

Capsugel® Dry-Powder Inhalation Capsule Portfolio

External Launch Presentation

May 23, 2019



Presenters Bio



**Marketing
Lead**



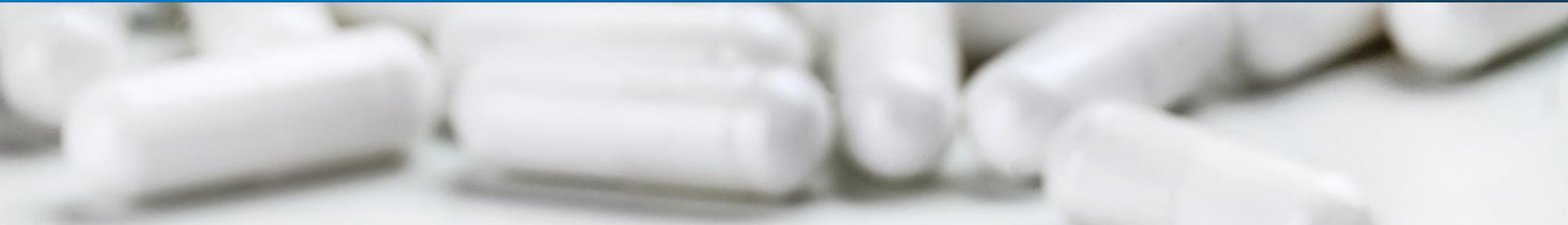
**Business
Development
Lead**



**Technical
Lead**

Why the Interest in DPI Today?

Capsugel® DPI Portfolio - May 2019

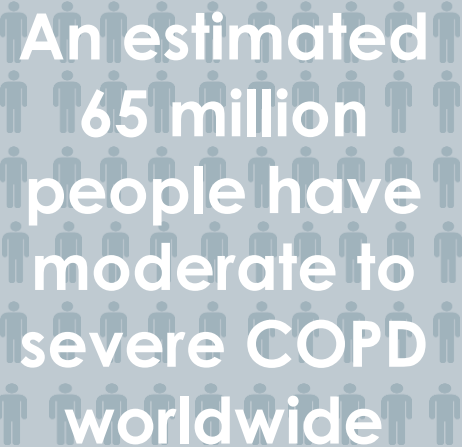


Trends in Pulmonary Pathologies

Global Statistics

Capsule
Delivery
Solutions

Lonza
Pharma & Biotech



An estimated
65 million
people have
moderate to
severe COPD
worldwide

About 334 million
people suffer from
asthma



Respiratory
diseases make up

5
—
30

most common
causes of death

3rd

Leading cause of death worldwide,
and the numbers are increasing

14%

Of children are affected globally and
it is the most common chronic
disease of childhood.

10%

Of all disability-adjusted life-years
(DALYs), a metric that estimates the
amount of active and productive life
lost due to a condition.

https://www.who.int/gard/publications/The_Global_Impact_of_Respiratory_Disease.pdf

Increased Interest for the Pulmonary Route

Capsugel®

Lonza
Pharma & Biotech

Systemic Application

- A non-invasive 'needle-free' delivery system
- Suitable from small molecules to very large proteins
- Enormous absorptive surface area, highly permeable membrane in the alveolar region
- Slow clearance in the lung results in prolonged residency in the lung
- Low enzymatic environment that is devoid of hepatic first-pass metabolism



Pulmonary Diseases

- High concentration directly to the disease site
- Minimizes risk of systemic side effects
- Rapid clinical response
- Bypass the barriers to therapeutic efficacy
- Achieve a similar or superior therapeutic effect at a fraction of the systemic dose

Dry Powder Inhalers in the News

UK Public Authority

Capsugel®

Lonza

Pharma & Biotech

08 April 2019

NICE encourages use of greener asthma inhalers

[Share](#)

People with asthma will be helped to choose the inhaler that is best for them, and best for the environment, by a new patient decision aid from NICE



A [new patient decision aid](#), released today, highlights that some inhalers have a much higher carbon footprint than others.

The aid will help people with asthma, alongside health professionals, to identify which inhalers could meet their needs and control their symptoms.

