROPLET GENERATION

3 FREEZING COLUMN



5 FROZEN LYNFINITY SPHERES

THE PROCESS

The process requires generation of a uniform controlled spray of liquid formulation into a cryogenically cooled freezing column.
The resultant frozen droplets are collected in a vacuum-insulated canister to be transferred manually for drying in a traditional lab freeze-dryer (not shown here). The module shown here allows flexibility to transfer the frozen droplets into any laboratory freeze-dryer available for use.
The LYnfinity LAB process can allow for reduced freeze-drying cycle times, faster reconstitution times with uniform pellets suitable for a variety of final container forms.

UTILITY REQUIREMENTS

Liquid Nitrogen	50 psig (recommended)
Gaseous Nitrogen	60 psig (recommended)
Compressed Air	90-95 psi (recommended)
Power Requirements *	120 VAC / 1 PH / 60 HZ (recommended) * for North America

Vents to Safe Space

LYnfinity

GLOBAL SERVICE TEAM

The **IMA Life Service Team** can deploy qualified personnel with the expertise, experience and instrumentation to carry out tests and assure a technical assistance at your site on your Freeze Drying equipment. Our network has an active presence all over the world. Our comprehensive support extends far beyond natural borders and cultural barriers. **No matter when or where you need us: you provide the challenge, we address the rest.**

Service Assistance worldwide for Freeze Dryers:

- BOLOGNA (Italy)
- MILANO (Italy)
- DUBLIN (Ireland)
- DONGEN (The Netherlands)
- PARIS (France)
- TONAWANDA, TEMPE, PALM BEACH, WINTERVILLE (USA)
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