Conversion to non-CFC MDI

Problems associated with conversion to HFA at two Russian enterprises

EXPERT GROUP MEETING ON ELIMINATION OF CFCs CONTAINED IN AEROSOL METERED DOSE INHALERS (MDI) IN THE COMMONWELATH OF INDEPENDENT STATES (CIS)
5-6 OCTOBER, MOSCOW

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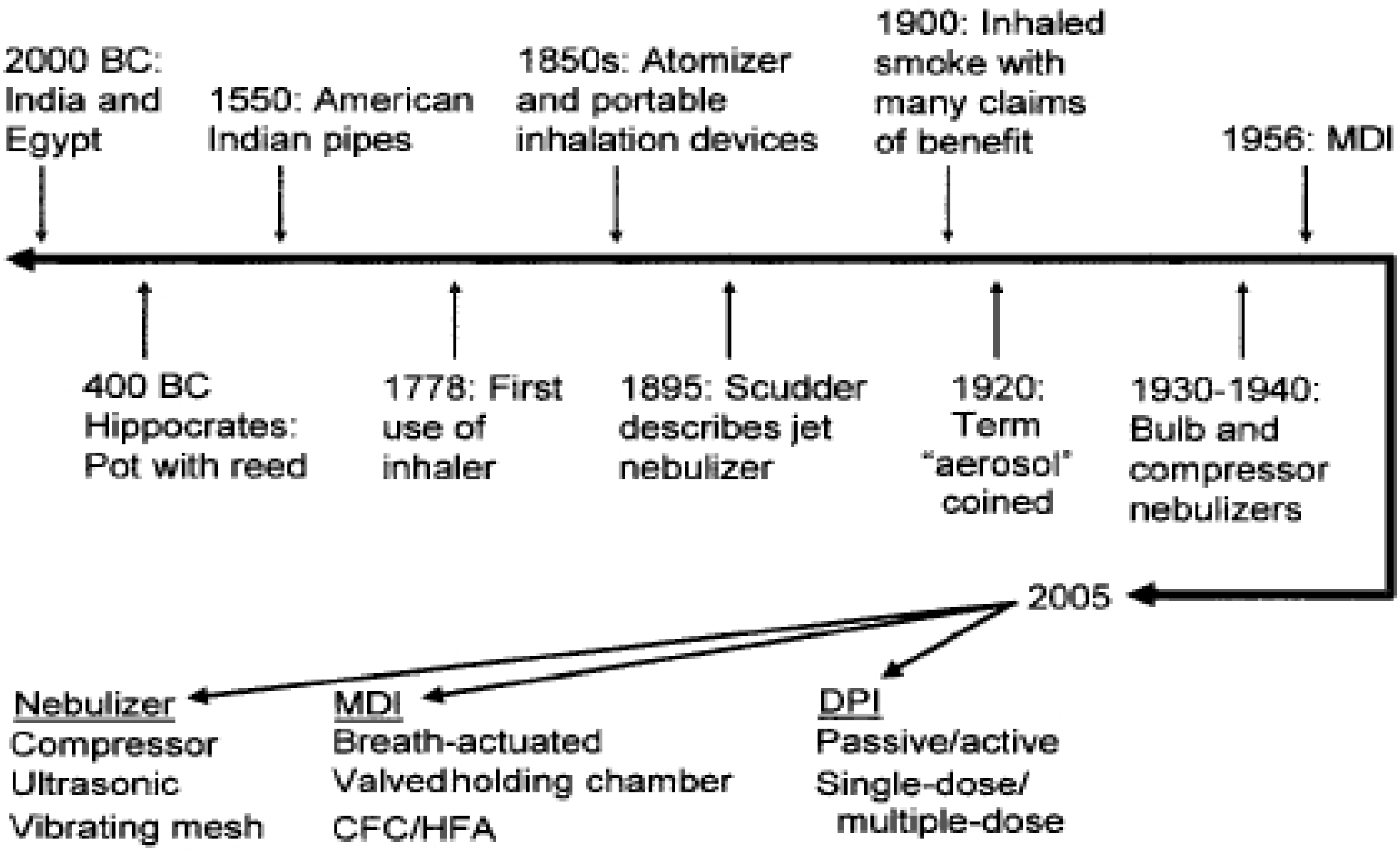
HISTORY OF INHALERS



MDI or DPI – OUR CHOICE?

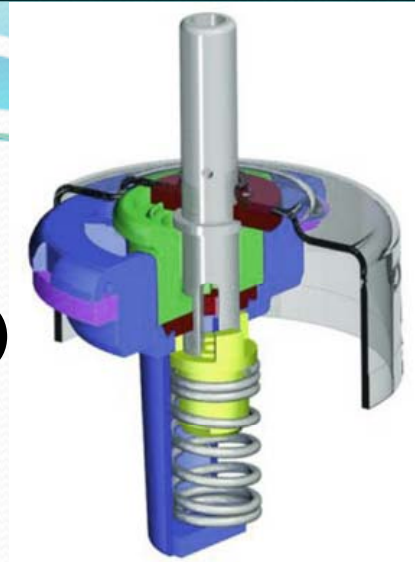
The use of inhaled aerosols allows selective treatment of the lungs by achieving high drug concentration in the airways and reducing systematic adverse effects. Not only is aerosol therapy used to treat lung disease, but increasingly inhalation is being explored as a method for systematic drug delivery (eg, inhaled insulin and inhaled narcotics) The effectiveness of inhaled drugs depends not only on the formulation, but perhaps even more on the delivery device and the patient's ability to use the device correctly. This is an important disadvantage. An increasing variety of MDIs and DPIs are becoming available. This has been driven by the development of new formulations and the impending ban on CFC propellants. The result is a proliferation of devices, resulting in a confusing number of choices for the health-care provider as well as confusion for patients trying to use these devices correctly.

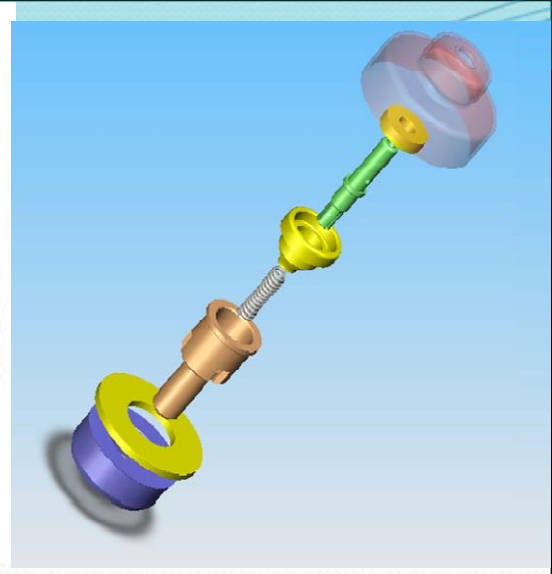
MDI - Background

Metered Dose Inhalers (MDIs)

- Pressurized system
- Contains liquefied gas (propellant)
  - Propellant suspends drug substance
  - Provides energy
- Surfactant - stabilize suspension formulation
- Co-solvents - formulation aid
- Dispense micrograms to milligrams API per actuation
- Small precise volume delivered (25 - 100 µl)

MDI - Background





Metered Dose Inhalers (MDIs)

- Sequence of events:
  - Formulation expelled from valve
  - Liquefied gas vaporizes
  - Propelling and dispersing drug substance

- Dispersed drug substance characterization
  - Particle size distribution (PSD)
  - Dose content distribution (dose content uniformity)

Pressurized Metered Dose Inhalers (pMDIs)

- Portable
- Apparently Easy to Use
- Remaining Product is Uncontaminated
- Tamper-proof
- Protects Drug from light, O_2 and H_2O
- Multiple Dose
- Accurate Dose Metering
- High Respirable Fraction
- Inexpensive
- Mature Technology / Established Vendors

DPI- Background

Dry Powder Inhalers (DPIs)

- Contains micronized drug substance with or without carrier
  Lactose - most common carrier

- Energy supplied by:
  - Patient inspiration
  - Compressed gas
  - Motor-driven impeller

- Current designs
  - Pre-metered
  - Device-metered

DPI - Background

Dry Powder Inhalers (DPIs)-Advantages

Typical advantages of dry powder inhalers are:

- Propellant freed design
- Less need for patient co-ordination
- Less potential for formulation problems (formulation stability)
- Less potential for extractables from device components
- Environmental sustainability