Where several inhalers could be viable options, patients can opt for the more environmentally friendly option, which may help to cut the health service's carbon footprint.^[1]

The new aid, partially funded by the [Sustainable Development Unit](#), also says that all used inhalers should be returned to local pharmacies for environmentally safe disposal or recycling.

NICE National Institute for
Health and Care Excellence

“

This aid will help people control their asthma, rather than have their asthma control them

Professor Gillian Leng, deputy chief executive, NICE

”

Source: www.nice.org.uk

Breakthrough Technology Staying Connected to Patients

Capsugel®

Lonza

Pharma & Biotech

Benefits from basic monitoring to comprehensive support to patient
(reminders, advice, dose recommendations, coaching)

e-Advancia®
Our high performance pump Advancia® combined with a reusable electronic add-on to improve patient compliance.

e-Novelia®
Our multidose eyedropper Novelia® for preservative-free formulations combined with electronic technology for enhanced patient experience.

Treatment information

- Electronic IFU
- Device positioning
- Tutorials
- Drop detection
- Remaining volume indication
- Wrong usage detection

Alerts

- Time to take dose
- Low battery
- Shelf life management

Rechargeable

Localization

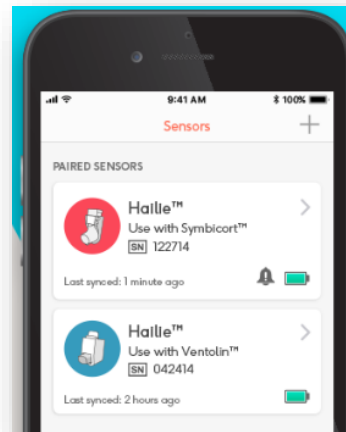
- Location tracking
- Threatening environment

Compliance

- Treatment history
- Compliance rate
- Reminders
- Next intake

e-Novelia®

Source: www.nemera.net



Adherium Launches Hailie™ Solution Direct-to-Consumer in the U.S. for Better Asthma and COPD Management

13 Aug 2018

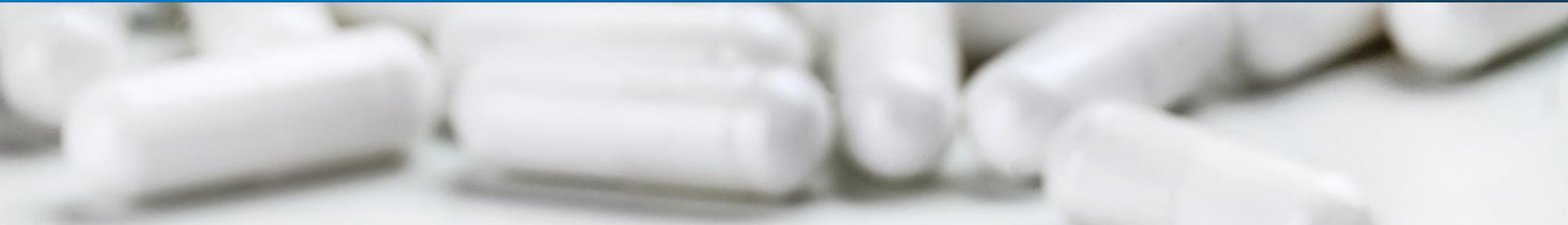
Source: www.adherium.com



Source: www.rs01x.com & www.rpc-bramlage.com

A Closer Look at the DPI Platform

Capsugel® DPI Portfolio - May 2019



A Wide Variety of Inhalation Delivery Technologies

Capsugel®

Lonza

Pharma & Biotech

Pressurized metered dose inhalers (PMDI)



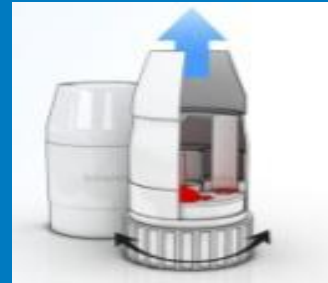
Commonly used in **emergency treatment**

Market share

33% drug sales & 69% of inhalers sold

Dry powder inhalers (DPI)

