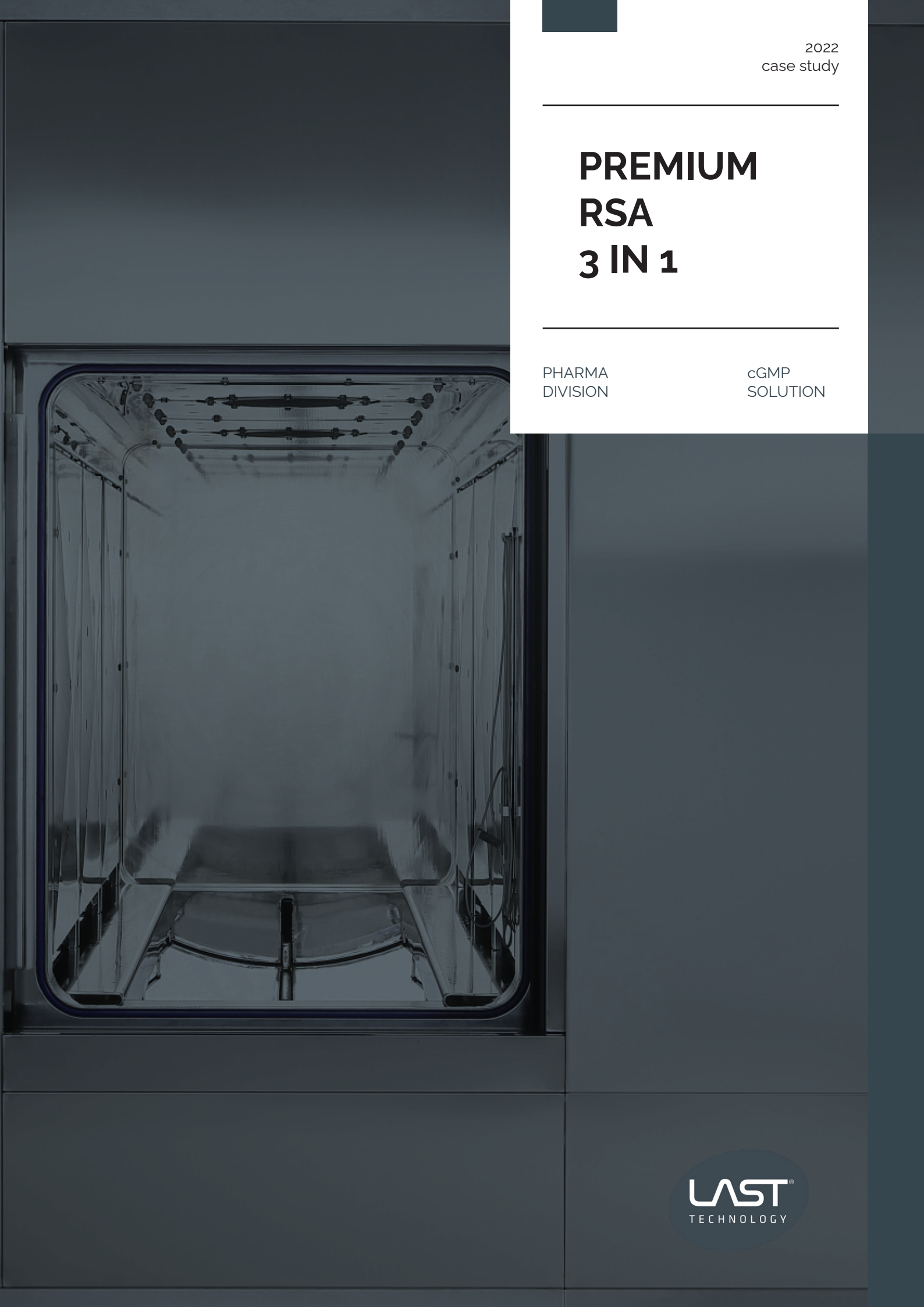
2022
case study

PREMIUM RSA 3 IN 1

PHARMA
DIVISION

cGMP
SOLUTION



LAST® TECHNOLOGY

The Customer Requirement

PROJECT INVOLVING A STERILISER WITH 3-IN-1 COMBINED PROCESSES

With the advent of Industry 4.0, many companies have felt the need to possess multifunctional, flexible machines that in addition to being able to vary the process type, can handle materials of a different nature; something they would have been unable to do in the past. This need also stems from an attempt to contain production costs and consequently review the production layouts.