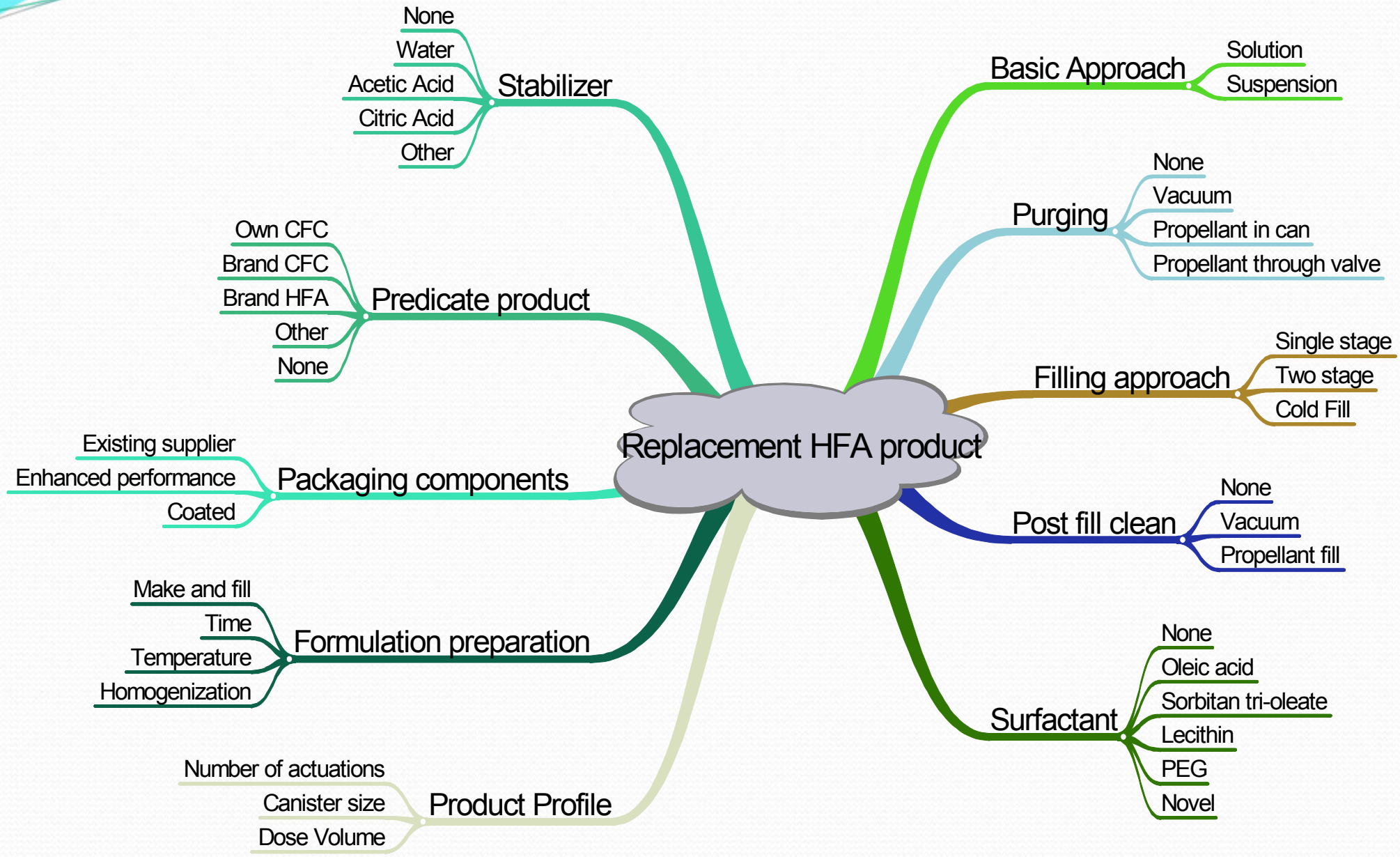
DPI - Background

Dry Powder Inhalers (DPIs)-Disadvantages

Typical disadvantages of dry powder inhalers are

- Dependency on patient's inspiratory flow rate and profile
- Device resistance and other design issues
- Greater potential problems in dose uniformity
- Less protection from environmental effects and patient abuse
- More expensive than pressurized metered dose Inhalers
- Not available world wide
- Development and manufacture more complex/expensive

Factors considered in MDI re-formulation



MDI Problem 1 -Difficulties in Compounding

Drug Delivery System

Dosing and performance

- Design
- Reproducibility
- Performance characteristics
- Affects safety and efficacy

Formulation compatibility

- Metering valve
- Canister lining - corrosion of underlying metal
- Drug absorption into plastic components
- Swelling
- Leaching

Definitions

Extractables:

– Compounds that can be extracted from elastomeric and plastic components, coatings of, and residues on a CCS component

when in presence of appropriate solvent(s) and under stressed extraction conditions

Leachables:

– Compounds that may migrate into the formulation from the elastomeric, plastic, coating of, or residues on CCS component,

– Contaminants from processing aids (e.g., lubricants, cleaning and washing agents) used during

- Processing of CCS components
- Manufacture of the drug product

– Contaminants from environment

The deliverables

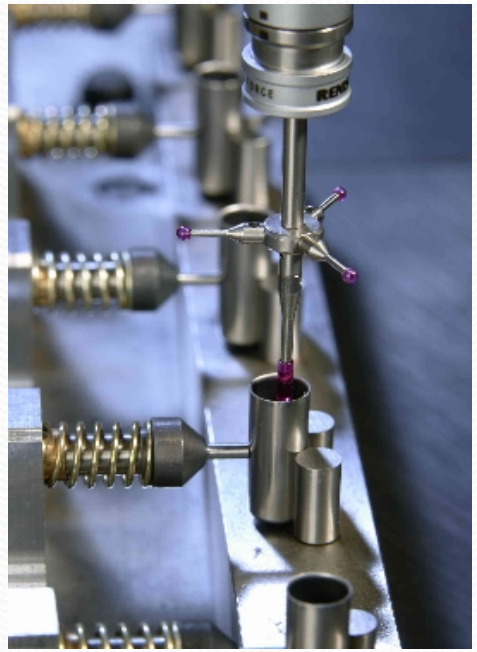
- A full manufacturing product specification detailing all active components, excipients and packaging components, in addition full performance specifications and test methods will be disclosed.
- Selection and rationale for the selection of the packaging components.
- A report summarizing any intellectual property considerations that the proposed approach may have for the client.
- Formulation data package containing all process steps, sequences, temperatures etc.
- A report demonstrating scalability of the formulation package, up to a maximum of a 5,000 canister single manufactured batch.

Continued

- A limited stability study confirming acceptable stability performance (compliance with agreed specification) **for a minimum of 6 months at 40C/ 75 RH.**
- Fully detailed analytical methods required for manufacture and release of the product and associated training etc. to support technology transfer.
- Assistance in the verification of local implementation of analytical methods (supply of reference standards and samples, second site analysis).
- On-site support during the manufacture of up to three verification and/ or registration batches of the formulation).
- **Chemistry, Manufacturing and Controls (CMC) data package** from in-house activities, to support local market authorization filing by client.
- Support to the client with applications for clinical trial notifications, new drug applications or applications for marketing

PRODUCT DEVELOPMENT PROTOCOL

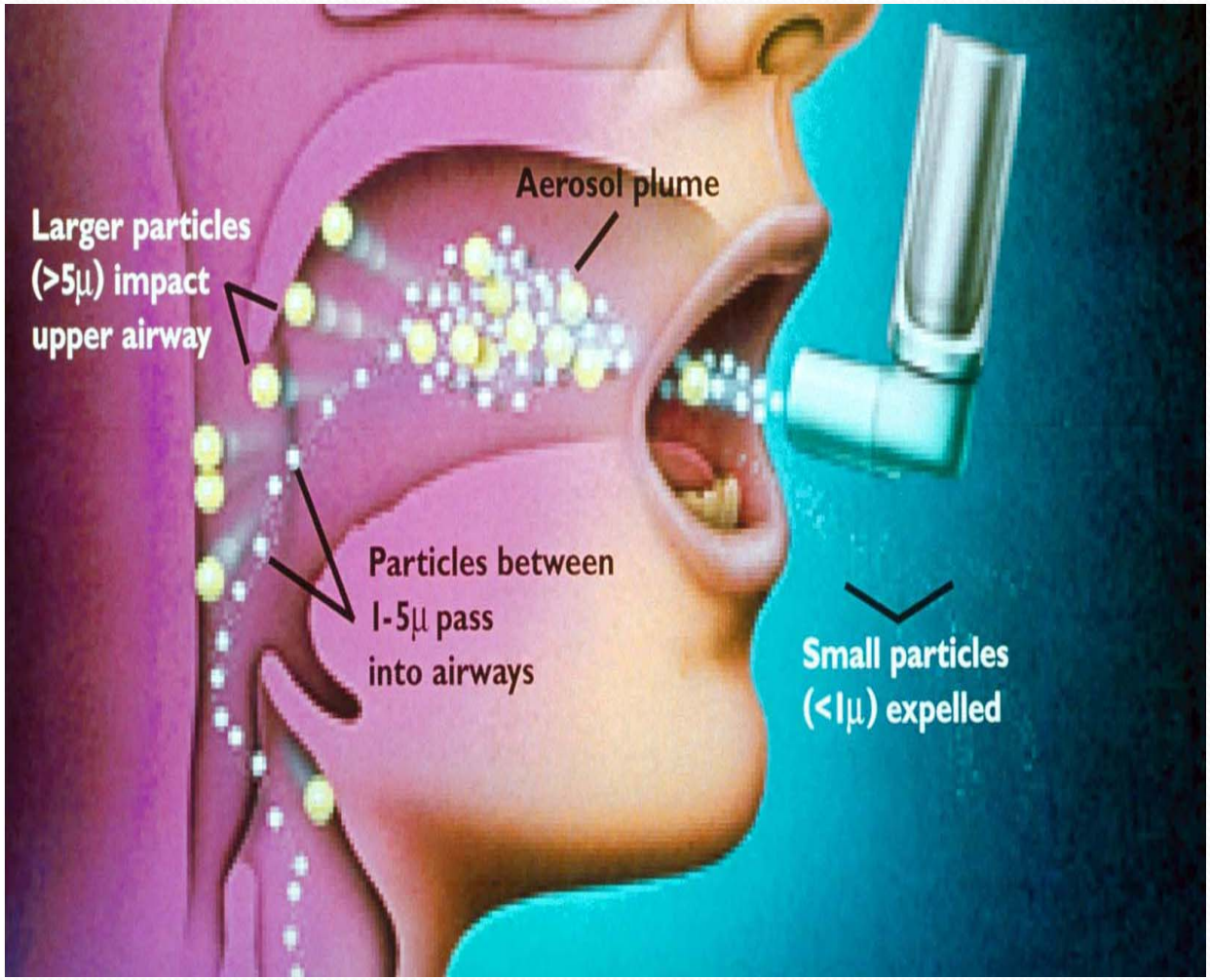
1. FORMULATION DEVELOPMENT
2. PRODUCT DEVELOPMENT
3. METHOD DEVELOPMENT AND VALIDATION (HPLC AND NON-HPLC)
4. PACKAGING COMPONENT DEVELOPMENT
5. SPECIFICATON DEVELOPMENT
6. PROTOCOL DEVELOPMENT
7. STABILITY STUDY
8. IN-VITRO BIOEQUIVALENCE STUDY
9. CHARACTERIZATION STUDY
10. PRE-CLINICAL TESTING



