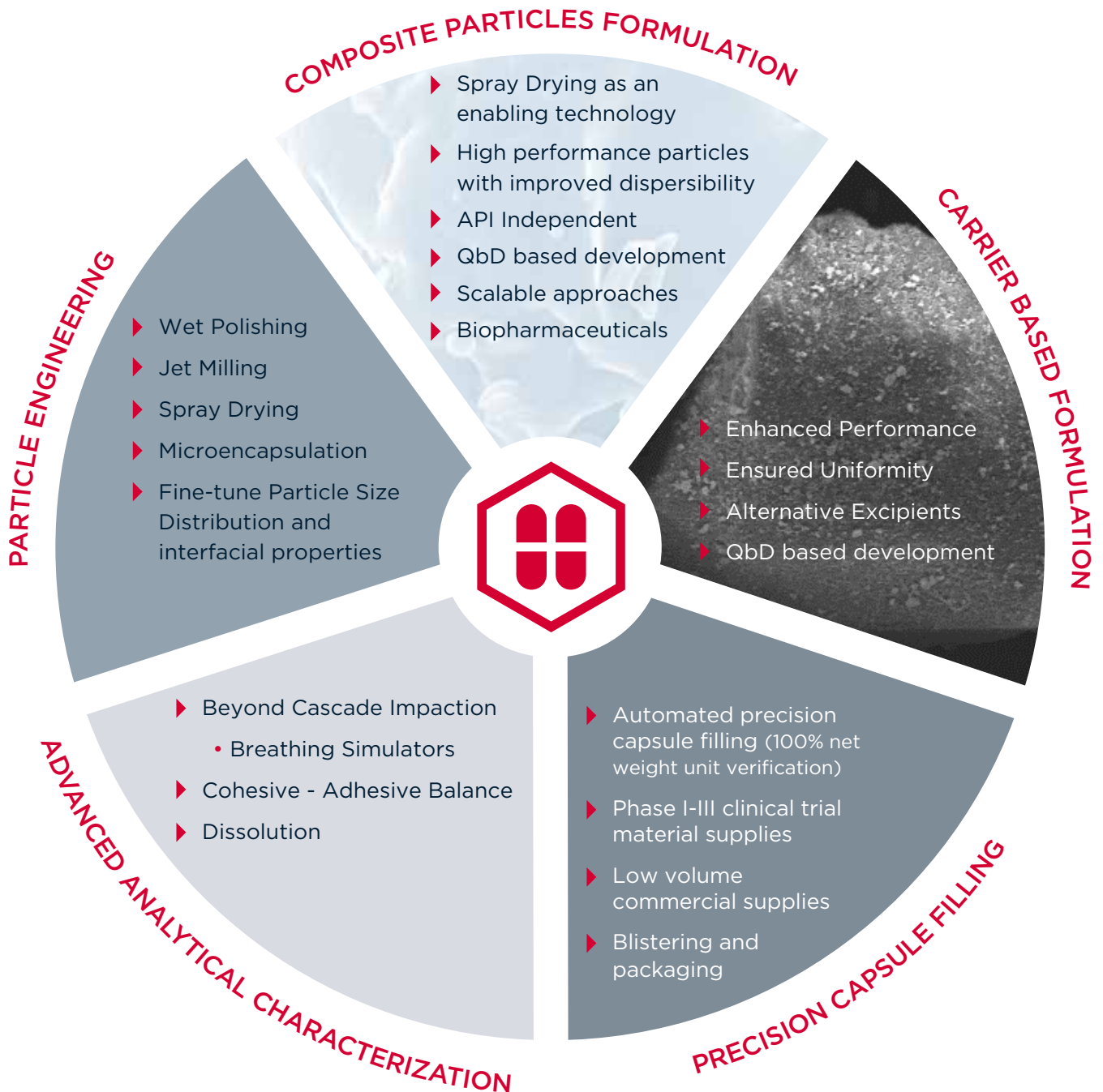


EVERYTHING FOR INHALATION



Integrated Inhalation Development Services



Drug Substance

- ▶ Polymorph control
- ▶ Small-scale to commercial manufacturing

Particle Engineering

- ▶ Wet Polishing
- ▶ Jet Milling
- ▶ Spray Drying
- ▶ Particle size control
- ▶ Scalability

Drug Product

- Carrier based Formulations**

 - ▶ Lactose based
 - ▶ Mannitol based
- Composite Particles**

 - ▶ Engineered particles
 - Leucine based
 - Mannitol based
 - API alone

Filling/Finishing

- ▶ Automated precision capsule filling
- ▶ Blistering & Packaging



Hovione's expertise and methodologies used to develop complex API synthesis and world leading spray drying approaches are applied to provide dry powder inhalation capsules for clinical and small commercial scales.

