



# Overview of challenges in developing HFA pMDI technologies

Jay Bhogaita

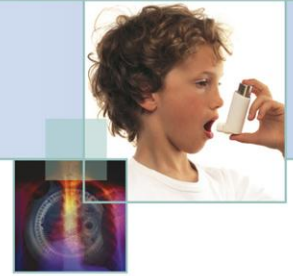
5<sup>th</sup> October 2011

Moscow



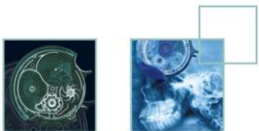
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# Key Requirements of pMDI Dosage Form

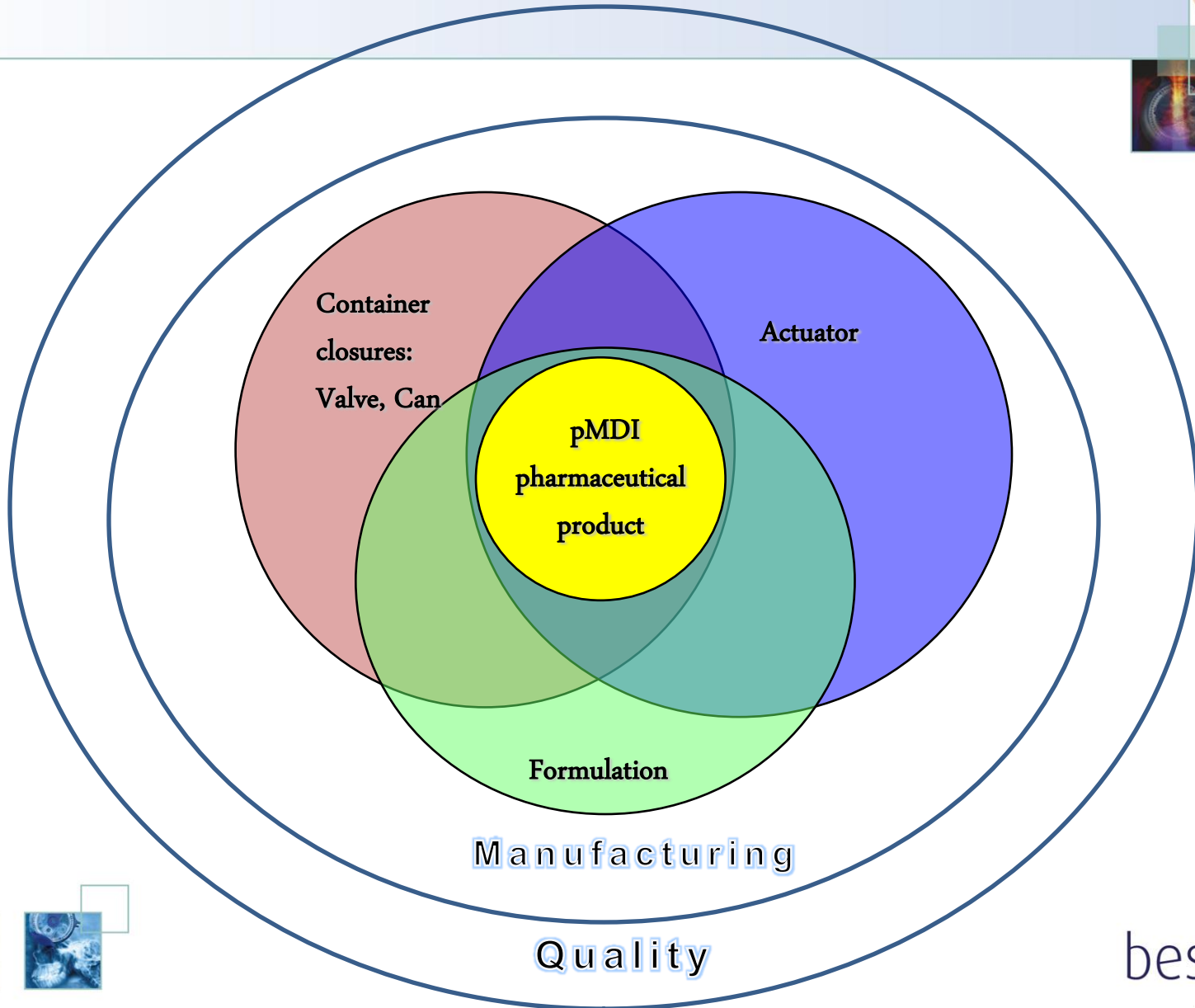
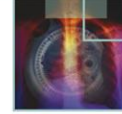


