The lyophilization carbon footprint and its energetic costs. How to relate the refrigerants GWP with the electrical consumption in a freeze dryer. An overview of the energy balances and the current refrigeration alternatives.

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Keywords: Lyophilization, freeze drying, carbon footprint, global warming, refrigerants, greenhouse gases, F-Gas regulation, heat and mass transfer, thermodynamics, liquid nitrogen.

Abstract

The environmental situation of world warming due to greenhouse gases emissions to the atmosphere is generating a radical transformation of human related energetic processes over the last decades. Lyophilization is high energetic intensive due the water sublimation at high vacuum and low temperatures, what historically has required the use of refrigerants with high Global Warming Potential (GWP). A clear understanding of the carbon footprint related to lyophilization and its energetic costs, is key for the freeze dryer users, and for the current and future technological transformations. This paper reviews the main energy consumptions for a 20m^2 freeze dryer, a case study to compare the current refrigeration alternatives.

1. INTRODUCTION

Energy consumption and global warming

Human energy consumption has suffered an exponential rise since the industrial revolution (XVIII century) when coal was rediscovered as a powerful an almost endless source of energy, mainly for the metallurgy, leading to the invention of the steam machine (for pumping out the water from the same coal mines first, but then, increasing the available mechanical energy for all the industries). Then electrical energy allowed the spread of the production sites far from the mines, boosting further the industry. **[1].**

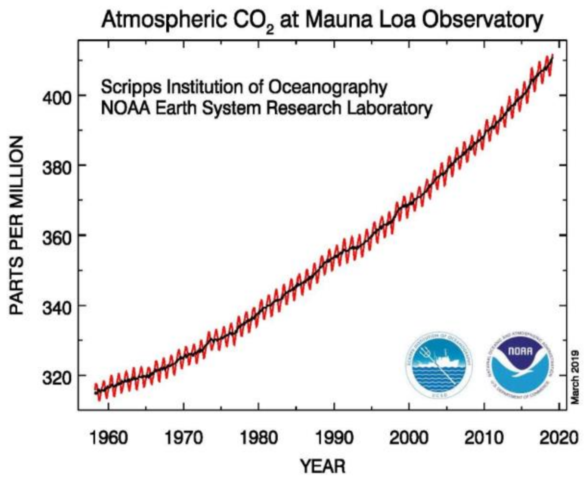

Figure 1: Steadily increasing concentrations of carbon dioxide in the atmosphere (in parts per million) observed at NOAA's Mauna Loa Observatory in Hawaii ***[2]***

Heat coming from burning coal and other fossil fuels could be transformed to electricity by a thermal cycle. Fossil fuels are (were) abundant at the globe by its accumulation over the centuries underground (starting as organic material, then with time, pressure and temperature, transformed into coal, petrol and gas).

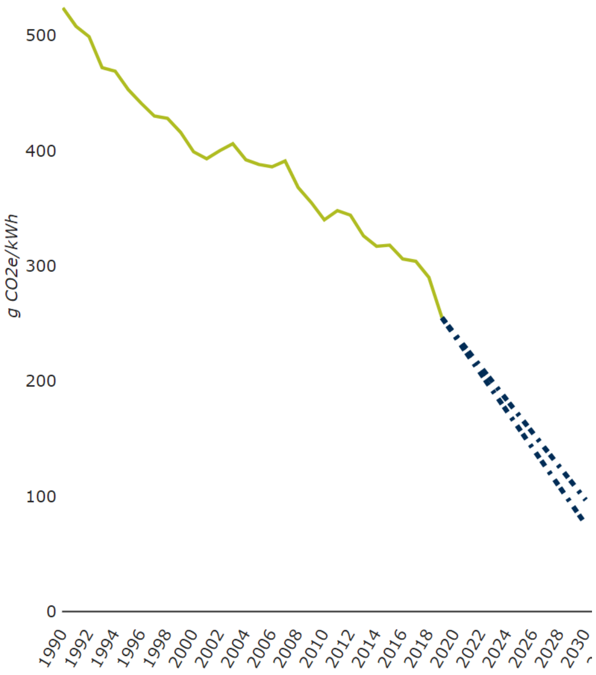

Figure 2: Greenhouse gas emission intensity of electricity generation at EU ***[3]*** *since 1990. Carbon dioxide emitted to the atmosphere per every kWh of electric energy produced. Average of all the energy sources. Renewable and not renewable.*

The combustion of fuels generates carbon dioxide (CO2) that is emitted to the atmosphere causing the global warming, as CO2 is transparent to the energy coming from the sun (heat radiation with short wavelength) but opaque to the thermal heat from the earth to the space (long wavelength heat radiation). The atmosphere is composed of 78% nitrogen, 21% Oxygen and 1% of other gases, among them CO2 with a concentration of 0.0407%. From 1960 the CO2 concentration has increased 47%, starting at a level of 0.0280% **[2],** see Figure 1.

And then the economical wealth due an increased industrial production helped the further scientific and technological development, also the humanistic awareness, of the limits of the planet, and even also the same material wealth. More and more efforts are now oriented to use less contaminant sources of energy, with less carbon dioxide emissions, see figure 2.

Thermal cycles. Efficiency. Refrigeration.

Heat transfer naturally occurs from a hot source with high temperature to a cold sink with lower temperature. By means of technology, with a thermal cycle, heat can be transformed in mechanical energy (work) and then to electricity (as in a steam machine with the hot source being the combustion of fossil fuels). But also, it is possible to reverse the thermal cycle, and then heat can be transferred from low temperature to high temperature by using electrical energy, in what is known as refrigeration.

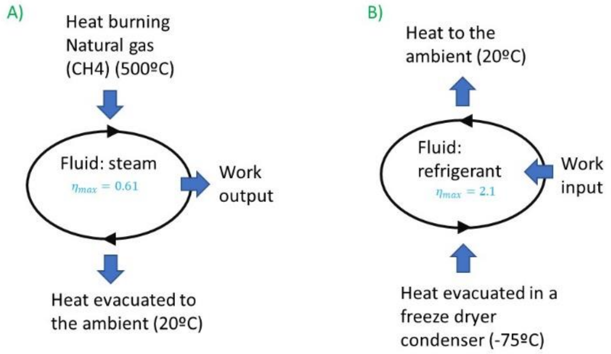

Figure 3: A) Thermal cycle with temperature levels of a natural gas power generation plant. B) Reversed thermal cycle with temperature levels from a freeze dryer (only condenser).

The technological devices operating with thermal cycles involve a fluid that is operating between two pressures, normally in closed loop, in steam machines the fluid is steam, in reversed thermal cycles the fluid is known as refrigerant.

The maximum efficiency of a thermal cycle is defined by the Carnot efficiency (temperatures in Kelvin):

$$\eta_{max} = \frac{T_h - T_c}{T_h} = \frac{Work\ output}{Heat\ burning\ Natural\ Gas}$$

$$\eta_{\max refrig} = COP = \frac{T_c}{T_h - T_c} = \frac{Heat\ evacuated\ condeser}{Work\ input}$$

The concept of maximum efficiency (Carnot) is the physical limit to transform heat to work and viceversa by a thermal cycle. These transformations entail some inevitable loss of energy, related to the temperature level of the heat, as high is the difference to the ambient temperature, higher is the quality of the available thermal energy.