Given that the pharmaceutical industry provides for customisable processes that differ from one another - according to the product being treated - it is easy to understand why up to now machines have been designed to handle only one load type.

For example, should a client require that surgical instruments, drapes and non-thermolabile rubber be treated in a hospital and clinical sterilisation setting, then the pharma sector increases the spectrum with solid and liquid substances provided in multiple types of packaging, such as vials, bottles, blister packs, pre-filled syringes, BFS containers, etc.

More specifically, the client - who works as a subcontractor (CDMO) - asked for a single machine that could sterilise different load types, according to their customers' requests. In this way, they could avoid having to procure multiple machines; with each of which only handling one load type.

In order to process the materials more fluidly, we distinguish the loads according to their physical state: solid or liquid.

The **solids** are in turn of a different nature, but generally grouped together in a single process that uses **saturated steam in a hermetic vacuum chamber.** This involves the use of special pumps.

Liquids, on the other hand, depending on the type of packaging, may require many different processes. In fact, they can be made of plastic, glass, sealed or open.
Currently, the following are used: cycles comprising a mixture of **air + steam** and cycles in which the sterilising agent is **superheated water.**

These machines' configurations vary substantially from one another, making it difficult for the market to offer solutions that incorporate everything needed to treat different load types in a single process or a single machine.

Preliminary points to consider before designing the right machine solution

Before homing in on innovative solutions to meet the client's needs, LAST Technology's engineering team pinpointed some irremovable points which formed the basis upon which a detailed analysis could be carried out:

- The machine had to comply with the EC, EudraLex and FDA directives, in addition to the cGMP good manufacturing standards, provided that it will be intended for pharmaceutical use.
- The machine had to remain rather flexible in order to be able to parametrise the machine and in turn, sterilise different load types.
- The internal and external surfaces had to be accessible to make cleaning and removing dirt easier, whilst the technical compartments had to facilitate maintenance operations.
- The safety conditions inside the chamber had to be established without compromising the sterility of the product being treated.
- A software sampling system had to be created to record process data (temperature and pressure) during every phase.
- A reporting system had to be created that integrated sample points, alarms signalled and operations carried out by the operator during the entire cycle.
- An automation and control system would have to be fitted to the machine; this user panel-controlled system would limit the operations needed to be performed by the operator.
- Energy-saving solutions had to be introduced which would allow the generated heat to be recovered and also minimise dispersion.
- Safety systems had to be designed to prevent the machine's doors from opening when it is vacuumed or pressurised.
- Safety valves would have to be used to protect both the machine and operator from high pressures that could be generated in the steam and pneumatic circuits.
- Constructive solutions had to be used to limit the propagation of the machine-produced noise.

Sterilisation

Sterilisation is the process that removes microorganisms - such as bacteria or spores - from objects or substances by administering heat, chemicals and radiation.

The project in question involved needing to unify various sterilisation processes in a single machine by administering moist heat, and staying away from any dry heat practices or chemical agents, such as ethylene oxide and radiation.

Moist heat gets its name from the fact that water in liquid or gaseous form is used to generate thermal energy.
The sterilisation processes that were considered for integration into a single device can therefore be summarised as follows:

- Saturated steam sterilisation
- Sterilisation using a mixture of air + steam
- Sterilisation via superheated water

During an initial meeting, the various processes were compared to outline the three process' similar and differing characteristics. In general, all processes are characterised by a pre-treatment or conditioning phase, an exposure phase (sterilisation) and a final phase: cooling and drying.