MDI Problem N^{0}2-Stability

Selection of

- Solution or
- Suspension



Solubilities in water and ethanol of various inhaled drugs

API	WATER	ETHANOL
Salbutamol Sulphate	Freely Soluble	Practically Insoluble
Salbutamol Base	Sparingly soluble	Soluble (96%)
Levalbuterol HCL	180 mg/ml (Freely)	Practically Insoluble
Formoterol fumarate	Slightly soluble	Sparingly soluble
Fluticasone Propionate	practically insoluble	slightly soluble 95% ethanol
Ipratropium Bromide	freely soluble	Slightly soluble
Mometasone furoate monohydrate	practically insoluble	Slightly soluble
Beclamethosone Dipropianate	Very slightly soluble	Freely soluble/ Sparingly soluble (96%)
Salmeterol Xinofoate	sparingly soluble	slightly soluble
Salmeterol Base	Slightly soluble	Sparingly soluble
Fenoterol hydrobromide	Soluble	Soluble
Nedocromil sodium	Soluble	
Triamcinolone Acetonide	practically insoluble	Sparingly soluble
SCG	Soluble	Practically Insoluble
Bambuterol hydrochloride	Freely Soluble	Soluble
Budesonide	practically insoluble	Sparingly soluble
Terbutaline Sulphate	1 g / 1-5 ml (Freely)	1 g / 250 ml (Slightly)

MDI - Solution/Suspension: Pros/Cons

- **Solution**

+ No need to control the particle size of the drug

+ Better content uniformity performance due to homogeneity of formulation

+ No need to agitate can before dose (easier patient use)

- Drug chemical stability issue

- **Suspension**

+ Better drug chemical stability over time

+ Easier to formulate due to insolubility of some drugs

- Content uniformity is more irregular mainly due to sedimentation, flocculation, creaming problems…

- Impact of drug particle size, morphology…

Solution/Suspension : Pros/Cons

=> Solution formulation: require significant amounts of Ethanol to dissolve the drug (when possible, which is not the case for Salbutamol for example)
=> Addition of significant levels of Ethanol have been reported to be associated with bad taste when used by patients (during the switch from CFC to HFA inhalers for example)
=> Requirements for the valve are as follows:
- for solution aerosol, need materials that offer good compatibility with Ethanol & good chemical compatibility with the drugs (to avoid chemical degradation)
- for suspension aerosol; critical to reduce the potential for increased actuation force/friction (as the powder may accumulate around functional gaskets)
=> Can lining for suspension: this is to prevent can wall adhesion which can occur in HFA suspensions (depending on suspension characteristics)
=> There is not real tendency in the world really. Suspensions remain dominant as Salbutamol accounts for the majority of sales and references (in numbers) and Salbutamol can not be formulated as a solution. Both solutions & suspensions are being developed by a number of companies.

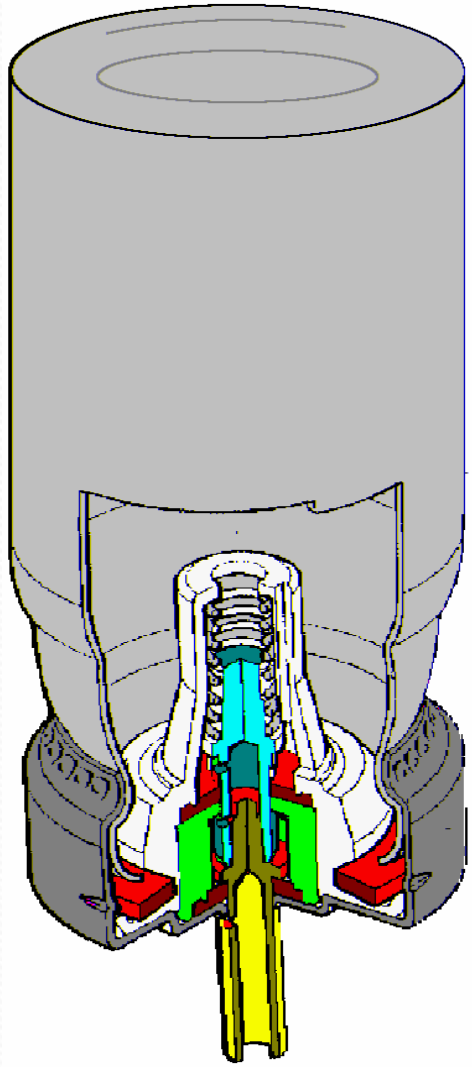
Budesonide formulations

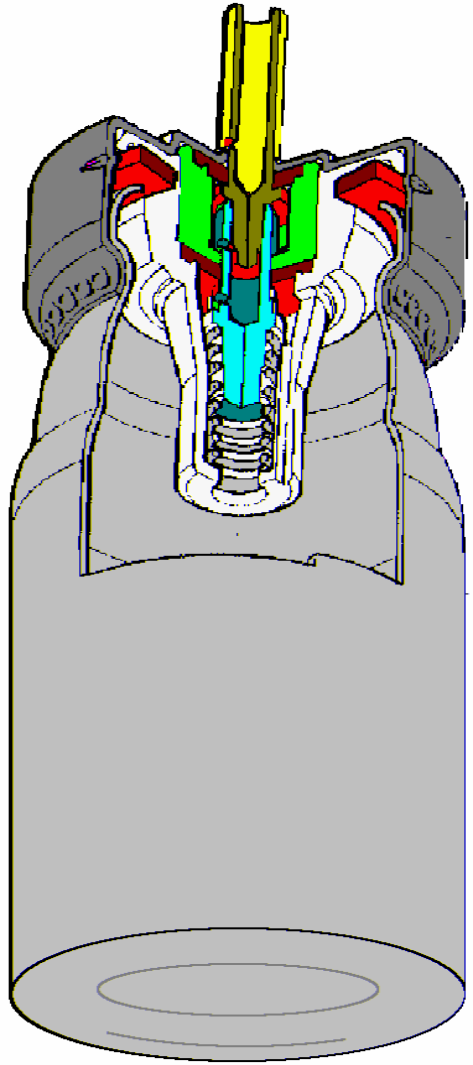
Product	Product Type	Company	Valve supplier	Formulation	Formulation Type
Aarane	SCG & reprotorol	Sanofi Aventis	Bespak	227	Suspension
Airomir	Salbutamol	3M	3M	134a + EtOH	Suspension
Allergospasmin	SCG + Reproperol	Asta	Bespak	134a + EtOH	Suspension
Alvesco	Ciclesonide	Altana/ Sanofi Aventis	3M	134a + EtOH	Solution
Atimos	Formoterol Fumarate	Chiesi	Bespak	134a + Surfactants	Solution
Atrovent	Ipratropium Bromide	BI	Bespak	134a + EtOH	Solution
Beclate HFA	BDP	Cipla		134a	?
Beclazone	BDP	IVAX	Bespak	134a + EtOH	Solution
Beclojet	BDP	Chiesi	Bespak	134a + Surfactants	Solution
Berodual	Fenoterol + Ipratropium Bromide	BI	Bespak	134a + EtOH	Solution
Berotec	Fenoterol Hydrobromide	BI	Bespak	134a + EtOH	Solution
Bonair	Salbutamol	Midas Care	Valois?	134a	Suspension
Budecort HFA	Budesonide	Cipla		134a	
Budiair	Budesonide Modulite	Chiesi	Bespak	134a + Surfactants	Solution
Butoasma	Salbutamol	Aldo Union	Bespak	134a + EtOH	Suspension
Evohaler	Salbutamol	GSK	Valois	134a Pure	Suspension
Flixotide	Fluticasone propionate	GSK	Valois	134a Pure	Suspension
Flohale HFA	Fluticasone propionate	Cipla		134a	Suspension
Foratec HFA	Formoterol Fumarate	Cipla		134a	?
Intal	Sodium Cromoglycate	Sanofi Aventis	Bespak	227	Suspension
Ipravent Forte HFA	Ipratropium Bromide	Cipla		134a	?
Meptin	Procaterol Hydrochloride	Otsuka	3M	227	Suspension
Osonide	Ciclesonide	Ranbaxy	Bespak?	134a + EtOH	Solution
QVAR	BDP	3M	3M	134a + EtOH	Solution
Salamol	Salbutamol	IVAX	Bespak	134a + EtOH	Suspension
Salbutamol	Salbutamol	Cipla	Bespak	134a + EtOH	?
Seretide Evohaler	Salmeterol xinafoate + Fluticasone propionate	GSK	Valois	134a Pure	Suspension
Seroflo HFA	Salmeterol xinafoate	Cipla		134a	?
Stomerin D	Isoproterol, Atropinmthylbromide, Dexamethasone	Fujisawa	Valois	227	Suspension
Tilade	Nedocromil Disodium	Sanofi Aventis	Bespak	227	Suspension

ICH/ EMEA/ FDA Stability conditions

- 25C +/- 2C 60RH +/- 5RH
- 30C +/- 2C 65RH +/- 5RH
- 40C +/- 2C 75RH +/- 5RH

Orientation?