In other words, in a thermal cycle, as high is the difference of the hot source from the ambient, cold sink, greater is the work that can obtained from the same available heat. In a refrigeration cycle, as high is the difference of the cold source from the ambient, hot sink, higher is the work needed at the reversed cycle.

In a freeze dryer an important amount of heat needs to be evacuated at the low temperature of -75ºC, to capture in form of ice, the vapors coming from the sublimation. Electrical heat is used to sublimate water ice from the product to vapors, and then the same heat needs to be evacuated by the refrigeration system, but now at a temperature level of -75ºC. Although we are talking about the same amount of (final) energy, the electric consumption (primary energy) to provide/evacuate the same heat will be different. To proper compare different types of energy, they should be transformed to the same quality level, normally the electricity level.

	Freezing (at 0ºC)	Sublimation (at -30ºC)	Condensation (at -75ºC)	Melting (at 0ºC)
Phase change enthalpy kJ/kg	-333.55	2839.1	-2852	333.55
Refrigeration energy (kWh)	21.68	-	185.38	-
COP refrigeration with R449A	1.9	-	0.26	-
Electric energy Refrigeration (kWh)	11.41	-	713	-
Electric energy heating (kWh)	-	184.54	-	21.68
Total required energy	**11.41**	**184.54**	**713**	**21.68**

Table 1: Energy for freeze drying 234kg of pure water. Refrigeration system with double stage compressor and R449A. (1kWh=3.600kJ). Sublimation and condensation represents 97% of the total energy (primary drying). Total energy=930.62kWh, sublimation and condensation=897.54 kWh.

Freeze drying is high energy intensive because of the water phase changes involved in the process: **freezing, sublimation, condensation and melting**, but also, because some of these processes needs a reversed thermal cycle at low temperature. The refrigeration technology has always tried to approach the maximum

Carnot refrigeration efficiency, and the development and use of high-performance synthetic refrigerants has historically been a convenient solution for it, nevertheless the use of this refrigerants is no longer possible because its high Global Warming Potential, and the New synthetic refrigerants with lower Global Warming Potential, are lacking the high performance of the past.

Synthetic refrigerants. Global Warming Potential. F-Gas regulation

Synthetic refrigerants are designed and manufactured for having the best performance depending on the refrigeration application (temperature range). Its boiling point at the low and high pressures of the cycle, are engineered for matching the two temperature levels, source and sink of heat. In a freeze dryer, during primary drying: the heat sink is the ambient (high temperature) and the source of heat is the condenser at -75ºC (low temperature)

The maximum thermal cycle pressure and temperature should not exceed the compressor limits, maximum pressure should be typically lower than 20bar (a) for piston and screw compressors, and maximum temperature should be below +75ºC (compressor discharge).

Additionally, the refrigerants should have proper thermophysical properties as high density, specially at low pressure when entering the compressor inlet, for an efficient compression, and high vaporization enthalpy, for handling more energy per kg of refrigerant.

Synthetic Refrigerant	GWP	Temperature	Pressure	Liquid density	Vapor density	Enthalpy of vaporization
		ºC	mbar	kg/m3	kg/m3	kJ/kg
R507 Forbiden refrigerant by F-gas regulation	3985	30	14.65	1024	79	130.2
		-60	0.64	1261	3.67	201.5
R449A Current allowed alternative by F-gas regulation	1282	30	14.09	1073	57	165.7
		-60	0.48	1391	1.71	244

Table 2: GWP, and boiling thermophisical properties of the already forbidden refrigerant R507 and its current substitute, the R449A

Then synthetic refrigerants allow, with a single refrigeration cycle, and a double stage compressor, a low temperature at the condenser with enhanced performance. As the refrigerant will boil at constant temperature at the evaporator, and liquify (opposite to boil) also at constant temperature at the condenser.

The major inefficiencies then will come only from the compression. All gas compression processes entail an undesired temperature increase that can not be used for refrigeration, as higher the pressure gradient to overcome, higher the temperature increase.

For the low temperature of -75ºC in freeze drying, the required pressure gradient to cover is excessive for a single step (without exceeding the maximum temperature of the compressor). For this reason an intermediate cooling during the compression is necesary, by a partial expansion of refrigerant, that also improves the efficiency of the process as more heat is exchanged at constant temperature, see figure 4.

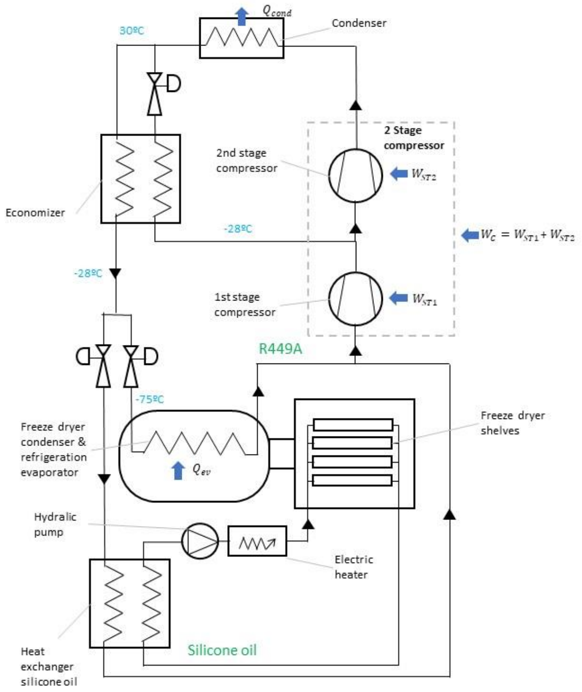

Figure 4: Refrigeration cycle with double stage compression. Qev -75ºC at the freeze dryer condenser, Qcond +30ºC the ambient. Note that the refrigeration cycle evaporator is the freeze dryer condenser, what should not be confused with the refrigeration cycle condenser.

But synthetic refrigerants present a main (and beyond help) disadvantage, its global warming effect (potential). Even if they operate in closed loops in thermal cycles, theoretically never released to the atmosphere, during maintenance, failures (leaks) and eventualities, these gases can be emitted to the atmosphere, causing high environmental impact. One kilogram of refrigerant can cause thousands of times more global warming than the same quantity of CO2. A freeze dryer can be more contaminant because of two eventual releases of its refrigerant, than in 10 years of continuous operation with the related CO2 emissions from its electrical energy consumption, as it is detailed at the following chapters of this whitepaper. The Global Warming Potential (GWP) relates the warming effect of gases by mass (kg), compared to CO2. R449A GWP is 1282, 1 kg of R449A has an equivalent warming effect than 1282 kg of CO2.

Worldwide governments, as it happened with the Chlorofluorocarbons (CFC), and the ozone layer depletion, are regulating by laws and restrictions the use and production of fluorinated gases (F-gases) with high Global Warming Potential (GWP), and even if the low temperature applications <-50ºC are exempt of prohibitions, its production and usage is expected to be marginal in the nearest future, because of the related price increase due its low demand (currently majorly for applications above -50ºC).