- To generate and deliver optimum respirable dose of a therapeutic agent
  - i.e deliver particle size of 2 - 5 $\mu$ m
- Demonstrated throughout the product's shelf-life
  - i.e. consistency between doses throughout product life
    - Accuracy and reproducibility

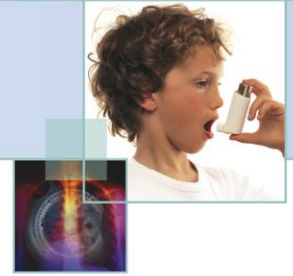
*Requires an approach which integrates formulation and container closure system at the outset*



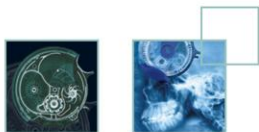
# The pMDI Pharmaceutical Product



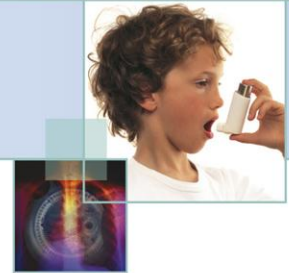
# Challenges in Formulating HFA pMDI systems



- Solubility
- Crystal growth potential (coarsening, Ostwald ripening)
- moisture
- Suspension properties (suspension formulations)
  - Stable dispersion
  - Particle size
  - Partial solubility
- Drug deposition on surfaces of CCS
- Compatibility of HFA formulation with materials of CCS
  - Dimensional integrity (physical changes)
  - Material stability (chemical changes)
  - Extractables/Leachables
- Spray characteristics



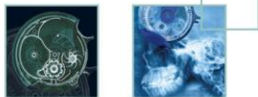
# Key Tests to establish acceptable product



- Net Content / Shot Wt
- API Content / Dose Wt
- Leakage
- Moisture
- Particle Size Distribution
- DCU: BOU, EOU
- Appearance
- Particulates
- Spray characteristics
- Pressure test

## Stability Protocol

	Initial	1 Month	2 Months	3 Months	6 Months
25C/60% RH	Yes	Yes		Yes	Yes
40C/75% RH		Yes	Yes	Yes	Yes