What Metrics?

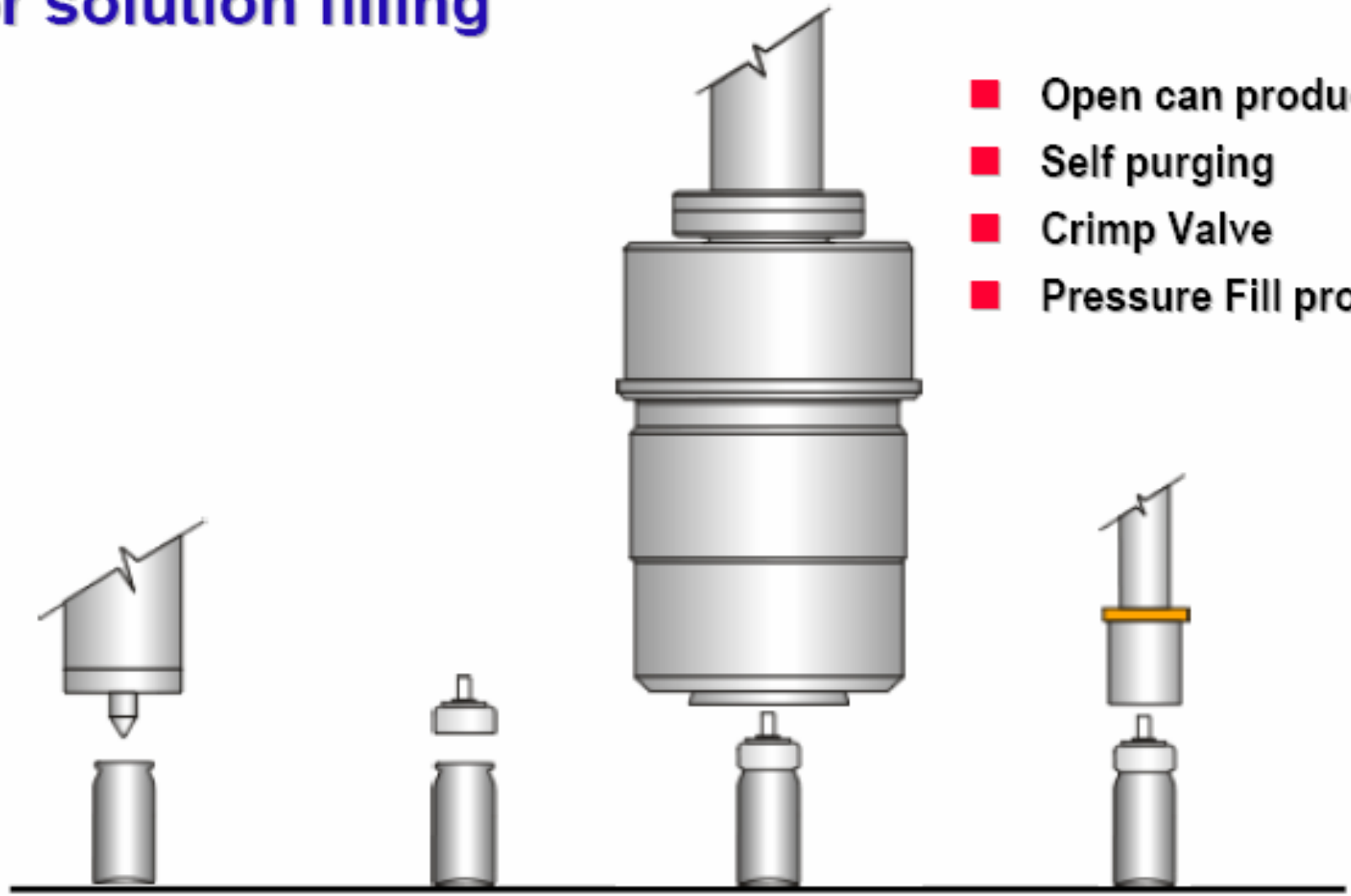
- Net Content total (n =10)
- Dose weight (n = 10)
- Propellant Leakage (n = 10)
- pH (if applicable)
- Assay of Active per can (n = 5)
- Dose content beginning and end including actuator deposition (n = 10)
- Moisture content (n = 5)
- Impurities (n = 5)
- Particle size distribution by cascade impactor beginning and end (n = 5)
- Particle morphology by optical microscopy (n = 3)

MDI Problem 3 – Selection of the filling method

A. HFC/Ethanol MDIs (Pressure Filled)
B. HFC MDIs (Pressure Filled)
C. HFC MDIs (Cold Filled)
D. Single-Dose DPI
E. Multi-Dose DPI

HFA Propellant system with low volume suspension or solution filling

- Open can product Fill
- Self purging
- Crimp Valve
- Pressure Fill propellant.