Carrier-based Formulations

Powder Blending

Precision Capsule Filling and Finishing

From Lab Scale to Pilot Commercial Scale



Diosna
(1 to 6L)



Mettler-Toledo
Quantos QS30
up to **100 caps/h**



MG2 FlexaLAB
up to **3000 caps/h**
(with 100% net weight verification)

Small Commercial Scale



Diosna
(10 to 60L)

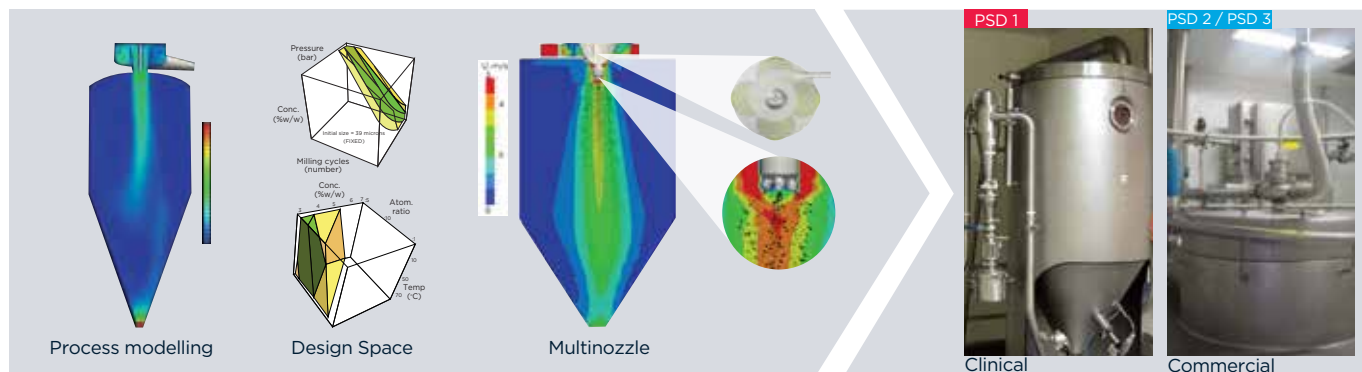


MG2 Tekna
up to **70,000 caps/h**
(with 100% net weight verification)

Composite Particles

Formulation via Spray Drying: more than 10 years of commercial experience

- ▶ **Spray Drying as an enabling technology for inhalation dry powder formulations**
 - Expedite scale-up following QbD principles
 - Fundamental process modelling (CFD)
 - Statistical modelling
 - Multinozzle approaches for preparing inhalation powders at large scale
 - Maximize yields with tailor-made cyclones and other advanced engineering solutions

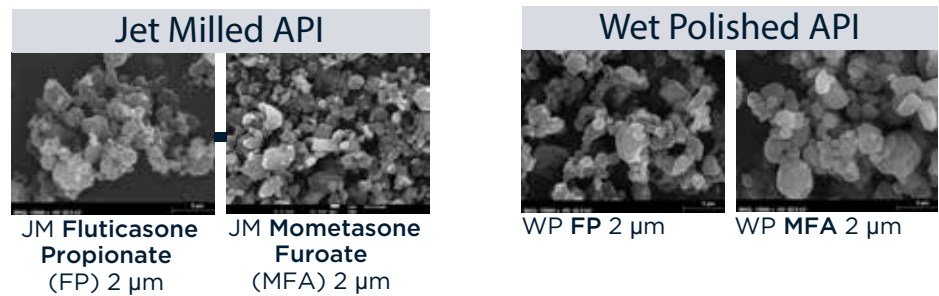


Particle Engineering Technologies

	Strengths
Jet Milling	Simple Solvent free
Wet Polishing	Reduced amorphization PSD control Reproducibility Scalability
Spray Drying	PSD control Reproducibility Scalability Thermo-labile compounds

- ▶ **Unprecedented particle size control**
 - Median particle size control down to 0.1 μm
 - Spans down to 0.6
 - At any scale

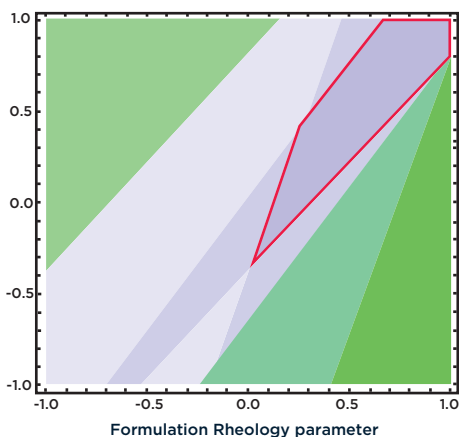
- ▶ **Control over interfacial properties**