PLACING ON THE MARKET PROHIBITIONS			
Doc.		**Products and equipment**	**Date of prohibition**
A	12	Stationary refrigeration equipment, that contains, or whose functioning relies upon, HFCs with GWP of 2 500 or more except equipment intended for application designed to cool products to temperatures below – 50 °C	1 January 2020
B	14	Stationary refrigeration equipment, that contains, or whose functioning relies upon, fluorinated greenhouse gases with GWP of 2 500 or more except equipment intended for application designed to cool products to temperatures below – 50 °C.	1 January 2024

Table 3: Adapted table from (A) Annex III of the REGULATION (EU) No 517/2014, fluorinated greenhouse gases and repealing Regulation (EC) No 842/2006 **[4],** *and Annex IV of the PROPOSAL amending Directive (EU) 2019/1937 and repealing Regulation (EU) No 517/2014* **[5],***. Doc (A) REGULATION, doc (B) PROPOSAL*

2. DICUSSION

The case study. Primary drying in a 20m^2 freeze dryer.

Every pharmaceutical formulation requires a specific freeze-drying recipe that will ensure the most efficient process (minimum drying time) with an optimal final product result, a well-formed dried cake that will provide the desired stability (preservation).

Freeze dryer usable surface area	m^2	20
6R vials (22mm diameter)	units	46800
Filling volume per vial	ml	5
Filling height	mm	16
Solid content (sucrose)	w/w	0.05
Total weight batch	kg	246.32
Total weight solid (sucrose)	kg	12.32
Total water content	kg	234
Product critical temperature (sucrose)	ºC	-32.4

Table 4: Case study, product and freeze dryer data

Typically, freeze drying cycles lasts two or three days, with the primary drying step (when pure ice is sublimated) as the longest and higher consumer of energy. It should not be confused with the peak consumptions during the cycle, that occurs at the beginning of the freezing (loaded shelves cooldown) and at the beginning of the primary and secondary drying (shelves warm up).

Cooling down and warming up the shelves entails cooling not only the shelves, but also the silicone oil that is circulating inside them, also the piping and components at the closed loop, as well as the vials filled with product. It shall be noted that during the cool down, the product needs to be frozen, and at the secondary drying warm up, pure ice is no longer present at the product.

Step Nº	Step description	Step time (h)	Refrigeration Power (kW)	COP	Electric power refrigeration (kW)	Electric power heating (kW)	Total electric power (kW)
1	**Freezing cooldown** • Shelves temperature from +20ºC to -60ºC	2	24	1.2	20	0	**20**
2	**Freezing hold** • Shelves temperature at -60ºC	2	1	0.26	3.85	1	**4.85**
3	**Transition to primary drying** • Cool down condenser from +20ºC to -75ºC • Lower chamber pressure (vacuum) from 1000mbar to 0.05mbar • Heating shelves from -60 to -20ºC	2	1	0.26	3.85	24	**27.85**
4	**Primary drying** • Shelves temperature -20ºC • Chamber pressure 0.05 mbar • Condenser temperature -75ºC	60	3	0.26	11.54	4	**15.54**
5	**Secondary drying heating** • Shelves temperature from -20ºC to +20ºC • Condenser temperature -75ºC	0.5	1	0.26	3.85	24	**27.85**
6	**Secondary drying hold** • Shelves temperature at +20ºC • Condenser temperature -75ºC	3.5	1	0.26	3.85	0	**3.85**
	Total time	**70**	**Average electric power**				**15.22**

Table 5: Case study cycle details by step: shelves temperature, pressure of the chamber and time. COP and energy values from a double stage compression refrigeration system with R449A. COP at step 1 freezing cool down is an average from 20ºC to -60ºC.

For a proper evaluation of the energies involved in a lyophilization process, it is proposed a case study, a 70h cycle with 6R vials filled with 5ml of 5% sucrose solution in a 20m2 freeze dryer, for a batch size of 46.800 vials. Sucrose is a commonly used excipient for freeze drying pharmaceuticals, with a critical temperature of -32.4Cº **[6]**, see table 3 for product and freeze dryer details.

During the primary drying the pressure at the chamber and the temperature of the shelves needs to be controlled to provide the highest possible heat to the product (for the fastest process) but maintaining the sublimation below the product critical temperature. In our case study the pressure of the chamber and the temperature of the shelves are maintained constant at the primary drying at 0.05mbar and -20ºC respectively, for a maximum product temperature of -32.64ºC. (at the end of the primary drying).

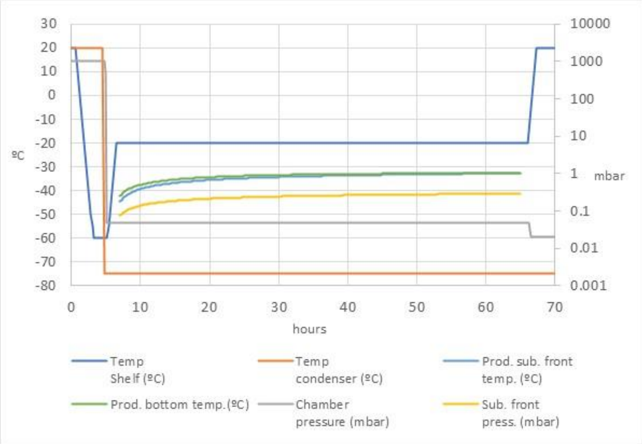

Figure 5: Case study cycle. Plotted: Temperature of the shelf (ºC), temperature of the condenser (ºC), Product sublimation front temperature (ºC), Product bottom temperature (ºC), Chamber pressure (mbar) and Sublimation front pressure (mbar).

As it can be seen both in table 4 and figure 5, the main and longest step of the freeze drying cycle is the primary drying (something typical with pharmaceutical products). As was also envisaged at the energy balances proposed in table 1, that sublimation and condensation (primary drying), are the water phase changes with higher energy demands. Even the not usable energy to cooldown and warm up the shelves of the freeze dryer (also oil and piping) is low compared to it (in the range of 10%).

The electrical power consumed during the primary drying is therefore close to the average electric power of the cycle (15.54kW to 15.22kW) as per the table 4, with a primary drying refrigeration COP of 0.26 (R449A). But would have been the same with a COP of 0.76 (R507), (7.95kW to 8.42kW), data not detailed at this paper but easy to obtain by recalculating the data of table 4).

At the following chapters of this whitepaper, only the primary drying step is used to simply and accurately compare different scenarios in terms of energetic consumptions, also to compare refrigeration alternatives.

Double stage refrigeration. From R507 to R449A. Losing efficiency

Almost all pharma production freeze dryers currently in operation (installed up to 50 years ago) are including double stage refrigeration. Even the compressor brands used are limited to only two or three main manufacturers. Piston semi hermetic compressors are used up to 30m^2 freeze dryers and screw units for higher usable surface areas.

Maybe the reason for this exclusivity, is related to the complexity (specificity) of the low temperature (-75ºC) technology. The professionals involved, from the engineer to the refrigeration technician, also maintenance crews, require a high level of expertise and knowledge. All freeze dryer users know that at least the collaboration of two experts is necessary for a successful freeze dryer long term operation, one internal at the pharmaceutical plant, and another external from the freeze dryer supplier.