# BK357 *The most widely marketed HFA valve in the world*

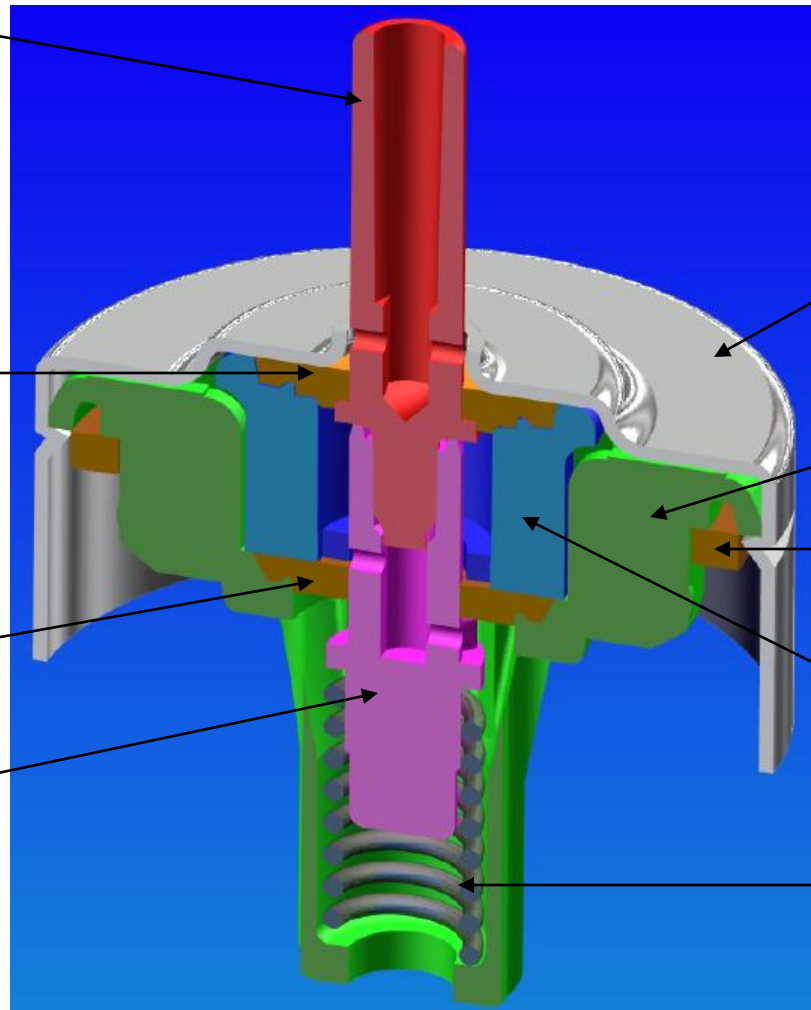


Core Extension

Outer Seat

Inner Seat

Core



Ferrule

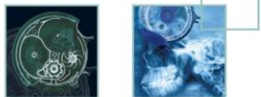
Body

Gasket

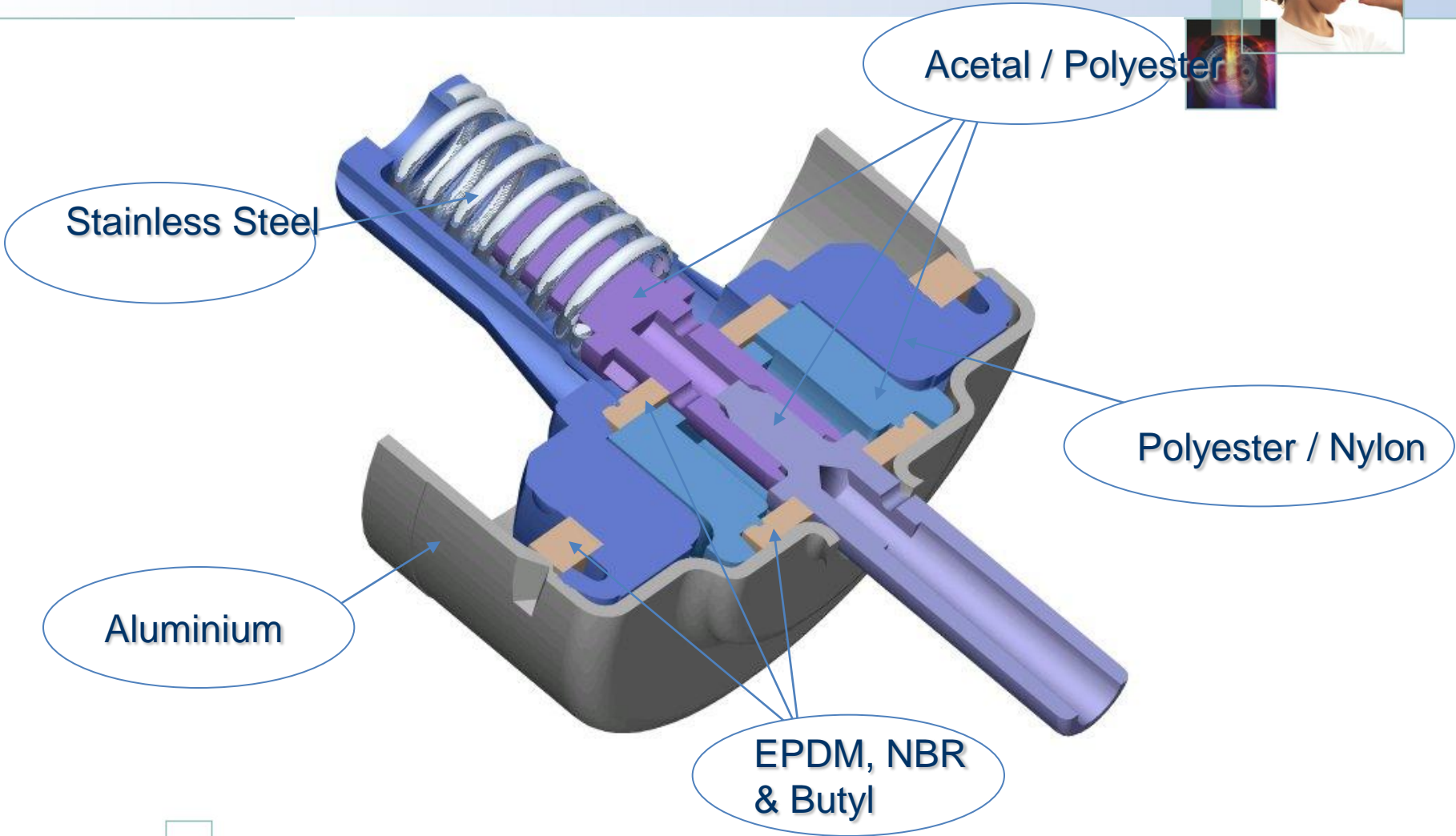
Metering Chamber

Spring

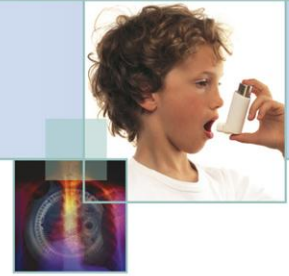
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# BK357 VALVE MATERIALS



# Actuators

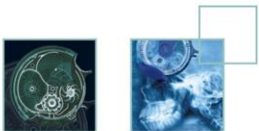


## Critical Parameters;

- Material choice
- Spray hole size
- Geometry

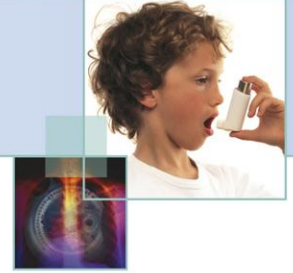
## Affect:

- Spray characteristics
  - Spray angle
  - Plume geometry
  - Speed
- Patient perception
- Fine particle fraction

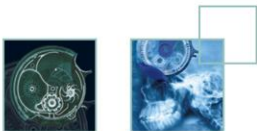




# Bespak's contribution to CFC Free pMDIs



- Full development of pMDI products as part of UN programmes
  - Iran
    - 3 products approved and marketed using Bespak HFA technologies
      - Salbutamol , BDP, Salmeterol
  - Bangladesh
    - 4 products approved and marketed using Bespak HFA technologies
      - Salbutamol, BDP, Salmeterol, Salmeterol + FP
  - Latin America
    - Salbutamol approved and marketed using Bespak HFA technologies