The individual processes

1. SATURATED STEAM

Saturated steam, intended as a process fluid, comes into contact with the solid load to be treated, thus releasing a large amount of thermal energy.

In order for this to be evenly distributed on all the load's surfaces, the air is fully extracted from within the sterilisation chamber, in order to exclusively saturate the volume with saturated steam.

The air is extracted by means of alternating depression phases, generated by the suction of a vacuum pump and sudden pressurisations by means of introducing steam. In addition to fully extracting the air, the temperature is increased until it reaches the set sterilisation value. This is the pre-treatment or conditioning phase.
The actual sterilisation phase follows which maintains the temperature for a pre-established time.

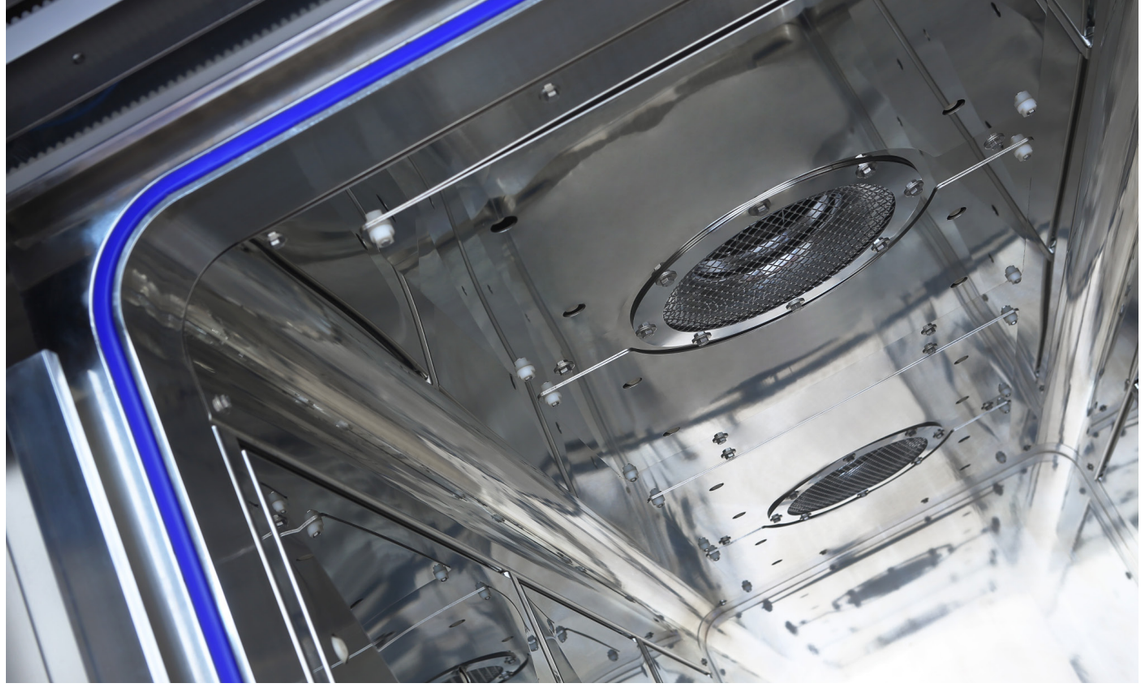
The final step - aka the load cooling and drying phase - is obtained by generating a high vacuum to promote the evacuation of any condensation and introducing water into the cavity. At the end of the vacuum phase, the pressure inside the chamber is restored to that of the external environment (atmospheric pressure).
This process can also be used to process **open or sealed liquids.**

The only difference is that a high vacuum cannot be used for the pre-treatment or cooling phase. Instead, bursts of steam that mechanically push the air out of the chamber are used. It is then pressurised and depressurised, without ever falling below a pressure value that could damage the load. In this way, much of the air in the chamber is expelled by gradually increasing the temperature.