The main technical challenges in a freeze dryer refrigeration system are related to the compressor lubrication oil that is mixed with the refrigerant and becomes highly viscous if accidentally ends at the low temperature region (due oil management system degradation), as well as presence in the loop of water coming from ambient humidity, leaked into the cycle at the subatmospheric regime. See table 2 for required pressures at -75ºC.

Additionally, differently to other industrial low temperature applications, the freeze-drying process requires to cooldown and warm up periodically (every batch) the refrigeration system, also periodically heating the shelves and the condenser during steam sterilization (up to +122ºC). Moreover, the refrigeration loads are not constant with notable peaks during shelves cooldown and warm up, see table 5. This periodic thermal stress challenges the refrigeration system, making the operation and maintenance to be very precise, and to be done by highly skilled, trained, and experienced personnel.

Synthetic Refrigerant	Refrigeration power (kW)	Electric power (kW)	Condensing heat (kW)	COP
R507 Forbiden refrigerant by F-gas regulation	3.0	4.0	7.0	0.76
R449A Current allowed alternative by F-gas regulation	3.0	11.5	14.5	0.26

Table 6: Performance of a refrigeration system with a double stage compressor, case study, primary drying. Comparing the forbidden R507 and its allowed alternative the R449A. Efficiency drops 65%.

Over the years, professionals have been acquiring a priceless and unique knowledge related to freeze dryers and its refrigeration systems, ensuring a robust and reliable operation. This may be the reason why there is high resistance for the substitution of the traditional refrigeration systems, replacing synthetic refrigerants (resistance both from the freeze dryer users side and from the manufacturers). Up today the preference is using alternative synthetic refrigerants with lower GWP that allows to maintain the well proven existing freeze dryer plant refrigeration subsystems with minor modifications alongside the refrigerant replacement.

Moving to hydrocarbons. Cascade refrigeration. Atex.

Since the first days of the history of the industrial refrigeration with reversed thermal cycles, hydrocarbons have been acknowledged as possible alternative refrigerants. Nevertheless, its flammability made them not the most adequate option, especially for direct expansion at a freeze dryer condenser. Also, their boiling point at the high and low temperatures made then not suitable for a refrigeration cycle compared to synthetic refrigerants. Propane (R290) and ethane (R170) could be good candidates but while the first has an excessively low pressure at -75ºC, the second has an excessive pressure at 30ºC, see table 7.

Hydrocarbons	GWP	Temperature	Pressure	Liquid density	Vapor density	Enthalpy of vaporization
		ºC	mbar	kg/m3	kg/m3	kJ/kg
R290 Propane	3	30	10.75	484.69	23.40	326.46
		-30	1.67	567.24	3.85	260.73
		-75	0.18	617.92	0.48	457.93
R170 Ethane	6	30	46.51	281.39	137.79	110.14
		-25	12.28	451.63	22.27	160.34
		-75	1.98	526.84	3.83	470.05

Table 7: GWP, and boiling thermophisical properties of propane (R290) and ethane (R170).

But, due the current environmental situation (also the energetic costs) some efforts have been devoted to overcome the technological barriers necessary to utilize hydrocarbons as refrigerant. For properly operating at the required temperature levels, cascade systems can be used, with two reversed thermal cycles, one at high temperature (HT, condensing at 30ºC, propane), the other one at low temperature (LT, evaporating at -75ºC). Then the HT evaporator evacuates the heat coming from the LT condenser in an intermediate temperature level see figure 6.

To mitigate the explosion risk associated to the high flammability of the hydrocarbons, an additional silicone oil loop is used as cooling medium between the freeze dryer and the hazard affected area where the cascade unit operates. The additional closed loop of silicone oil is cooled at -75ºC at the refrigeration system to then travel to the condenser, also to cool the shelves oil loop. See also figure 6.

Natural refrigerant Refrigerant	Refrigeration power (kW)	Electric power (kW)	Condensing heat (kW)	COP
HT cycle R290	4.6	2.2	6.8	2.08
LT cycle R170	3.0	1.6	4.6	1.88
Cascade **R290HT** **R170LT**	**3.0**	**3.8**	**6.8**	**0.79**

Table 8: Performance of a cascade refrigeration system. High Temperature (HT) cycle with propane (R290) and Low Temperature (LT) cycle with ethane (R170), case study, primary drying. Individual performance of each cycle and global cascade performance.

Then the risk of explosion is limited to the refrigeration system and depending on the ambient/zone where to be installed, different precautions should be taken to be under the ATEX directive and to obtain the ATEX certification. If there is the possibility of installing the refrigeration system outdoors, the explosion risk can be mitigated.

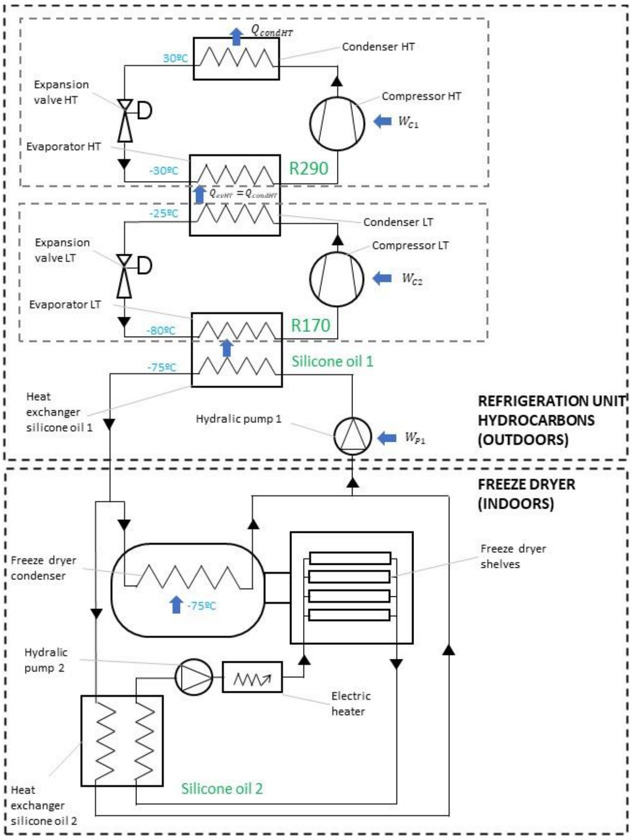

Figure 6: Cascade refrigeration diagram with hydrocarbons. High temperature loop (HT) with propane (R290), low temperature loop (LT) with ethane (R170)

It shall be noted, that even if having some good advantages, adding an additional silicone oil loop entails losing temperature level, as every heat exchanger requires at least 5 degrees of temperature difference between the two streams for the heat transfer, therefore the ethane needs to evaporate at -80ºC for attaining -75ºC at the silicone oil.

Additionally, it shall be also noted that cascade systems have been historically avoided when possible. A system composed of two linked circuits has double components, with a higher failure risk and higher sources of leaks.

Air as a refrigerant.

Refrigeration by compressed air is a proven technology used at the industry for different applications, as the air conditioning at aircrafts. By means of a compressor coupled to a turbine, air is compressed and then cooled with the ambient temperature, for in a following expansion (at the turbine-expander) be cooled down.

The main drawback of this so-called reversed Bryton cycles **[7]** that works in all the stages with the refrigerant (air) in gas state, is the loss of efficiency due the heat exchanges are not performed at constant temperature. Additionally heat exchange between gases requires an increased contact surface, due its poor heat transfer properties, involving large heat exchangers in the process.

