

COSTER
MACHINERY DIVISION

Making MDI valves, actuators and filling equipment suitable for HFA



MDIs HAVE GROWN IN POPULARITY SINCE THEIR INTRODUCTION IN THE LATE 1950s.

USED BY MILLIONS OF PEOPLE FOR A WIDE VARIETY OF DISEASES, SUCH AS ASTHMA AND COPD.

MDIs CONTAIN ACTIVE APIs DISSOLVED OR SUSPENDED IN A PROPELLANT.

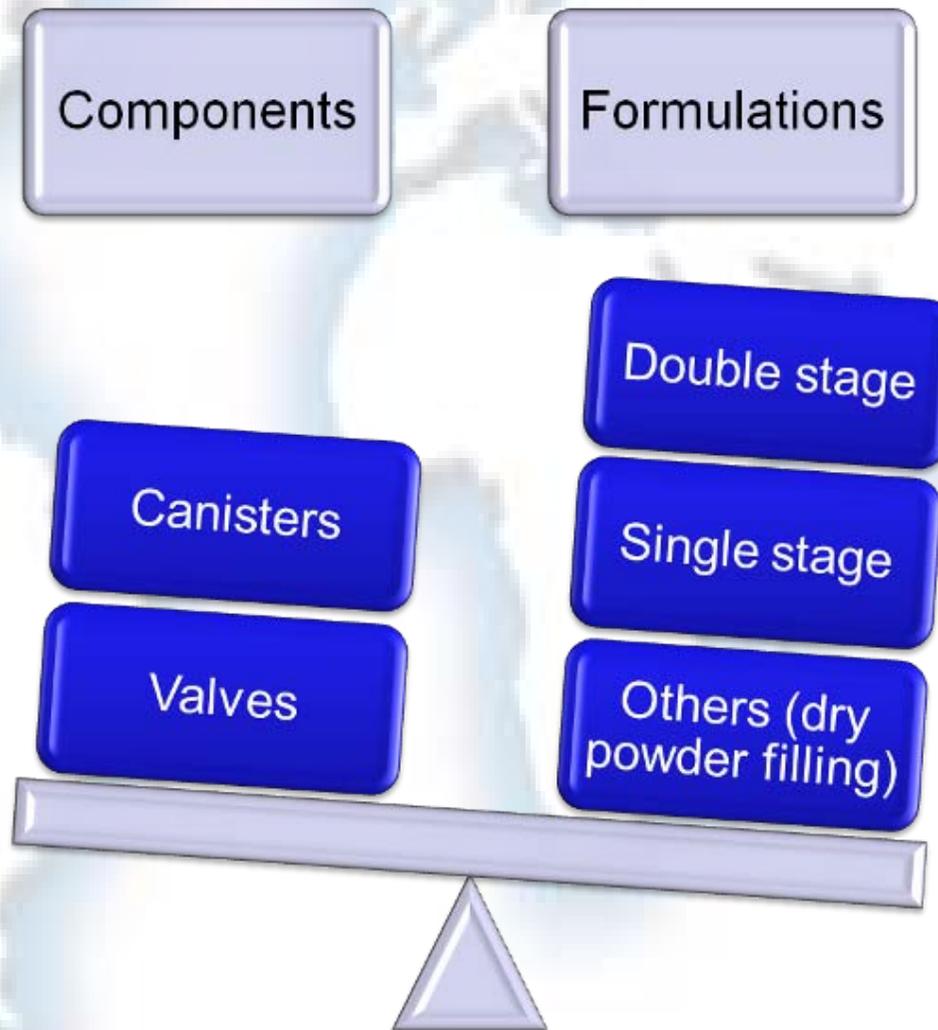


Currently, two different propellants are still used in the world: old formulations with CFC and new formulations with HFA

HFA - 134a	CFC - R 12
Gas Properties	Gas Properties
Liquid phase	Liquid phase
<ul style="list-style-type: none">• Liquid density (1.013 bar and 25 °C (77 °F)) : 1206 kg/m³	<ul style="list-style-type: none">• Liquid density (1.013 bar at boiling point) : 1486 kg/m³
<ul style="list-style-type: none">• Boiling point (1.013 bar) : -26.6 °C	<ul style="list-style-type: none">• Boiling point (1.013 bar) : -29.8 °C
<ul style="list-style-type: none">• Latent heat of vaporization (1.013 bar at boiling point) : 215.9 kJ/kg	<ul style="list-style-type: none">• Latent heat of vaporization (1.013 bar at boiling point) : 166.95 kJ/kg