    - Others under stability



# Bespak's Contribution to CFC Free pMDIs



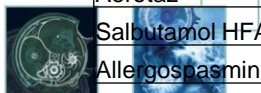
Product	Product Type	Company	Valve supplier
Aeroduol	ipratropium bromide + fenoterol	Aerocare	Bespak BK357
Aeromol	salbutamol	Aerocare	Bespak BK357
Aeronide	budesonide	Aerocare	Bespak BK357
Buto Asma	salbutamol	Aldo Union	Bespak BK357
Atroaldo	ipratropium bromide	Aldo Union	Bespak BK357
Atroaldo	salmeterol+FP	Aldo Union	Bespak BK357
Tilade	nedocromil disodium	Aventis	Bespak BK357
Azmasol	salbutamol	Beximco	Bespak BK357
Decomit	BDP	Beximco	Bespak BK357
Bexitrol	Salmeterol	Beximco	Bespak BK357
Bexitrol-F	Salmeterol + FP	Beximco	Bespak BK357
Cesonide	Ciclesonide	Beximco	Bespak BK357
Iprasol	ipra + sal	Beximco	Bespak BK357
Aeronid	budesonide	Beximco	Bespak BK357
Nitrosol	nitroglycerine	Beximco	Bespak BK357
Atrovent	ipratropium bromide	Boehringer Ingelheim	Bespak BK357
Berodual	fenoterol + ipratropium bromide	Boehringer Ingelheim	Bespak BK357
Berotec	fenoterol hydrobromide	Boehringer Ingelheim	Bespak BK357
Oxivent	oxitropium bromide	Boehringer Ingelheim	Bespak BK357
Beclojet	BDP	Chiesi	Bespak BK357
Budair	budesonide	Chiesi	Bespak BK357