1
Fill Product Suspension or Solution Low Volume Fill

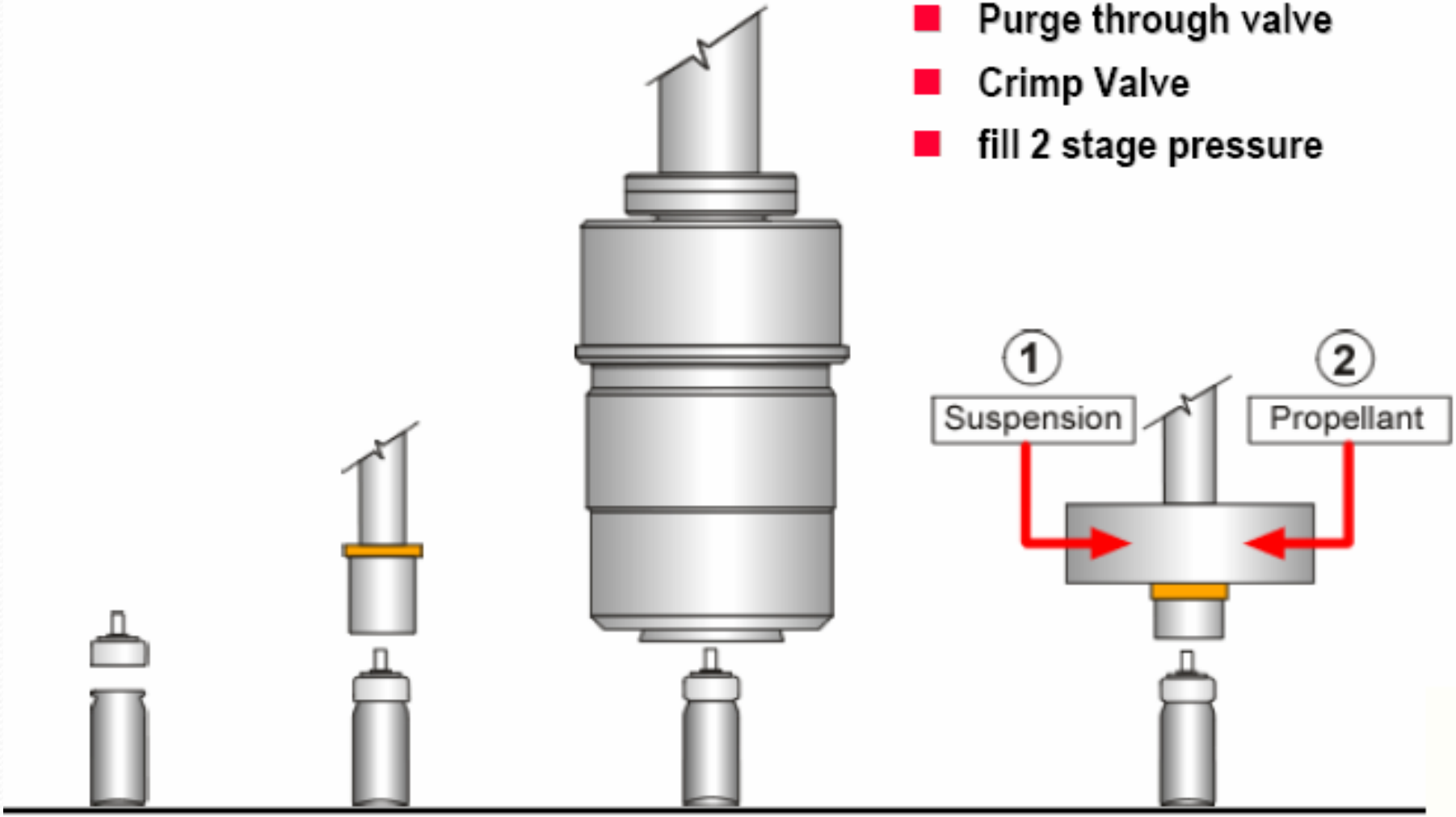
2
Place Valve

3
Crimp Valve

4
Fill HFA Propellant

HFA Propellant system with dual filling

- Purge through valve
- Crimp Valve
- fill 2 stage pressure



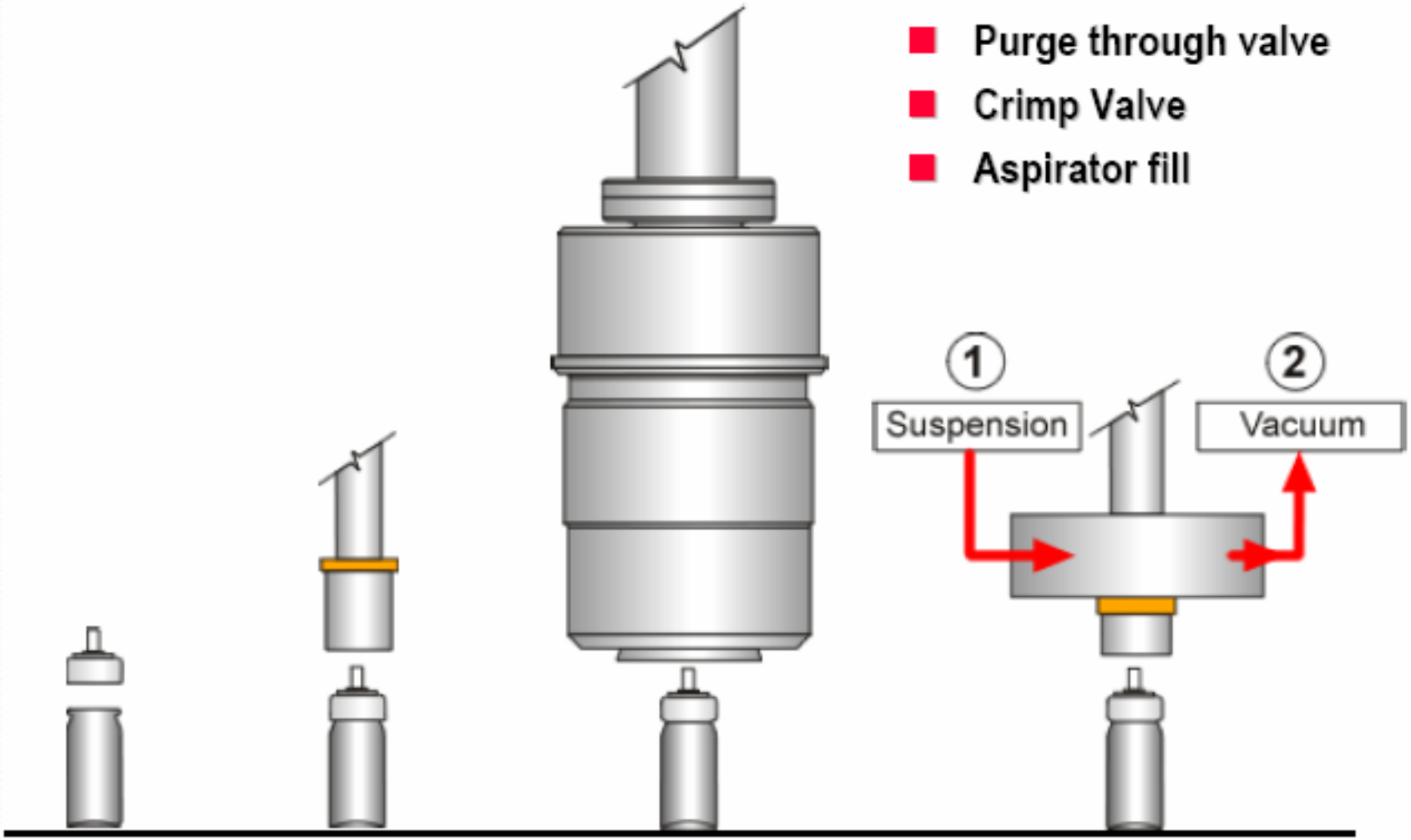
1
Place Valve

2
Purge through
Uncrimped Valve

3
Crimp Valve

4
Fill HFA Suspension then
flush with propellant fill
(Glaxo patent)

HFA Propellant system with Aspirator filling



Don’t have to look the same to be equivalent

Impact of choosing the GSK approach

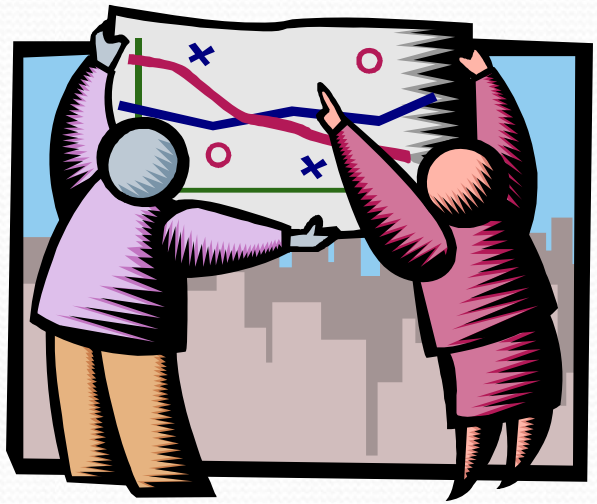
Salbutamol (sulphate) MDI						
Item	Existing CFC Formulation			Likely HFC Formulation		
	Quantity per MDI	Price US$	Cost/Can US$	Quantity per MDI	Price US$	Cost/Can US$
CFC-1 1	4.45 gm	4.2578 US$/Kg	0.019	-	-	0
CFC-12	12.45 gm	5.9 US$/Kg	0.0735	-	-	0
Ethanol	-	-	0	.		
HFC-134a	-	-	0	17.3 gm	8.5 US$/Kg	0.147
Aluminium Monobloc Can	1	0.115	0.0739*[1]	1	0.115	0.21*[4]
Metering Valve	1	0.151	0.151*[2]	1	0.25	0.4*[5]
Actuator	1	0.118	0.118*[3]	1	0.118	0.118*[4]
Unit boxes	1		0.0016			0.0016
Other Costs Components			0.0225			0.0225
Salbutamol (sulphate for non CFC)	.0236gm	890	.021	No significant change		.021
Oleic Acid	0.001	1 .0752	0.0011			
Cost per MDI	US$ 0.4816			US$ 0.9201		
I.O.C per MDI at N.P.V $ 0.4385						

Or the 3M approach

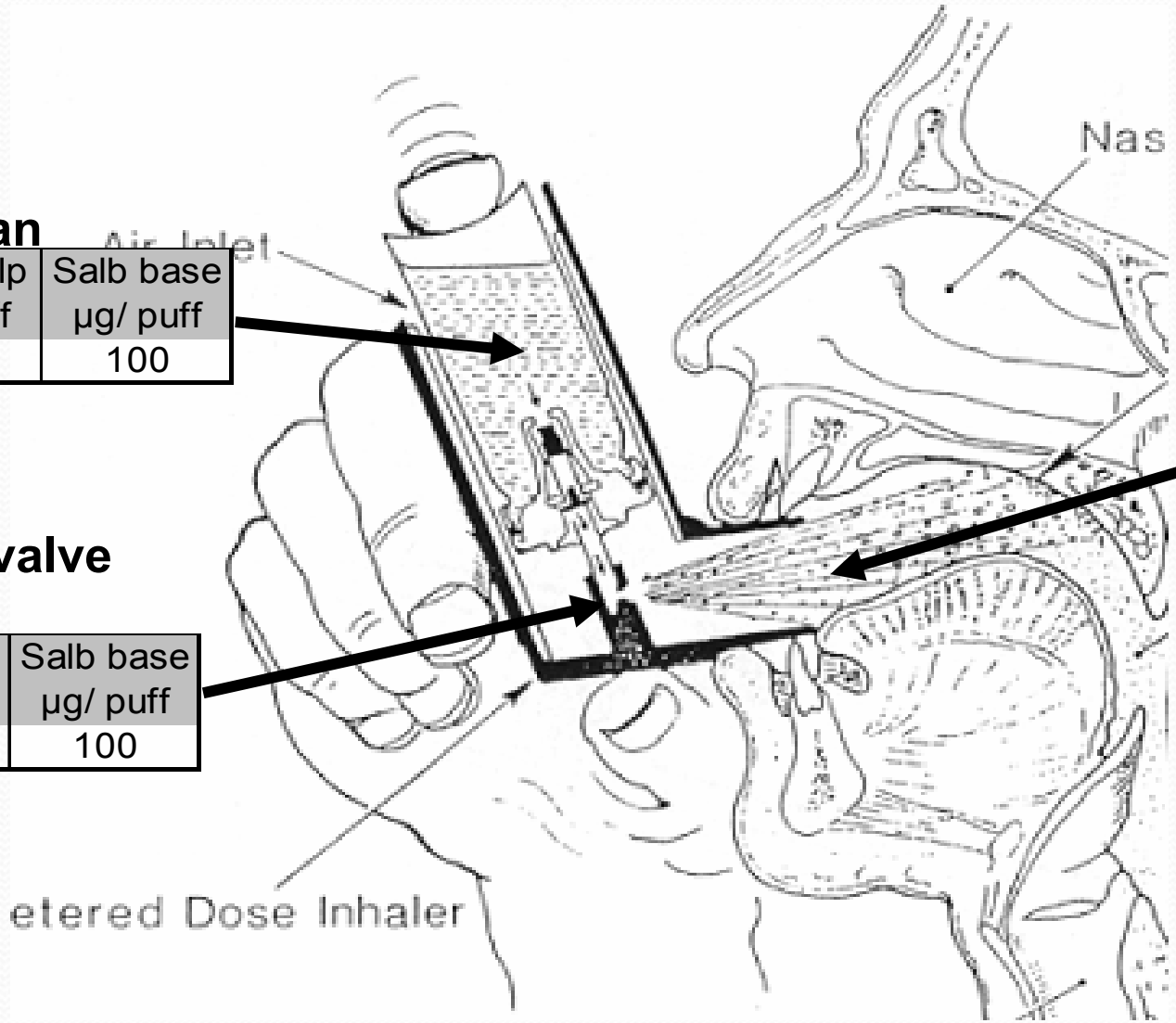
Salbutamol (sulphate) MDI						
Item	Existing CFC Formulation			Likely HFC Formulation		
	Quantity per MDI	Price US$	Cost/Can US$	Quantity per MDI	Price US$	Cost/Can US$
CFC-11	4.45 gm	4.2578 US$/Kg	0.019	-	-	0
CFC-12	12.45 gm	5.9 US$/Kg	0.0735	-	-	0
Ethanol	-	-	0	.876 gm	2.67 US$/Kg	0.00234
HFC-134a	-	-	0	16.65 gm	8.5 US$/Kg	0.1412
Aluminium Monobloc Can	1	0.115	0.0739*[1]	1	0.115	0.0739*[1]
Metering Valve	1	0.151	0.151*[2]	1	0.25	0.25
Actuator	1	0.118	0.118*[3]	1	0.118	0.118*[3]
Unit boxes	1		0.0016			0.0016
Other Costs Components			0.0225			0.0225
Salbutamol (sulphate for non CFC)	.0236gm	890	.021	No significant change		.021
Oleic Acid	0.001	1.0752	0.0011	0.001	1.0752	0.0011
Cost per MDI	US$ 0.4816			US$ 0.63164		
I.O.C per MDI at N.P.V $ 0.1500						

Considerations

- Valve costs can vary from $ 0,18 to $ 0,45.
- Choice of formulation may necessitate expensive cans, etc.
- Do not over specify.
- Actuator orifices will be smaller.
- CFC prices will continue to accelerate upwards.