The most important features in the HFA filling process for MDIs





MDI components and formulations have a direct impact in the filling process and equipment

Machinery is strictly linked with:



Type of valve and canister for the feeding system



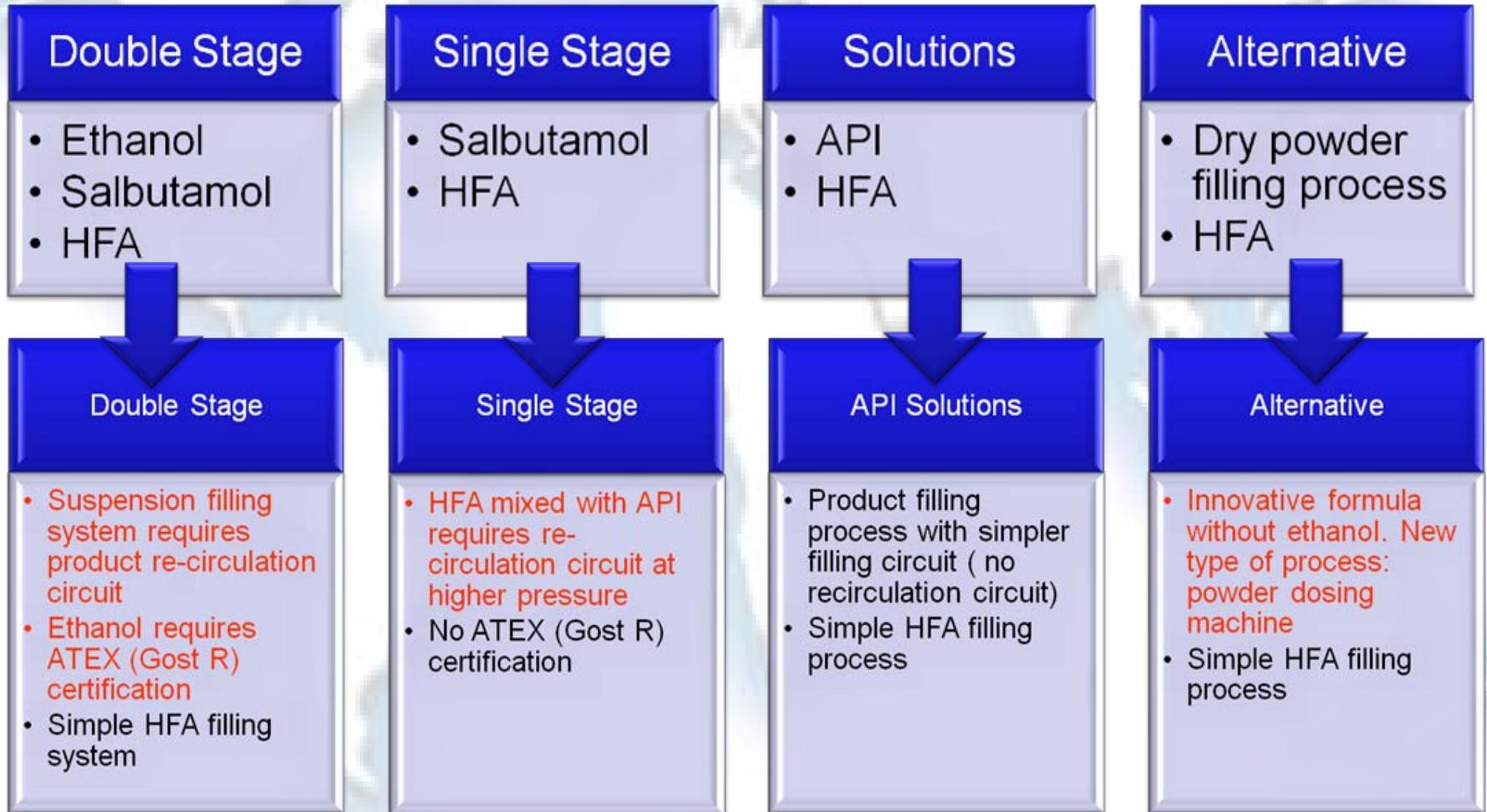
Type of product (solution or suspension) for the product filling system



Type of propellant (CFC or HFA) for the gas filling system



In the Salbutamol filling process the equipment depends on different aspects





In the future, formulations will combine more than 2 APIs in one product. Equipments should be flexible and suitable for different combinations of APIs, valves, canisters and type of propellants.