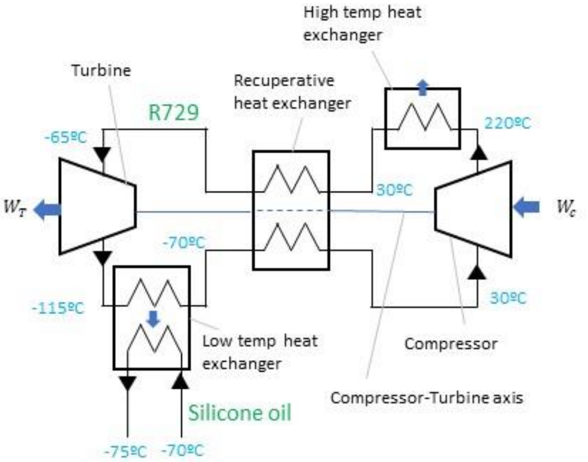

Figure 7: Air Bryton refrigeration system with compressor-turbine and an intermediate recuperative heat exchanger. Refrigerant, air (R729). Operation point of -75ºC at the silicone oil outlet.

Nevertheless, nowadays there are standalone solutions for low temperature, based in the reversed Bryton cycle, that are finding a notable space at the market. By means of a recuperative heat exchanger (see Figure 7), a low temperature at the turbine inlet can be maintained, and then in the following expansion, reach de required final low temperature.

Centrifugal compressor turbo-expanders at high speeds up to 82.000rpm, are able to provide the required compression ratio to air for the refrigeration, without an intermediate expansion. Due its symmetric geometry, centrifugal turbine/compressors, can absorb the thermal expansion of high discharge temperatures. Also, no lubrication oil is required at the process stream (air).

High temperature (ºC)	30	30	30	30	30
Low temperature (ºC)	-90	-85	-80	-75	-70
Refrigeration power (kW)	3.25	3.5	3.75	3.925	4.1
Mecanical power (kW)	12.8	12.8	12.8	12.8	12.8
COP	0.25	0.27	0.29	0.31	0.32

Table 9: Refrigeration power and electrical consumption vs oil outlet temperature. From Mirai air refrigeration system, model Mirai Cold 10T ***[8]***

On the other hand, there is a technological challenge at the bearings that are going to allow the high speeds at the rotative shaft with a perfectly equilibrated motion. The main technological expertise is related to the manufacturing, adjustment, operation and maintenance of this highly valuable component, see Figure 7.

Figure 8: Mirai turbo expander [9]

Another drawback of air refrigeration is its lack of flexibility to provide the required increased cooling power for the shelves cooldown at the freezing step, see table 4. Although it can provide higher refrigeration power for higher cooling temperatures, it is not sufficient to overcome the different heat loads of all the freeze drying cycle, differently to the other refrigeration alternatives presented at this paper, see figure 9.

Then an additional refrigeration solution needs to be implemented at the freeze dryer for the high refrigeration loads.

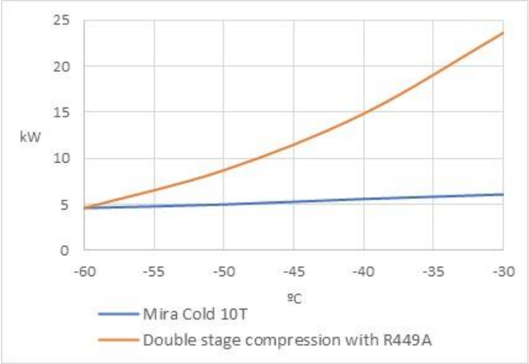

Figure 9: Refrigeration power for low temperature levels up to -30ºC, for Mirai Cold 10T and the equivalent refrigeration system with a double stage compressor and R449A. Starting at 4.6kW refrigeration power at -60ºC. High temperature level 30ºC.

Liquid Nitrogen

Liquefaction of gases is a well-known technology, where a gas like nitrogen, oxygen or natural gas, is cooled down enough to be below its boiling point. The main advantage of a liquified gas is that at pressures close to atmospheric, its density is high compared to its gaseous state, even at high pressures, see table 9. This allows liquified gases to be transported and stored in large volumes. While natural gas can be transferred at high pressures (around 200bar) and temperatures around the atmospheric in pipes between countries, it needs to be liquified at -161ºC for being transported in high volumes by sea.

A liquified gas is cold, it is transported, supplied, and stored using low temperature insulation, including cryogenic tanks (vacuum insulated for small volumes or perlite for large tanks).

Despite insulation, ambient heat ends at the cold liquid slowly boiling it, as an inevitable loss. A tank filled with a liquified gas, with time will loss all its content, if it is not previously consumed. When financially viable, losses can be liquified again by a specialiced refrigeration system or used as fuel in case of Natural Gas at sea tankers.

When used only for transport purposes, liquified gases are typically gasified before its use. In hospitals, oxygen and nitrogen are stored in site, in moderate volumes, in cryogenic tanks (periodically refilled) and gasified on demand by atmospheric evaporators that use the ambient air as source of heat. Finally, the low pressure gas at room temperature can be used for medical purposes.

State	Pressure (bar a)	Methane		Nitrogen	
		Temp. (ºC)	Density (kg/m3)	Temp. (ºC)	Density (kg/m3)
Gas	200	20	162	20	228
Gas	1	20	0.66	20	0.87
Saturated vapour	1	-161	1.80	-196	4.57
Saturated liquid	1	-161	423	-196	807

Table 10: Methane and nitrogen densities at different pressures and temperatures, also liquified. Natural Gas is composed by around 90% of Methane. Boiling temperatures referred at the saturated states. There is constant temperature during boiling from liquid to gas, or vice versa during the liquefaction.

Due the large volumes transported (also for safety), LNG gasification is carried out at the harbors, when the ship tankers reach its destination, typically sea water is used as source of heat, and from the harbor the LNG now Natural Gas (NG) is further distributed pressurized in pipes.

Liquid nitrogen (LN2) when used as coolant agent for a freeze dryer, is supplied periodically to the pharmaceutical plants (typically every week) and stored on site in cryogenic tanks. When cooling is needed, the freeze dryer will make use of the LN2 to cool a first silicone oil loop to -75ºC with a cryogenic heat exchanger. This silicone oil will circulate inside the condenser and also inside a second heat exchanger, evacuating heat from the second oil loop for the freeze dryer shelves, see figure 10.

Only few cryogenic valves and a heat exchanger are included at the refrigeration system of a freeze dryer using liquid nitrogen, compared to the other refrigeration alternatives presented at this paper, what entails very low maintenance and almost negligible failures, being a real advantage for end users in terms of reliability and robustness. When operating with LN2, cooling energy at low temperature is not generated by the freeze dryer, it is only a consumer of an already cold liquid. The refrigeration is done centralized in a liquefaction plant (producing the required LN2 for all the consumers in the territory). Nevertheless, on the other hand, the boiling temperature of liquid nitrogen at atmospheric pressure is -196ºC, which entails a substantially low related maximum Carnot Efficiency, see table 11.