POROUS, NON-POROUS AND LIQUID

60°C - 134°C

SATURATED STEAM + AIR/STEAM MIXTURE + SUPERHEATED WATER



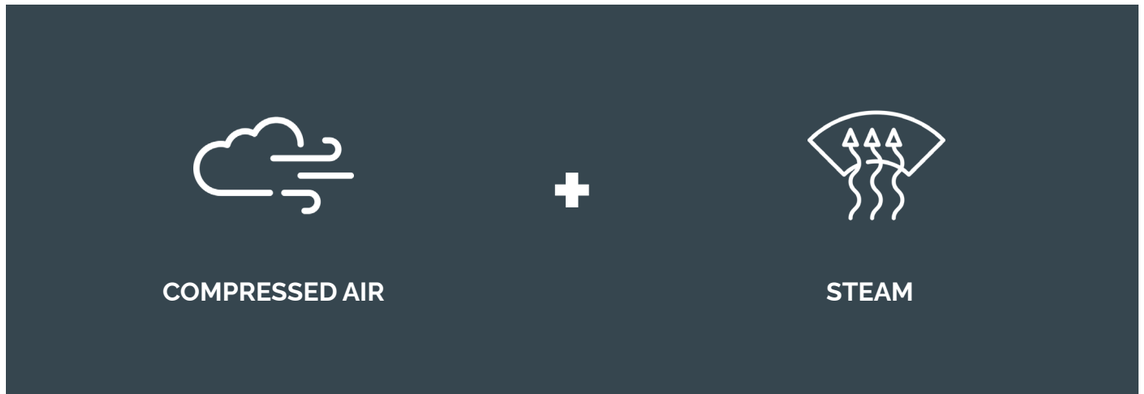
2. AIR + STEAM

For this type of sterilisation, steam is still the process fluid, but liquids stored in hermetically sealed containers will be treated instead.

Only air is heated by injecting steam into the chamber. Fans that continuously mix steam with air will operate to ensure that the heat is evenly distributed on the load; used primarily for glass or plastic containers.

Next follows the sterilisation phase and the cooling phase is at the end. To prevent the containers from breaking during this last phase, a counterpressure sterile air is introduced into the chamber to balance the overpressure inside the container/product.

The cooling efficiency is increased thanks to the aforementioned fans that allow the hot air + steam mixture to reach the surfaces of the exchangers, located inside the chamber and powered with cooled or glycol water.



3. SUPERHEATED WATER

This process is ideal for sterilising all products stored in plastic containers that could deform upon contact with steam, e.g. bottles, bags and vials containing pharmacological or physiological injectable solutions.

The load is sprayed directly with superheated water. The water is loaded into the machine and heated to the treatment temperature (this typically ranges between 105°C and 121°C) by means of steam-powered heat exchangers.

Meanwhile, the difference in pressure (Delta P) between the inside of the load and inside of the chamber is compensated for by introducing compressed air.
The water is continuously recirculated between the chamber and the exchangers, thus ensuring a stable temperature for a set time.

The chamber's internal pressure is modulated during every process phase by means of compressed air.

Once the sterilisation phase is complete, the load is cooled by the same water, but by this time cooling it through cooled or glycol water-powered exchangers.

The project

We strove to create a chamber able to facilitate air expulsion during the pre-treatment/ conditioning phases - most especially for the air + steam processes - and to make the temperature as homogeneous as possible.

For this reason, the team decided to build a circular chamber, complete with two doors that would be automated by means of horizontal linear displacement. The chamber is also equipped with a cavity to ensure greater stability during the sterilisation phase and to cool the liquids treated with saturated steam processes or with a mixture of air + steam.

The chamber and entire machine have been designed specifically for use in the same temperature conditions ranging from -10 to +143°C (the minimum and maximum admissible temperature) and in pressure conditions ranging from -1 to +3 bar (the maximum depression and maximum admissible pressure, respectively).

As a result of these data, the machine fell into category III, as indicated by the 2014/68/EC regulation. The vessel was designed according to the calculation indications of the ASME VIII Div. 1-15 code.