Different filling systems already installed in the machine or suitable to be upgraded

Universal canisters feeding system (e.g. cut edge cans)

Universal valves feeding system (e.g. Different mounting cup height of the valve)

Propellant filling system suitable for different type of propellants (CFC, HFA, LPG)



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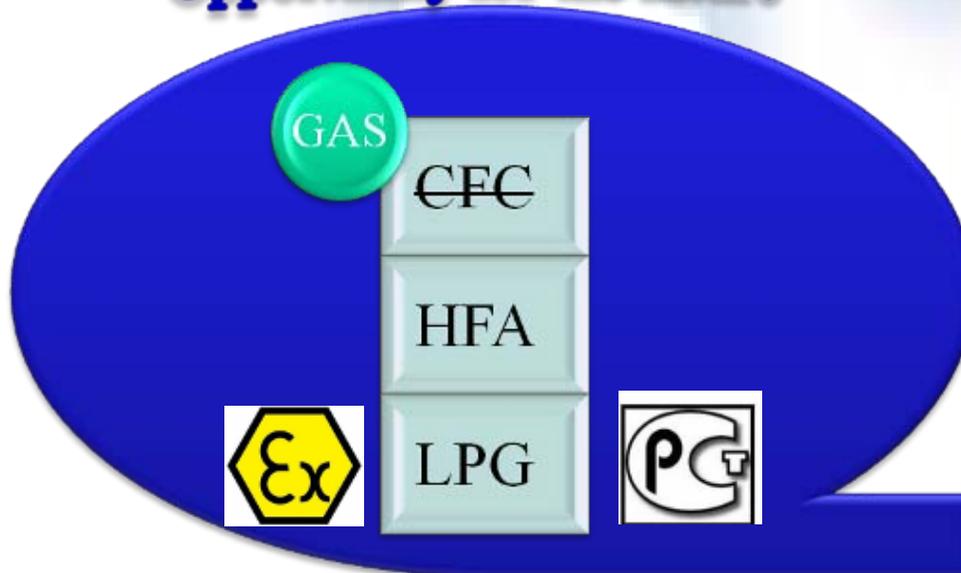
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Opportunity for the future



Metering cylinder with lower capacity (1ml) combined with larger capacity (20 ml)

Automatic system with fast changeover for different canister height

Vibrator bowls able to manage different shoulder heights of the valves

Ceramic plunger suitable for powder suspended in the gas (HFA or others)



Inspections

- System to check crimping operation.



- Coster is conducting new studies for leak detection by using thermal control system with UNIMI University of Milan
- System to check functionality of the valves.



In summary

- HFA is widely used in different pharma applications
- Formulations have a direct impact in the process and therefore in the equipment
- When using alcohol or LPG the machines should be a Gost R (ATEX) certified
- Equipment must be flexible and ready to accommodate new formulation developments



MDI valve

- One of the most complex and challenging work for Coster was developing MDI valves suitable for HFA formulations
- Coster has worked and continues to work with its customers throughout the whole process to successfully transition from CFC to HFA valves
- The MDI valves have been validated by pharma companies in different geographical regions
- They are being widely used with a variety of formulations:
 - Suspensions & solutions
 - With & without ethanol
 - Single & double stage filling





MDI valve

- The valve is one of the most critical MDI components
- Coster valve has a reduced contact area between gasket and formulation
- Plastic materials and gaskets are EP/USP compliant
- Production process takes place in an ISO 7 classified Clean Room, according to ISO 15378:2006 cGMP standards
- Extractables analyses have been carried out by an external certified Lab and are available
- A Technical Dossier including regulatory, performance and compliance data supports our customers when submitting their registration applications



ISO 7 Clean Room and Lab





MDI Actuator

- The shape and size of the API particles have a direct impact on the formulation efficacy
- The right particle size grants that the medication reaches the lower airways
- Coster has developed MDI actuators with a specific spray hole shape and dimension:
 - A proper nebulization can be granted
 - Softer spray with no cold throat effect
 - Limited deposition in the actuator mouth piece
- A Technical Dossier including regulatory, performance and compliance data supports our customers when filing their registration applications





Coster offers its valve know-how and expertise as well as its core competencies to support customers in their CFC to HFA transition





R&D Activities

- Coster collaborates with local Universities and Int'l Research Centers on an ongoing basis
- A pilot MDI filling lab is currently being set up
 - Filling tests with different APIs
 - Wide range of analyses foreseen
 - Customer training & visits
 - Located in a Bio-park in Northern Italy



Local presence

- VA Intertrading, Coster Agent for Russia & CIS countries, with their Moscow office, can provide a turnkey solution and local support by supplying:
 - MDI valves
 - MDI actuators
 - MDI cans
 - MDI filling equipment
 - APIs





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