- ▶ **Advanced Engineered Particles for low and high dosages**
 - Microencapsulation
 - Nanocoating
- ▶ **API alone**

QbD for Integrated Product Development

Enhancing aerodynamic performance while ensuring manufacturability: finding the right formulation composition



- Individual optimal zones for Fine Particle Fraction $5\mu\text{m}/\text{ED}$, Emitted Dose and Rejection Rate
- Intersection of optimal zones for Emitted Dose and Rejection Rate
- Intersection of optimal zones for Emitted Dose with acceptable Rejection Rate
- Individual acceptable zones for Fine Particle Fraction $5\mu\text{m}/\text{ED}$, Emitted Dose and Rejection Rate
- Intersection of acceptable zones for two parameters
- Sweet spot



Capsule Filler



Fine Particle Fraction



Device Performance

State of the Art Analytical Characterization for Dry Powder Inhalation

▶ Particle/Physical Characterization

- PSD by Laser Diffraction (Malvern and Sympatec)
- Computerized microscope imaging for particle characterization
- DVS
- Ultra-pycnometer
- XRPD
- DSC
- Thermogravimetric analysis
- Scanning electron microscopy

▶ Formulation Characterization

- Fast Screening, Andersen Cascade and Next Generation Impactors
- Dosage Unit Sampling Apparatus (DUSA)
- Dissolution testing
- Breath simulators (closer to in vivo deposition)

▶ Particle/Chemical Characterization

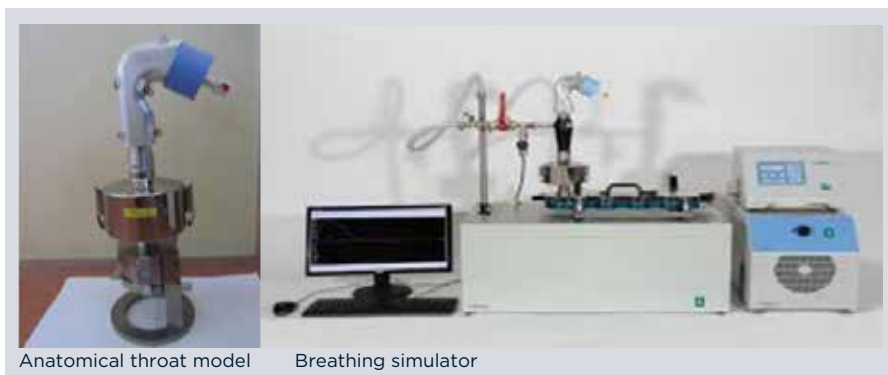
- UHPLC, HPLC and GC
- Karl Fischer
- GC/MS and LC/MS
- Ion Chromatography
- UV
- NIR and FTIR
- Dissolution tester

▶ Biopharmaceutical Characterization

▶ Microbiology

Beyond Cascade Impaction Evaluation

The use of anatomical throat models and breathing simulators allows formulation development under conditions mimicking different target patient populations.



Anatomical throat model

Breathing simulator

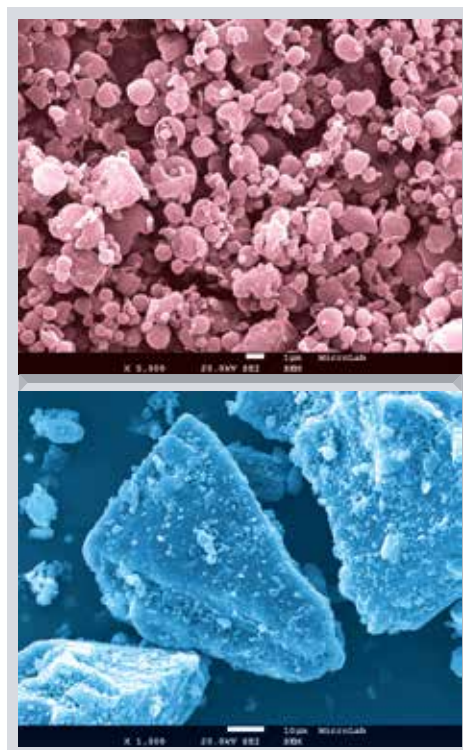
Dissolution testing is an integral part of the development of inhalation formulations.

Portfolio of Off Patent APIs

► The experts in customized APIs for Inhalation

Hovione's inhalation grade APIs are designed at the particle level to bring unique performance to your formulation.

- Acclidinium
- Budesonide
- Ciclesonide
- Fluticasone
- Formoterol
- Glycopyrrolate
- Indacaterol
- Mometasone
- Salbutamol
- Salmeterol
- Tiotropium
- Vilanterol



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