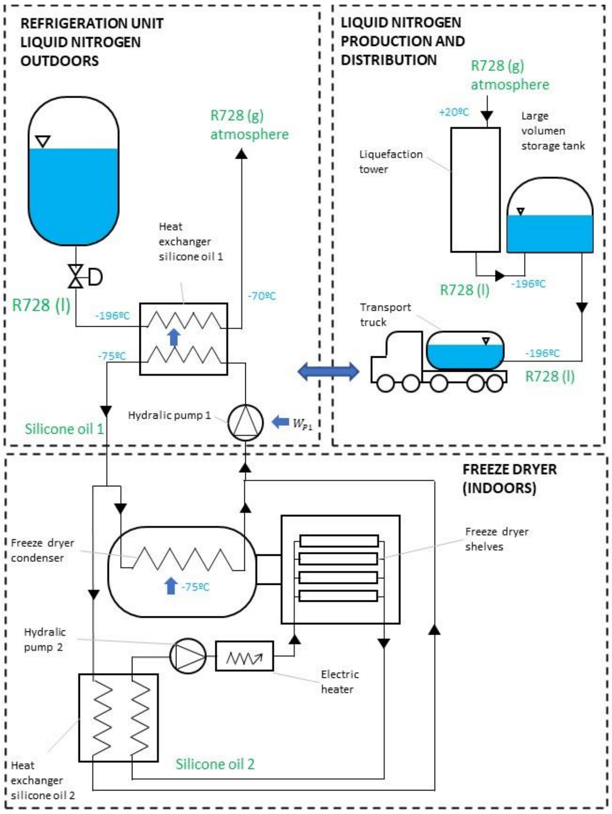

Figure 10: Freeze dryer with liquid nitrogen cooling.

Specifying a Coeficient Of Performance for liquid nitrogen refrigeration is complex as it depends on numerous parameters, starting by the real efficiency of the liquefaction plant, and then adding all the related losses during the delivery to the consumer, then also considering the boil off in the storage buffer tank until the liquid is consumed.

Liquid nitrogen is provided at atmospheric pressure at the pharmaceutical plant, transferred to the buffer cryogenic tank, and pressurized to 3-5 bar(a) for having the necessary pressure difference with the ambient to make the liquid circulate inside the freeze dryer cryogenic heat exchanger.

Stored at the buffer cryogenic tank, the liquid close to the walls becomes warmer due the heat loads from the ambient but does not boil (as the boiling temperature has increased due the pressure rise) and by convection travels to an upper level, at the liquid surface, stratifying the tank (liquid gradient temperature along tank height). Then the LN2 supply temperature is variable during the operation of the freeze dryer (what is handle it by the freeze dryer control by a proportional valve, but what entails a different refrigeration consumption for the same heat load, and a variable global refrigeration efficiency).

Freeze dryer		
Refrigeration power. Primary drying. Case study.	kW	3
LN2 gassification enthalpy from -196ºC 1 bar(a) to -70ºC 1bar (a)	kJ/kg	332.75
LN2 flow rate primary drying	kg/h	32.46
Liquefaction plant		
LN2 flow rate primary drying	kg/h	32.46
GN2 liquefaction enthalpy From 20ºC 1bar (a) to -196ºC 1 bar(a)	kJ/kg	426.55
Refrigeration power LN2 liquefaction From 20ºC 1bar (a) to -196ºC 1 bar(a)	kW	3.85
LN2 liquefaction plant efficiency (*)	-	0.218
Electric energy required for LN2 liquefaction	kW	17.64
Overall COP Refrigeration with LN2 (**)	-	**0.170**
Max Carnot efficiency Th 20ºC, Tc -196ºC	-	0.36

Table 11: Refrigeration power and electrical consumption LN2 refrigeration system. At the freeze dryer, GN2 exhausted at -70ºC to the atmosphere, at liquefaction plant GN2 inlet at 20ºC, see Figure 9. (*) LN2 liquefaction plant efficiency from [10]. (**) Overall Cop Refrigeratio Efficiceny=3kW/17.64kW

Then due the complexity of the different phenomena involved with the LN2 logistics, it is considered no losses (no heat loads) from the LN2 plant to the freeze dryer supply, what entails a greater overall Refrigeration COP, less electrical consumption. Nevertheless, as it can be seen in table 11, this refrigeration alternative presents the lowest refrigeration COP, and consequently the greater electric consumption.

Also to be considered in this refrigeration alternative, are its human hazard involved. Although nitrogen is an inert gas, present in a concentration of 78% at the atmosphere, as in liquid form is stored with high density, in case of an spill or major leak, can displace the oxygen and then can cause anoxia to the operators. Then part of the LN2 facilities are installed outdoors (cryogenic buffer tank), also is advised to include in the facility alarm oxygen detectors, specially indoors.

Finally, it shall be also taken in consideration the special design and components selection when operating with cryogenic temperatures. Due the low temperatures involved, materials, as metals but also plastics, should be compatible with the rigidity and contraction that will cause the cryogenic liquid. Electronics and actuators are separated from the process (at valves), also safety relief valves need to be included in between two valves that can be closed trapping the cryogenic liquid that with time will be gasified increasing dangerously the pressure.

The cryogenic heat exchanger cooling silicone oil with LN2 deserves also a special mention, as it needs an special design to avoid the silicone oil to be frozen in the process, what can cause clogging at the silicone oil loop. (one of the only important failures that presents this alternative, for example during a short electric shutdown).

3. RESULTS

Along this paper five different refrigeration alternatives are reviewed: Double stage compression with synthetic refrigerants (with the already forbidden R507, and its current substitutive the R449A, with low Global Warming Potential), a cascade system with hydrocarbons (R290 and R170), compressed air refrigeration (R729), and finally, liquid nitrogen cooling (R728).

Based on a primary drying stage, with a condenser temperature of -75ºC, the related Coefficients Of Performance of the five alternatives are also detailed.

The energy balances for a complete freeze-drying cycle on a $20m^2$ freeze dryer case study (table 4), has allowed to detail the average electrical consumption, and also conclude that the almost constant electrical power during the primary drying is a good representation of the average consumption of the whole cycle.

Then it has been possible to fairly compare the five refrigeration alternatives, assuming a refrigerant accidental release, during an operation time frame of 10 years, of two complete full loads of refrigerant (only accounted for the synthetic refrigerants alternatives, as the GWP of hydrocarbons is negligible, and for air and nitrogen is zero).

The refrigeration system for the synthetic refrigerants alternatives is composed by three independent reversed thermal cycles, each with a 30 Horse Power, piston, double stage compressor, with a total refrigerant load of 90kg (30kg of refrigerant per thermal cycle).

It shall be noted also, that other energetic consumptions like from the vacuum system, electronic components and sensors, hydraulic cylinder, CIP hydraulic pump and liquid ring pump, also the energy for supplying the steam for the SIP, are not accounted at the thermal balance, for simplicity, and also because would not have had a major impact on the results presented, neither impact the comparison, as these consumptions are the same for the four alternatives.

CO2 emissions

At table 12 are detailed the total emissions in a 10-year period, for the five refrigeration alternatives, as per the assumptions previously detailed at tables 3 and 4. Nevertheless, for the reader shall be easy to recalculate different scenarios by modifying the inlet data.