3 main types



Reservoir



Capsule



Blister

Mainly used in **preventive therapy**

Market share

51% drug sales & 24% of inhalers sold

Non-Portable Nebulizer Devices



Used in **emergency & preventive treatments**

Market share:

9% of drug sales & 5% of inhaler sold

Soft Mist Inhaler (New generation PMDI)



Used in **preventive therapy**

Market share:

7 % of drug sales & 2% of Inhaler sold

Source: IMS

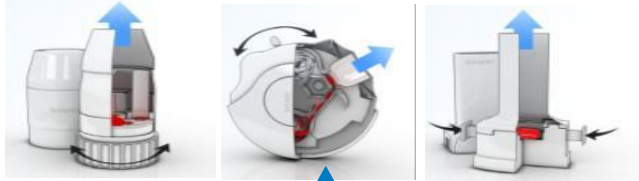
Benefits of Capsule-Based DPI Systems

Capsugel®

Lonza

Pharma & Biotech

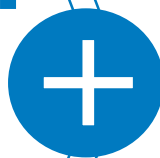
Drv-Powder Inhaler



Patient
Compliance



- No need for coordinated device actuation and patient inhalation
- Open the path for **connected device** and improved patient compliance



- Ease of use, **commitment**, **self-assessment** of full medication dose delivered

Capsule-Based DPI



Cost-
Effective



- Device flow-rate/inhalation requirements **can be adapted** to targeted patient population
- **High dose** carrying capacity
- Different level of **sophistication** available



- **Easy to manufacture** (standard filling equipment)
- Wide offer of **off-the-shelf devices**

Compatibility



- Potential **drug stability** advantage



- Compatible with **standard** carrier-based formulations and **new engineered particles** (Jetmill, Spray-Dried), ideal platform for combination drugs

Eco-
Friendly



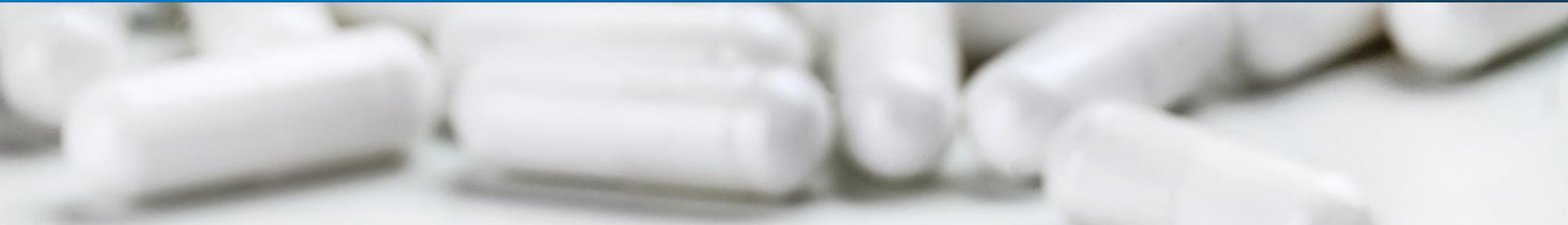
- No propellant



- **Re-usable device**, **biodegradable capsule**

What is Capsugel® Zephyr™?

Capsugel® DPI Portfolio - May 2019



Features & Benefits – DPI Capsules Portfolio

Capsugel®

Lonza

Pharma & Biotech

OUR OFFER

A portfolio of high-quality capsule solutions based on different polymers and compositions, and product customization services, that includes:

- Coni-Snap® Gelatin
- Coni-Snap® Gelatin PEG
- Vcaps®
- Vcaps® Plus

Features	Benefits
Customized shell through polymer selection and capsule size selection. Standardly available in Size 3; on demand in alternative sizes	Allows flexibility in meeting DPI device requirements (e.g. piercing, opening, etc.) and dose for specific indications.
Customization through moisture and lubricant contents	Offers a wide range of emitted dose performance within the frame of a given formulation can specific device
Specific moisture levels	Provides stability of drug over time by picking the right robust capsule that fits needs, from standard to moisture-sensitive and/or hygroscopic powder formulation.
Specific manufacturing process, dedicated in-process controls and strict release criteria. Achieves inhalation microbiological quality through respecting applicable GMP and Capsugel® standards, but non-use of preservatives, ethylene oxide or irradiation treatment.	Achieve consistent and robust performance for optimal emitted dose, within the frame of a given formulation and specific device. Ability to approach pharmaceutical market and patients without undesired molecules in contact with formulation.
Appearance customization through color, printing and transparency	Supports patient compliance and product branding/recognition
Reduced weight variation of the capsules through individual weight sorting. Up to +/- 1 mg in Size 3.	Supports accurate dosage of API in the capsules
Pilot batches with different features/functionalities for trial runs	Supports our customers' Quality by Design product development