The piping was designed in line with pharmaceutical regulations (ASME BPE-2019), by means of hygienic "tri-clamp" ferrules. The piping was orbitally welded at full TIG penetration, in order to promote the circulation and drainage of liquids on suitable surfaces.
As far as combining the three processes was concerned, automatic diaphragm valves with an AISI 316L stainless steel body were inserted to disconnect the hydraulic circuit, whenever necessary.

More specifically, the machine was equipped with a line that breaks the vacuum whilst drying the saturated steam-treated load and filtering the compressed air. The line allows air - extracted from the external environment or the compressed air line - to be introduced into the chamber after being filtered in an absolute-rated hydrophobic filter (0.22 microns).

The search for the right filtering system was an important investment in terms of time, as the team strove to find the best system capable of guaranteeing product sterility at the end of the sterilisation phase.

A great deal of effort was put into developing the control software. The team's main intention was to automate as many machine processes as possible by limiting the operator's duties to process selection and manual operations (such as loading and unloading).

Rsa Premium

The chamber's interior - like all the elements that come into contact with the process fluids - are made of AISI 316L stainless steel, whilst the external structures are made of AISI 304.

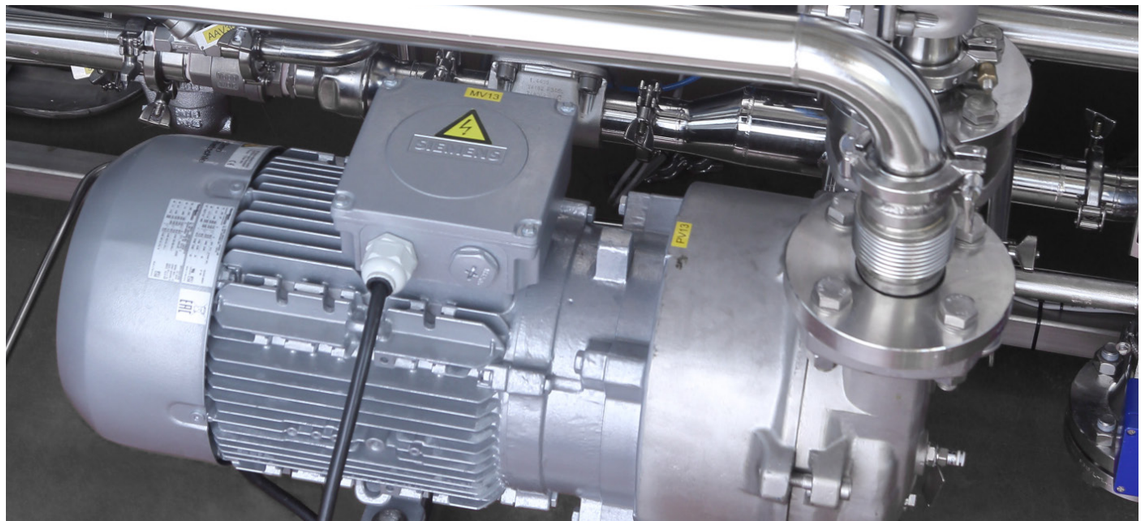
The machine boasts a unit comprising two external exchangers - that heat and cool the water sprayed during the superheated water process - and four exchangers inside the chamber; the latter of which allow for temperature control and the more rapid cooling for processes that use a mixture of air + steam.

Two fans have been installed on the top of the chamber to ensure that the air + steam mixture is evenly distributed.
To ensure the safety of the hydraulic circuits, the machine has been equipped with safety valves calibrated specifically to protect:

- the chamber (calibrated to 2.5 bar);
- the cavity (calibrated to 2 bar);
- the pneumatic circuit (calibrated to 4.5 bar).

Pressure and level sensors, pressure transducers and temperature probes were distributed for an in-depth process control at specific points on the machine. For example, inside the chamber for the operator to put inside the liquids/sample containers. In this way, the internal temperature of the liquids can easily be monitored and compared with the temperature inside the chamber.

To save water, the team provided the option to allocate and store the amount of water needed to perform the superheated water cycles, at the bottom of the chamber. The operator can decide whether or not to drain the process water or reuse it for a new cycle.



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