MDI Delivery Problem 4 - Ventolin Evohaler as declared



In can

Salb Sulp µg/ puff	Salb base µg/ puff
120	100

From valve

No loss

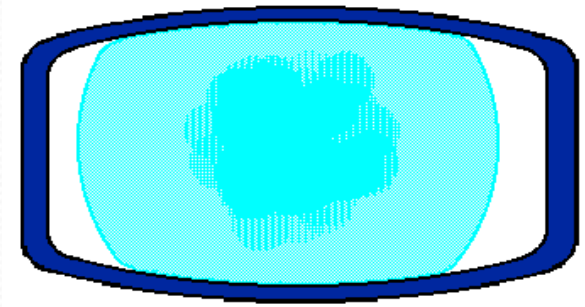
Salb Sulp µg/ puff	Salb base µg/ puff
120	100

From Act

10% loss

Salb Sulp µg/ puff	Salb base µg/ puff
108	90

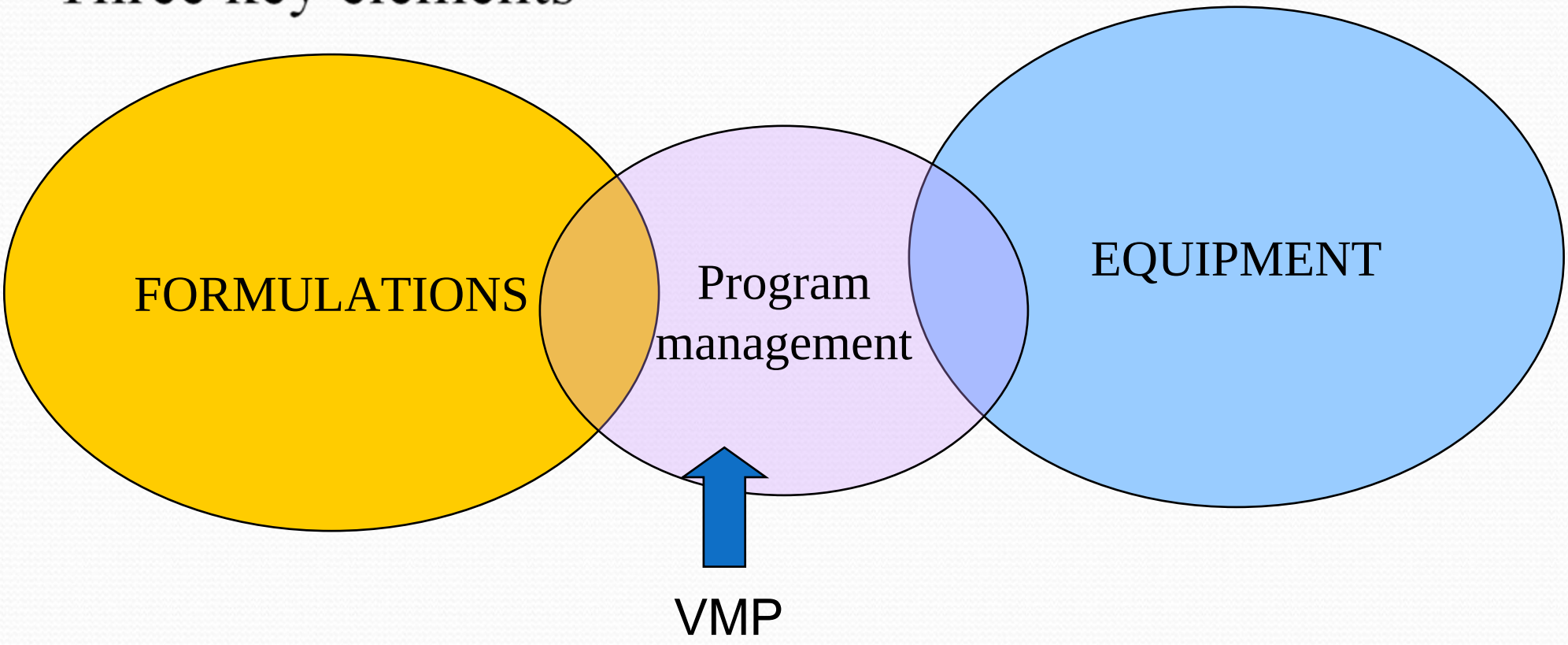
Typical published actuator loss



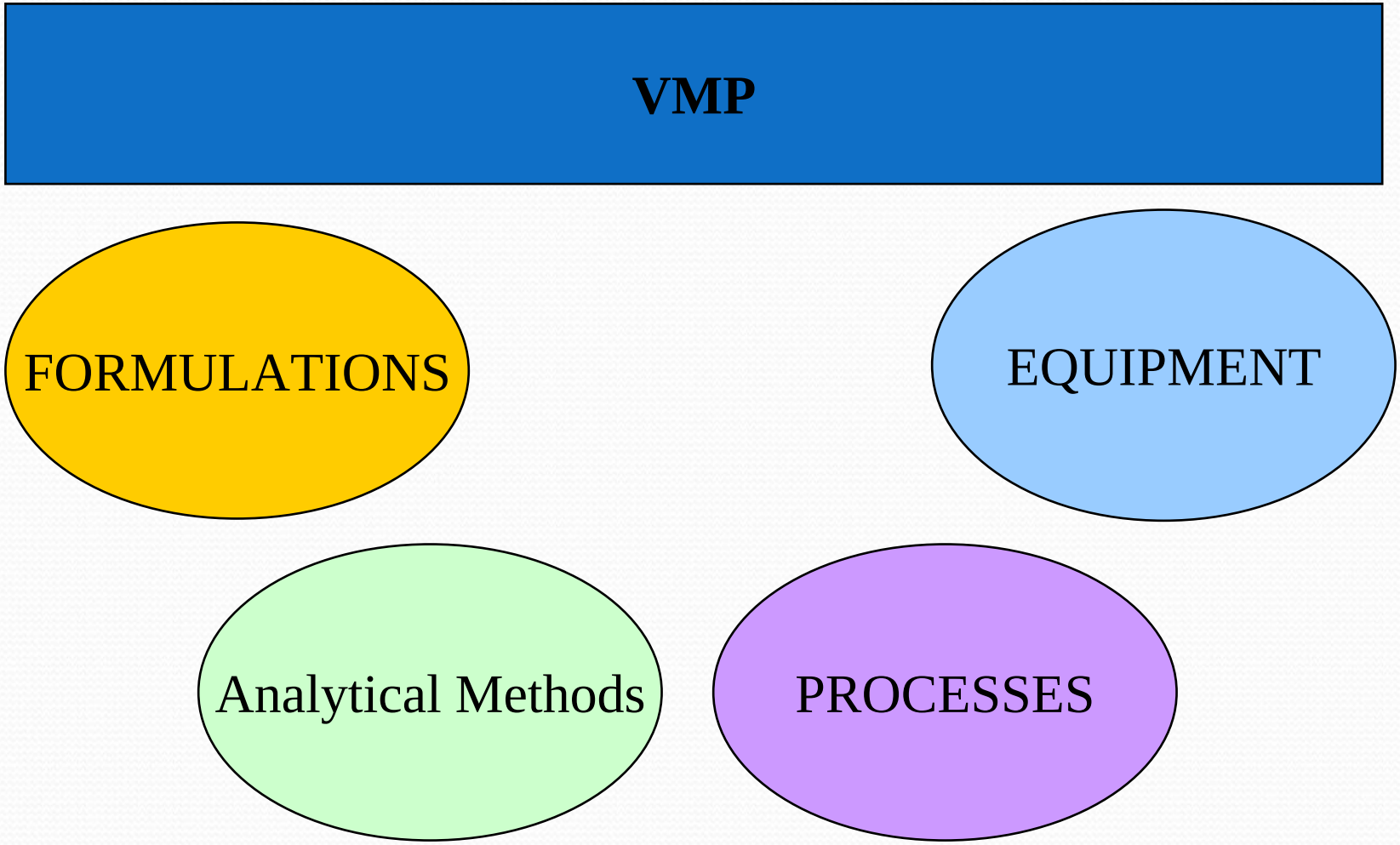
Company	Product	Declared Ex-Valve µg/ puff	Declared Ex Mouthpiece µg/ puff	Loss %
GSK	Ventolin	120	108	10.0
3M	Airomir	120	108	10.0
Boehringer Ingelheim		21	17	19.0
3M	Qvar 40	50	40	20.0
3M	Qvar 80	100	80	20.0
GSK	Flovent 44	50	44	12.0
GSK	Flovent 110	125	110	12.0
GSK	Flovent 220	250	220	12.0
GSK	Serevent	25	21	16.0
AstraZeneca *1	Symbicort 80/ 4.5	91	80	12.1
AstraZeneca *1	Symbicort 160/4.5	181	160	11.6
GSK	Seretide	As per the individual losses above		12 and 16