Capsugel® Zephyr™ Portfolio Products

Coni-Snap®



Coni-Snap® Gelatin DPI

- **VP:** the cost effective solution for less challenging formulations
- **Target segments:** Innovators & Generics
- **Target geographies:** worldwide

Coni-Snap®



Coni-Snap® Gelatin-PEG DPI

- **VP:** the more robust gelatin-based solution
- **Target segments:** Generics
- **Target geographies:** worldwide



Vcaps® DPI

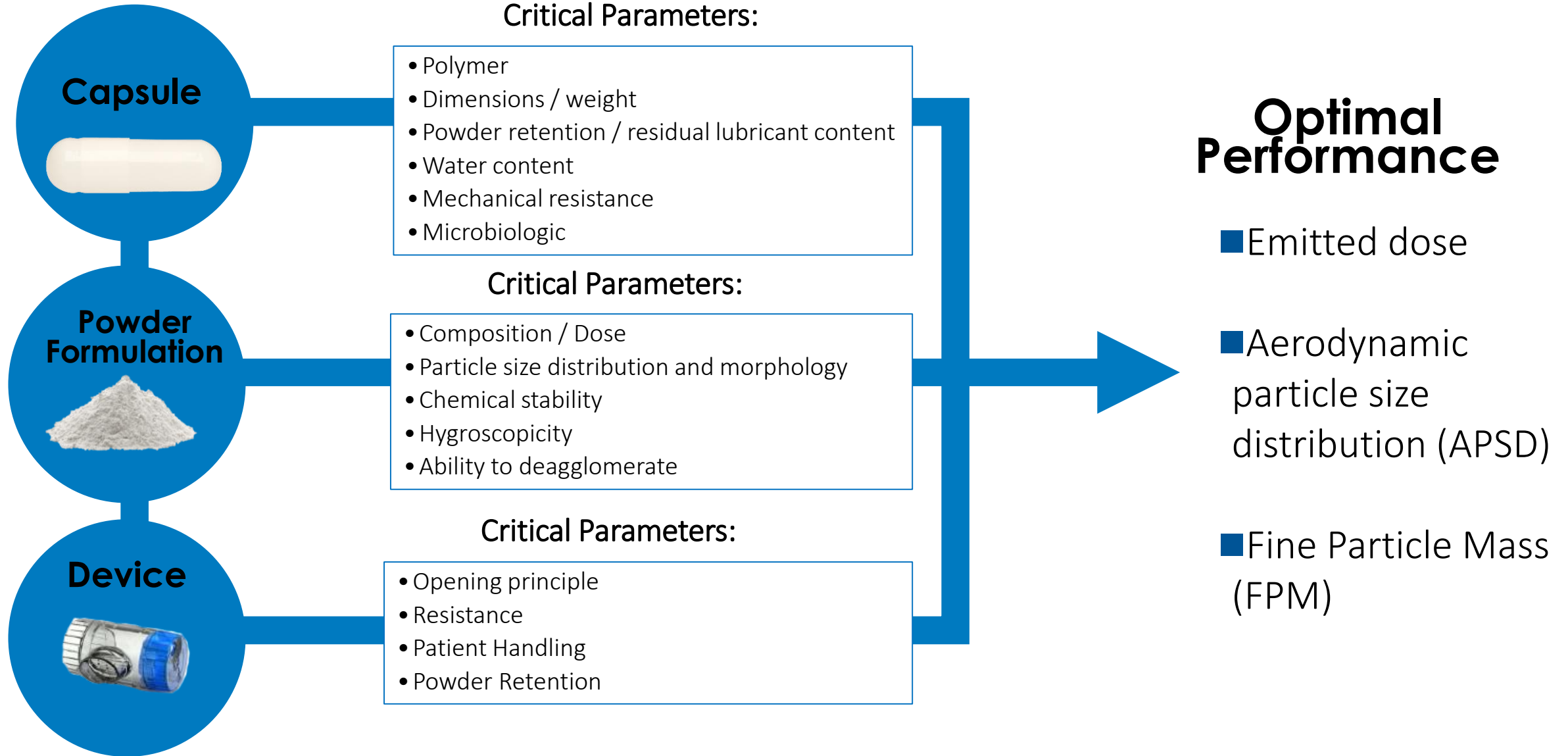
- **VP:** the superior HPMC performer with very low powder retention
- **Target segments:** Innovators & Generics
- **Target geographies:** worldwide