Refrigeration alternative		**Double stage compression Synthetic refrigerants**		**Cascade refrigeration Hydrocarbons**	**Air refrigeration turboexpander**	**Cooling by Liquid Nitronen**
Refrigerant		R507	R449A	R-290 R-170	R729	R728
Refrigerant Comercial name		Freon	Opteon	Propane Ethane	Air	Liquid nitrogen
Carbon foot print due the refrigerant used						
Quantity of refrigeratnt	kg	90	90	-	-	-
GWP	-	3985	1282	3 6	0	0
Assumed refrigeration loads lost in 10 years	-	2	2	-	-	-
Eq CO2 emmited 10 year maintenance	**tn**	**717**	**231**	**Negligible**	**0**	**0**
Carbon foot print due electric consumption						
Electric heat for sublimation	kW	3	3	3	3	3
Refrigeration COP@-75ºC		0.76	0.26	0.79	0.37	0.17
Electricity for refrigeration	kW	3.9	11.5	3.8	8.1	17.6
Total electric power	kW	6.9	14.5	6.8	11.1	20.6
Annual use	h	6570	6570	6570	6570	6570
Annual electric consumption	MWh	45	95	45	73	135
Emission intensity of electricity generation EU 2019	kg CO2 /MWh	0.255	0.255	0.255	0.255	0.255
Total CO2 10 year operation	**tn**	**116**	**243**	**114**	**186**	**345**
Total carbon foot print						
Total Eq CO2 emmited to the atmosphere in 10 years	**tn**	**833**	**474**	**114**	**186**	**345**

Table 12: CO2 total emissions. Case study (see table 4 and table 5)

For the annual operation time, it is considered an optimized and continued production over the year, with the necessary steps between batches (Product unloading, defrosting, CIP, SIP, leak test, integrity test and product loading) and 15 days per year of freeze dryer shut down for maintenance.

Energetic costs

The energetic costs (electricity costs) depend on the power generation mix of each country (also the available energetic resources).

At the time this paper is being written, the energetic scenario at the EU is highly impacted by the war at Ukraine, with the related stoppage of supply of Natural Gas from Russia, what is entailing an important electricity price rise. At table 12 is presented the electricity costs for the case study at EU, USA and China.

	Electricity (MWh)	Cost EU (€)	Cost USA (€)	Cost China (€)
Double stage compression R449A	95	27,055	7,526	7,716
Cascade refrigeration hydrocarbons	45	12,688	3,529	3,619
Difference between technologies	51	14,367	3,997	4,098

Table 13: Annual Electricity Costs. Case study, only for two refrigeration alternatives: with double stage compressor with R449A, and cascade refrigeration with hydrocarbons (see table 4 and table 5). EU 284€/MWh, USA 79€/MWh and China 81€/MWh

4. CONCLUSIONS

Freeze drying is high energy consuming, because of the phase changes involved in the process, but also due the heat evacuation at the low temperature of -75ºC to trap (at the condenser) the removed vapors from the product.

Refrigeration in a freeze dryer is a critical subsystem that requires specialized, skilled, and trained personnel, to adjust and supervise the operation of the unit, also for the annual maintenance. The preference of the freeze dryer users and manufacturers is continuing with the well proven traditional refrigeration technology with minor modifications alongside the substitution of the refrigerant used.

Synthetic refrigerants have a high Global Warming Potential (GWP) and its use is being regulated and limited with laws that foresee its prohibition in the following years, see table 3. The maximum allowed GWP for the refrigerants is being progressively lowered, making the freeze dryer users/manufacturers to use alternative synthetic refrigerants as the R449A, with the drawback of a lower efficiency.

Refrigeration alternatives

After analyzing a case study with five different refrigeration alternatives (see figure 11), it can be concluded that, as expected, the traditional refrigeration systems **(double stage compression with synthetic refrigerants)** have a major impact to the Global Warming with higher CO2 equivalent emissions. Even using the current refrigerant alternative, the R449A with a notable GWP reduction compared to the already forbidden R507, the equivalent emitted CO2 is still high, not only because of the possible accidental refrigerant release to the atmosphere, but also due the high electric consumption caused by the poor refrigeration efficiency/performance.

The **cascade system with hydrocarbons (R-290 + R-170)** presents the lowest equivalent emissions of CO2 among the four alternatives, having negligible GWP from the refrigerants, and with a high refrigeration performance, even including an additional silicone oil loop for the condenser and shelves heat exchanger. Nevertheless, it requires a careful design (to be done case by case), and also a risk analysis including the explosion risk due the flammability of the hydrocarbons, for being under the Atex Directive, and including the Atex Certification. Also, perhaps, the cascade system with hydrocarbons, even with explosive gases, can be considered a technology close enough to the traditional systems (double stage compression), allowing the current refrigeration specialists for freeze dryers, to be adapted and updated for this new to be technology, and by this way not leaving apart the refrigeration knowledge and skills present in the existent net of professionals. On the other hand, a cascade refrigeration system has higher risk of failure because is including an increased number of components, and it may be required to review the redundancy measures. The pharma industry needs to minimize the risk of any undesirable eventual stoppage of the freeze drying cycle, for avoiding to compromise the high valuable batch under production.

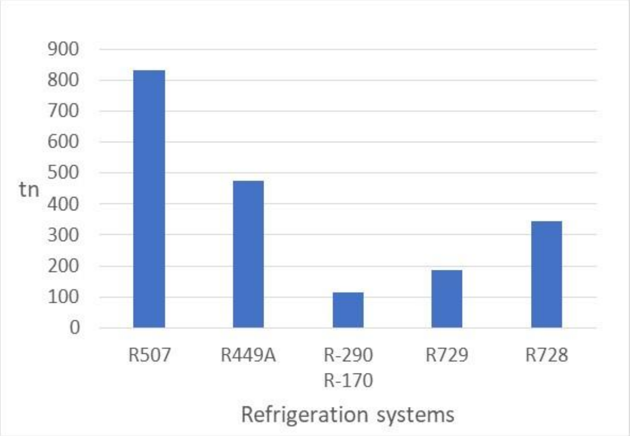

Figure 11: CO2 equivalent emissions. Case study (see table 4, table 5 and table 12) for five different scenarios regarding the refrigeration system.

Refrigeration by air (R729) is more than a fair alternative, with the second lowest level of equivalent emissions. It has zero GWP and not risk of explosion compared to the cascade with hydrocarbons. Only the lowest efficiency of the reversed Bryton thermal cycle involved, causes more emissions due an increased electrical consumption. Also, the nature of the refrigeration technology can be a barrier for the current refrigeration experts. The challenges involving the compressor-turbo expander spinning at really high speeds are of a totally different nature than for the traditional mechanical refrigeration. Finally, differently to the other alternatives, refrigeration by air lacks the capability of absorbing the peak refrigeration load at the freezing step, then and additional refrigeration solution needs to be implemented, as a silicone oil buffer inertia tank storing cooling energy.

Cooling by liquid nitrogen (R728) is a powerful and reliable option, also with zero GWP. Meanwhile the cryogenic storage tank will remain filled, there is negligible risk of failure at the refrigeration system for a robust freeze drying process. The cold generation is externalized and only a lack of supply of liquid nitrogen to the pharmaceutical plant can entail a risk to the pharmaceutical production. On the other hand, due the really low boiling temperature of the liquid nitrogen (-196ºC) and its related maximum Carnot efficiency for the liquefaction, also due the complexity of the air distillation process, the refrigeration efficiency is notably low compared to the other refrigeration alternatives.