MDI problem 5 – Organization of production

Three key elements



Validation Master Plan

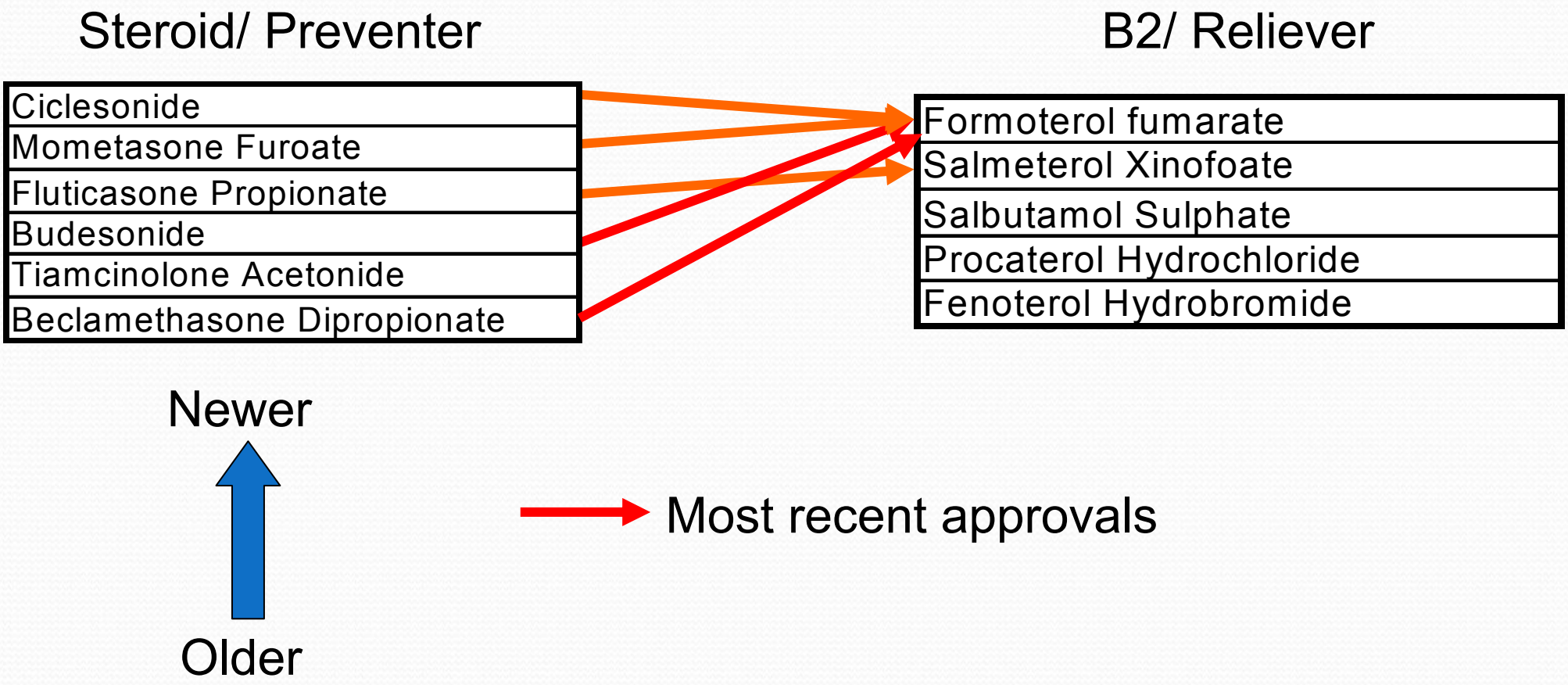


MDI Problem 6 – Lack of new formulations

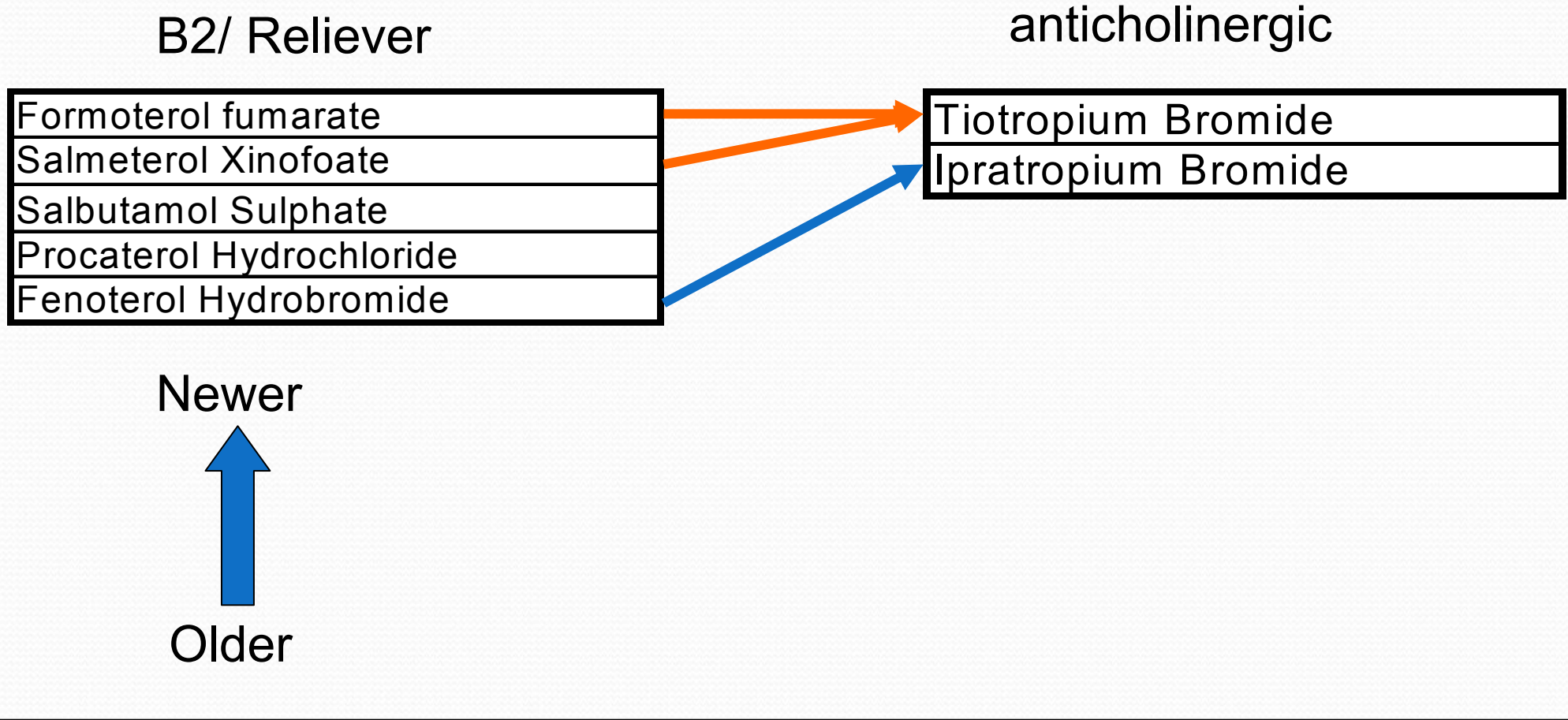
Some products more advanced

	Early Stage development	Late stage developmnet	Launch 1	Launch 2	Launch 3	Launch 4	Launch 5	Launch 6
Beclamethasone Dipropionate								
Budesonide								
Budesonide/ Formoterol fumarate								
Ciclesonide								
Fenoterol hydrobromide								
Fluticasone Propionate								
Formoterol fumarate								
Ipratropium Bromide								
Ipratropium Bromide/ Fenoterol hydrobromide								
Ipratropium Bromide/ Salbutamol Sulphate								
Mometasone Furoate								
Procaterol Hydrochloride								
Salbutamol Sulphate								
Salbutamol Sulphate/ Beclamethasone Dipropionate								
Salmeterol Xinofoate								
Salmeterol Xinofoate/ Fluticasone Propionate								
Terbutaline Sulphate								
Tiotropium Bromide								

Asthma Combinations?



COPD Combinations?