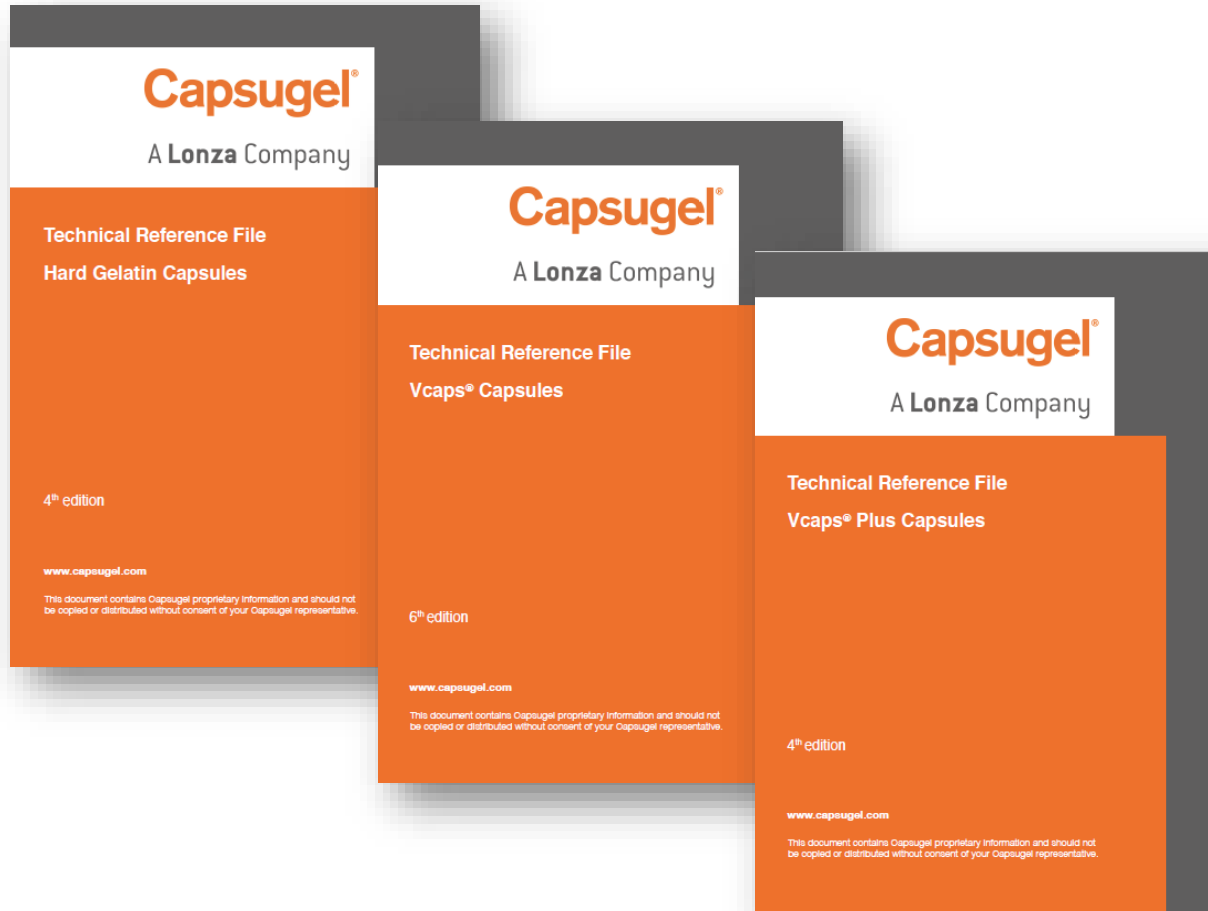
Vcaps® Plus DPI

- **VP:** the glossy and transparent HPMC capsule with consistent performance
- **Target segments:** Innovators & Generics
- **Target geographies:** worldwide