# Bespak's contribution to CFC Free pMDIs

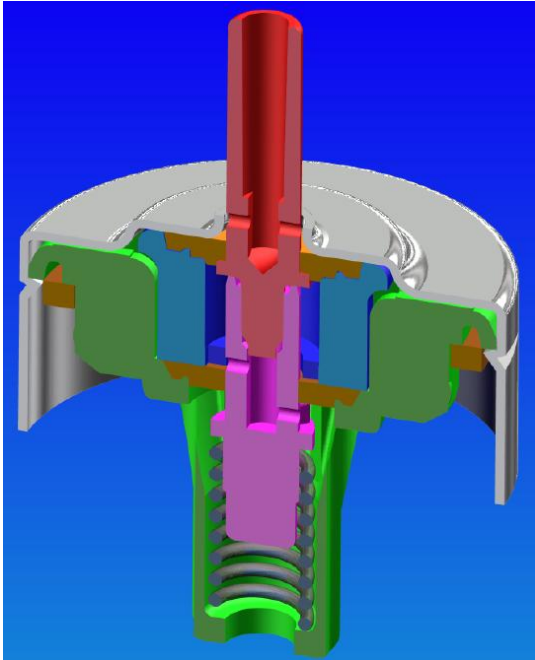
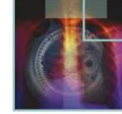


Product	Product Type	Company	Valve supplier
Clenil Modulite	beclometasone	Chiesi	Bespak BK357
Foster	BDP + Formoterol	Chiesi	Bespak BK357
Formoterol Modulite / Foradil	formoterol	Chiesi / Novartis	Bespak BK357
Budesonide	budesonide	Cipla	Bespak BK357
Beclate	BDP	Cipla	Bespak BK357
Aerocort	BDP + Levalbuterol	Cipla	Bespak BK357
Ciclohale	Ciclesonide	Cipla	Bespak BK357
Simply One	Ciclesonide + Formoterol	Cipla	Bespak BK357
Serobid/Neovent	Salmeterol	Cipla	Bespak BK357
Levolin	levalbuterol	Cipla	Bespak BK357
Seroflo	salmeterol+FP	Cipla	Bespak BK357
Flohale	FP	Cipla	Bespak BK357
Ipravent	Ipratropium bromide	Cipla	Bespak BK357
Duolin	ipra + sal	Cipla	Bespak BK357
Azmavent	salbutamol	Cipla	Bespak BK357
Airlevo	levalbuterol	Glenmark	Bespak BK357
Serevent	salmeterol	GSK	Bespak BK357
Albuterol & Salamol	salbutamol	IVAX	Bespak BK357
Beclazone	BDP	IVAX	Bespak BK357
Dulera	mometasone + formoterol	Merck	Bespak BK357
Gerivent	salbutamol	Merck Generics	Bespak BK357
	nitroglycerine	Pharmasol	Bespak BK357
Xopenex	levalbuterol	Sepracor	Bespak BK357
Sultolin	salbutamol	Square	Bespak BK357
Beclomin	BDP	Square	Bespak BK357
Aerotaz	salbutamol	Sun	Bespak BK357
Salbutamol HFA	salbutamol	Valeas	Bespak BK357
Allergospasmin	SCG + reproterol	Viartis	Bespak BK357



# BK357

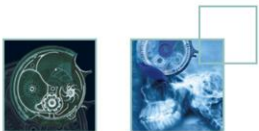
*The most widely marketed HFA valve in the world*



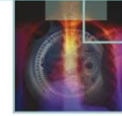
Believed to be the most widely used valve in terms of:

- Customers
- Territories
- Formulation types

Bespak produce over 100m HFA actuators per year



# Summary of key principles in HFA pMDI Development



- Formulation type
  - Suspension
  - Solution
- Formulation ingredients
- Choice of appropriate container closure system
  - Valve (materials, performance)
  - Actuators (critical dimensions, materials)
  - Cans (coated, uncoated, material)
- Manufacturing method
  - Single stage
  - Two stage
- Quality and Regulatory criteria
  - Incoming materials and components
  - Manufacturing controls
  - Release testing



*A complex system but success already proven*



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