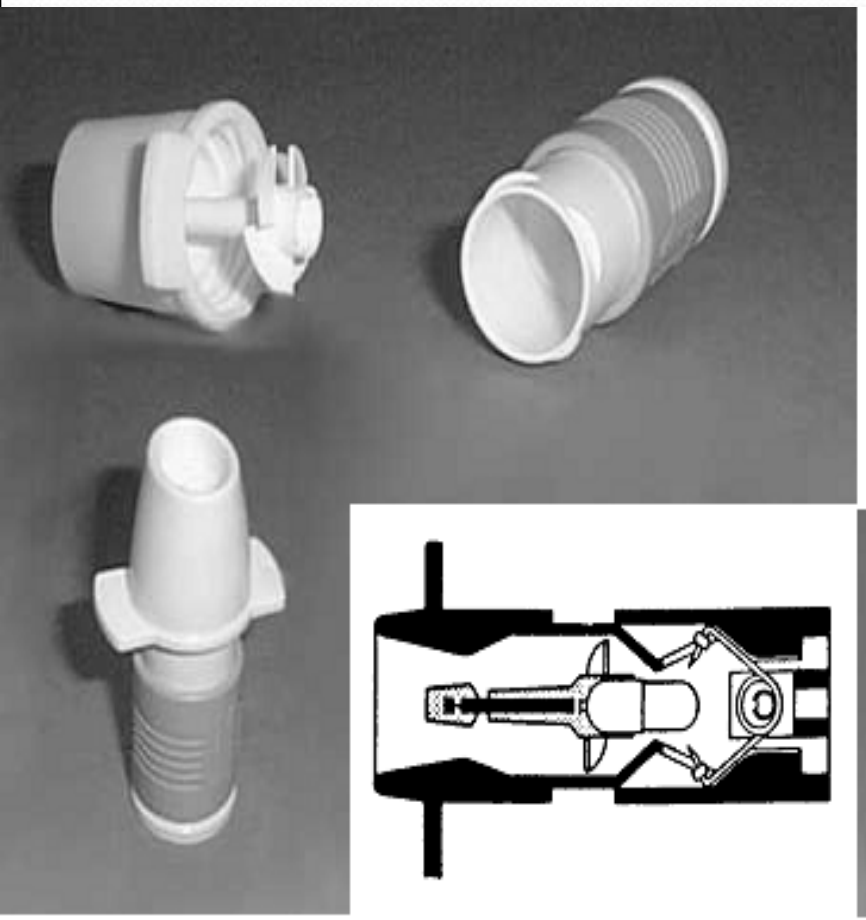


A new GEF project considerations

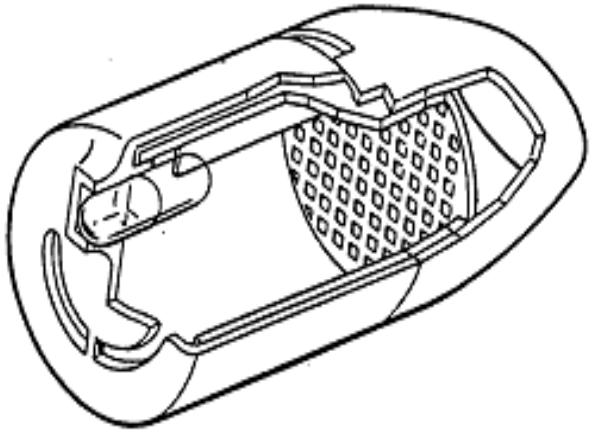
- 1. No production of Beclamethazone –with a preventive active in the RF and in CISs;
- 2. A very small export of Russian MDIs into the CISs;
- 3. There is not CFCs for MDI production in the RF due to the MP;
- 4. The cost of MDIs will be increasing in next years;
- 5. A new propellant HCF-134a is an intermediate substance being controlled by the KP, GWP – 1300;
- 6. The DPIs were developed in the world as an alternative delivery mechanism to pressurized MDI - they are ease to use – unit dose and multi dose –very low cost, no propellants, high dose carrying capacity and Potential drug stability advantages;
- 7. Relative expensive DPI production.

Three “classic” unit-dose DPIs

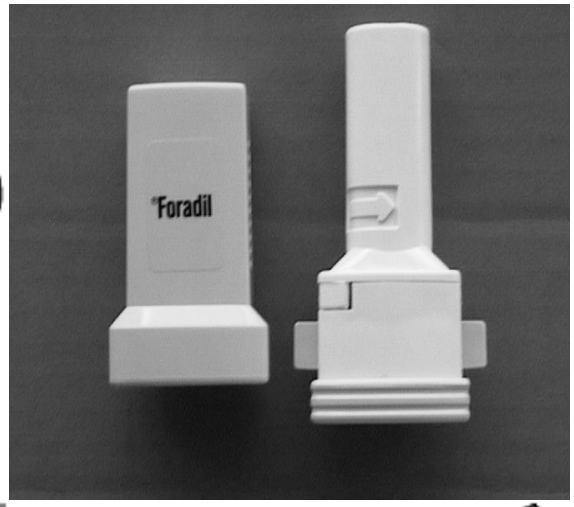
Spinhaler™

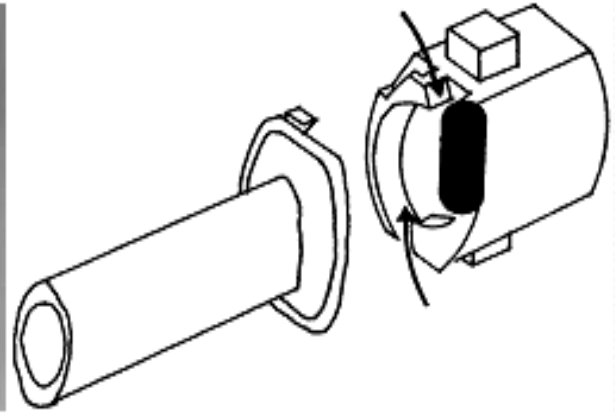


Rotahaler™



Aerolizer™





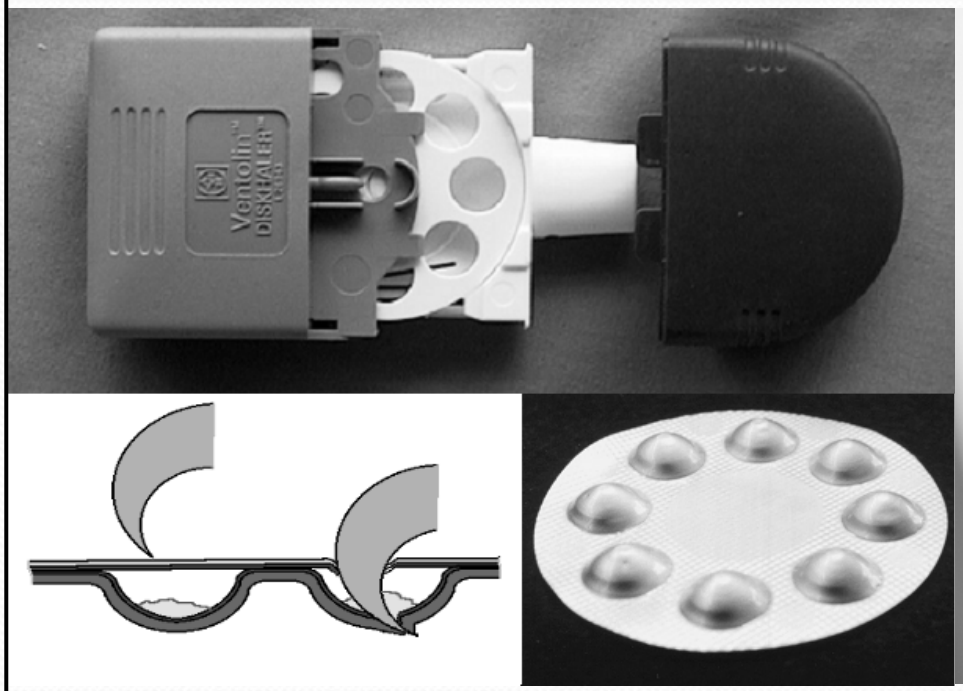
Sanofi-Aventis

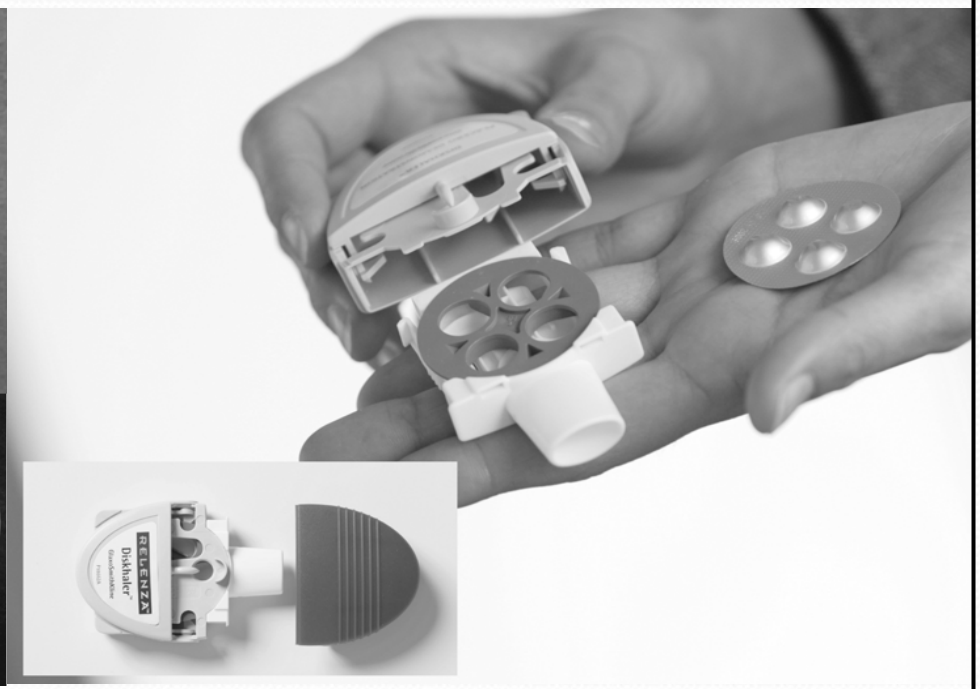
GlaxoSmithKline

Novartis

The original Diskhaler™ and the version developed for Relenza™

Diskhaler™





GlaxoSmithKline

Cost effectiveness by multi-dose DPI development and production

- 1.Development of a new multi-dose DPI for a single active, 2-3 years, costs US$ 2.0-3.0 million
- 2. Mold tool costs US$ 2.4 million
- 3. Device automatic assembly, cost US$ 1.0 -1.5 million
- 4. Installation of an automated filling and packing line, costs US$ 1.0-1.5 million
- **Total investment will be about US$ 6.0 million.**


Thank you