Critical Parameters and Performance



Dimensions of capsules are available in the respective Technical Reference Files



Size	1el	1	2el	2	3	4el	4	5
Weight								
mg	81	76	66	61	48	40	38	28
Tolerance mg	±5	±5	±5	±4	±3	±3	±3	±2
Capacity								
Capsule volume ml								
Powder density *								
0.6 g/ml								
0.8 g/ml								
1 g/ml								
1.2 g/ml								
Length of the caps								
Body inches								
Tolerance inches								
Body mm								
1 g/ml								
1.2 g/ml								
Cap inches								
Tolerance inches								
Cap mm								
Tolerance mm								
External diameter*								
Body inches								
Body mm								
Cap inches								
Cap mm								
Overall closed length								
Inches								
Tolerance inches								
mm								
Tolerance mm								

Note: Sizes 000 and 5 are Snap Fit®
 * Europe only
 ** All tolerances ± 0.002 inches or 0.05 mm unless otherwise specified. These data can be used for selecting packaging material dimensions.
 *** The overall closed length specifications at filled capsule can still vary to a small extent.

Size	1el	1	2el	2	3	4el	4	5
Weight								
mg	81	76	66	61	48	40	38	28
Tolerance mg	±5	±5	±5	±4	±3	±3	±3	±2
Capacity								
Capsule volume ml	0.54	0.50	0.41	0.37	0.30	0.25	0.21	0.13
Powder density *								
0.6 g/ml	324	300	246	222	180	150	126	78
0.8 g/ml	432	400	328	296	240	200	168	104
1 g/ml	540	500	410	370	300	250	210	130
1.2 g/ml	648	600	492	444	360	300	252	156
Length of the capsule parts (
Body inches	0.697	0.654	0.656	0.601	0.535	0.538	0.480	0.366
Tolerance inches	±0.018	±0.018	±0.018	±0.018	±0.018	±0.018	±0.018	±0.016
Body mm	17.70	16.61	16.66	15.27	13.59	13.69	12.19	9.30
Tolerance mm	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46	±0.40
Cap inches	0.413	0.385	0.382	0.352	0.318	0.308	0.284	0.244
Tolerance inches	±0.018	±0.018	±0.018	±0.018	±0.018	±0.018	±0.018	±0.016
Cap mm	10.49	9.78	9.70	8.94	8.08	7.84	7.21	6.20
Tolerance mm	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46	±0.40
External diameter**								
Body inches	0.261	0.261	0.240	0.239	0.219	0.199	0.199	0.184
Body mm	6.63	6.63	6.09	6.07	5.57	5.05	5.05	4.68
Cap inches	0.272	0.272	0.250	0.250	0.229	0.209	0.209	0.193
Cap mm	6.91	6.91	6.36	6.35	5.82	5.31	5.32	4.91
Overall closed length***								
Inches	0.804	0.765	0.780	0.709	0.625	0.621	0.563	0.437
Tolerance inches	±0.012	±0.012	±0.012	±0.012	±0.012	±0.012	±0.012	±0.016
mm	20.4	19.4	19.3	18.0	15.9	15.8	14.3	11.1
Tolerance mm	±0.3	±0.3	±0.4	±0.3	±0.3	±0.3	±0.3	±0.4

Note: Sizes 000 and 5 are Snap Fit®
 * Europe only
 ** All tolerances ± 0.002 inches or ± 0.06 mm. The data above is an indication of the external diameter and should not be considered as an actual/insert criteria (due to the tapered shape of the capsule and the difficulty to measure the exact diameter). These data can be used for selecting packaging material dimensions

For narrower weight specification, Lonza has capacities in weight-sorting of capsules.