Next steps to the future. Recommendations for seafarers.

The future of refrigeration for the freeze-drying technology is still unclear, mainly due the regulations exception for temperatures lower than <-50ºC (see table 3). Then consequently, the freeze-drying industry is delaying any required major changes.

Depending on the specific circumstances of each freeze dryer user, any of the refrigeration alternatives proposed in this paper can be an adequate solution. A pharmaceutical plant with more than 10 large freeze dryers in operation, including the traditional refrigeration system, with double stage compressors, will prefer to remain with the same technology in a future expansion of the plant, rather than acquiring a freeze dryer with a new (and different) refrigeration system. As all the units are using the same components (same spare parts) and are being supervised and maintained by the same team (specialized with the traditional technology).

The same would happen to a similar plant with existent freeze dryers all connected to a common silicone oil loop refrigerated by liquid nitrogen. In these cases, the pharmaceutical plant is typically close to a nitrogen liquefaction plant: with liquid supply assured and having good agreements in pricing for the LN2, based on the large and constant consumption over the year. A new freeze dryer to be installed at the plant, will follow the same characteristics of the existent ones, and will be integrated in the existent silicone oil loop.

Even also pharma producers that are going to start with freeze dried products, will rely on proven traditional technologies, rather than be the first ones innovating with a new refrigeration system in the market.

Nevertheless, more and more drug producers are starting to rely in the new ecological approaches with low electrical consumption and using low GWP refrigerants (hydrocarbons cascade and compressed air). Motivated by the unsafe scenario of the nearest future regarding the refrigerant prohibitions, also by ecological consciousness and economical savings in electricity. Every year, more and more ecological units are installed, starting to be not any more an innovation, and increasing their heritage in the market.

Depending on the configuration of the pharmaceutical plant, if there is not possibility to install the refrigeration system outdoors, and/or an explosion proof design wants to be avoided, the refrigeration by compressed air seems to be the most adequate solution. On the other hand, a cascade refrigeration system with hydrocarbons (even with risk of explosion) allows to have the high refrigeration efficiencies of the past and is a closer technology to the freeze dryers refrigeration experts.

Three of the five alternatives presented at this paper share the necessity of an additional silicone oil loop, as a cold carrier for the condenser and the second silicone oil loop (for the shelves). Even if some efficiency is lost due the electrical consumption of the hydraulic pump to make the oil circulate, also due the related heat added that should be additionally overcome by the refrigeration system, and additional silicone oil loop can be a crucial advantage of compatibility. The same oil loop feeding multiple freeze dryers can be refrigerated by multiple (and different) cooling units, allowing upgrades in the future and being adapted to the new regulations to come, also having the advantages of redundancy and safety. It is common in medical low temperature refrigeration, to include a safety liquid nitrogen cooling that will cover an eventual electrical failure, being the normal operation by mechanical refrigeration because of the energy (cost) savings.

An additional silicone oil loop also allows to include buffer (thermal inertia) tanks to make the refrigeration systems work with a more stable heat load and in a more limited range of temperatures. Then the constant and stable operation of the refrigeration system will minimize the thermal stress and its related failures

In any case, it seems crucial to have a global agreement among freeze dryer users, also including the freeze dryers manufacturers, to face the challenges of the future. F-Gas regulations (and its market consequences to the refrigerants production) are affecting the same, to all the different applications in the industry, and perhaps the specifity and complexity of the freeze drying technology is going to require special care and intention for the new ecological challenges to come.

Starting from the different applicability of the prohibitions of fluorinated gases over the globe; it is well known that while in some countries it is going to be almost impossible to be supplied with synthetic refrigerants for low temperature (even if allowed by the regulation exceptions), other countries will continue normally its production and freeze dryer users will continue with its use.

Perhaps the solution could be technological, breaking the resistance to the change by assuring enhanced freeze dryers robustness, reducing the risk of the extreme operation of the refrigeration systems over the continuous production batches. Low temperature refrigeration experts are always claiming that the risky stage at low temperature is during the cooldown of the system, then when the unit is at the low temperature regime, is at its most safe and reliable state. Maybe the refrigeration systems can only be warmed up and cooldown again once a year for maintenance (differently to the aprox 87 times batches over the year in our case study).

5. FINAL COMMENTS

Notes about the author

Carlos Amor has been working with high vacuum and low temperature technologies for more than 10 years. He is graduated in Industrial Engineering and specialized in thermal energy, currently working for obtaining his Phd in freeze drying.

With over 10 years of experience on the pharmaceutical market: sales, process design and optimization, for freeze drying equipment and related machinery.

Founder of Lyoptimus Thermodynamics, he is specialist in simulation methods to optimize freeze drying processes. Focused on creative solutions for pilot scale batches for biologic drugs, and to adapt current processes to the new GMP Annex 1.

Additional notes from the author

I started to think about the content of this whitepaper during an A3P freeze drying event at Lyon, in March 2023. The main topics during the three days event were the applicability of the new Annex 1 of GMP to the freeze-dried products production, and the ecological perspective for the freeze dryers. Exceptional and spiring speeches from different experts were hold, providing valuable data and insights, about the refrigeration systems, the refrigerants GWP, and also about the process energetic consumptions.

On my way home it was necessary for me to rethink and evaluate by myself the situation, partly because I do not understand clearly something until I do not calculate and review in deep the topic, also I needed to put together the different proposed ideas at A3P. I needed to relate the refrigerants GWP potential with the equivalent CO2 emitted due the electric consumption.

I was suspicious that all the efforts for reducing the GWP of the refrigerants could be useless, because at the end, the CO2 emitted due an increased electrical consumption (due a low efficiency of the refrigeration system), could be superior to the equivalent CO2 from the eventual release of refrigerant to the atmosphere. Specially I was suspicious because the F-Gas regulations are applied the same for all the refrigeration applications at the industry, and freeze drying could have exceptional characteristics. After this review, is more than clear for me, how important is to regulate and control refrigerants by its GWP, as one accidental release of a synthetic refrigerant of the freeze dyer can be equivalent, or more contaminant, than 10 years of operation of the same

I hope the reader will find this text clarifying and useful, as for me has been writing it. I made an effort to detail all the assumptions considered, I also provided all the used references. I tried to be impartial among the five refrigeration alternatives, although I had some preferences before starting the analysis. My initial perception of the situation has changed after doing this careful review.

All the presented results are obtained by thermodynamic calculations; heat balances considering the second thermodynamics law, efficiency at the thermal cycles. The compressors performance has been obtained making use of the available simulation software from the manufacturer Bitzer **[11].**

The primary drying step of the freeze drying cycle has been simulated according to the general agreed assumptions on the literature, for more details see my previous white paper **[12]** (*How Lowering the Pressure may Improve the Freeze-Drying Recipes and Accelerate the Lyophilization Cycles for Compounds with Low Critical Temperatures. New Biotechnological Active Ingredients*.)

Many thanks for reading so far, you are more than welcome to let me know about your comments/clarifications, please write me an email to: carlos.amor@lyoptimus.com

Figure 12: Carlos A. Amor

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