Chemical & Microbiological Specifications

Capsugel®

Lonza
Pharma & Biotech

In addition to specifications and information available in the Technical Reference File of Capsugel® Coni-Snap® Hard Gelatin Capsules, Vcaps® and Vcaps® Plus HPMC capsules, below specifications apply:

Test	Specification	Method reference	
		Coni-Snap® Hard Gelatin Capsules	Vcaps® / Vcaps®PlusHPMC Capsules
Lubricant content	Less than 500 ppm	CP019b	VCP016B / VCP016B
Total viable aerobic count			
Total Aerobic Microbial Count	Less than 100 cfu per gram	CP031	VCP031 / VCPP031
Total Yeasts/Moulds Count	Less than 10 cfu per gram	CP032	VCP035 / VCPP035
Specified micro-organisms			
Bile-Tolerant Gram-Negative	Absence in 1 gram	CP048	VCP048 / VCPP048

Inhalation microbiological quality through respecting applicable GMP and Capsugel® standards, without use of preservatives, ethylene oxide or irradiation treatment

DPI Capsule Performance

Capsugel® DPI Portfolio - May 2019



Adsorption - Desorption Isotherms

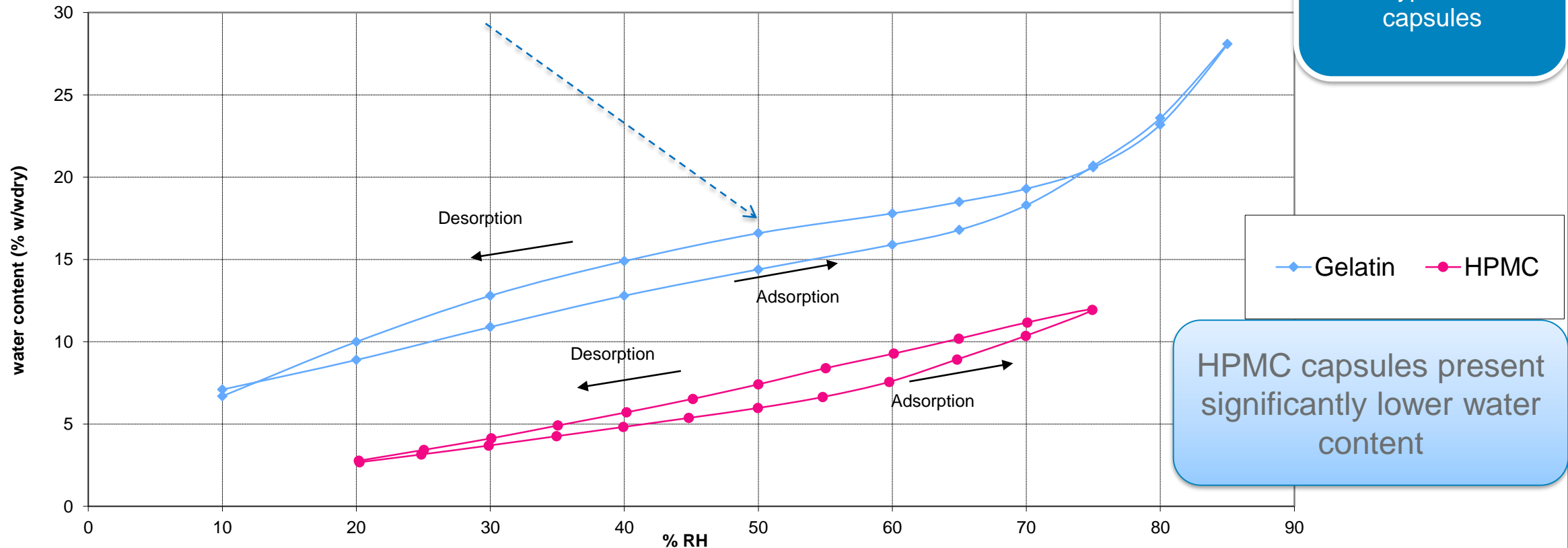
Capsugel®

Lonza

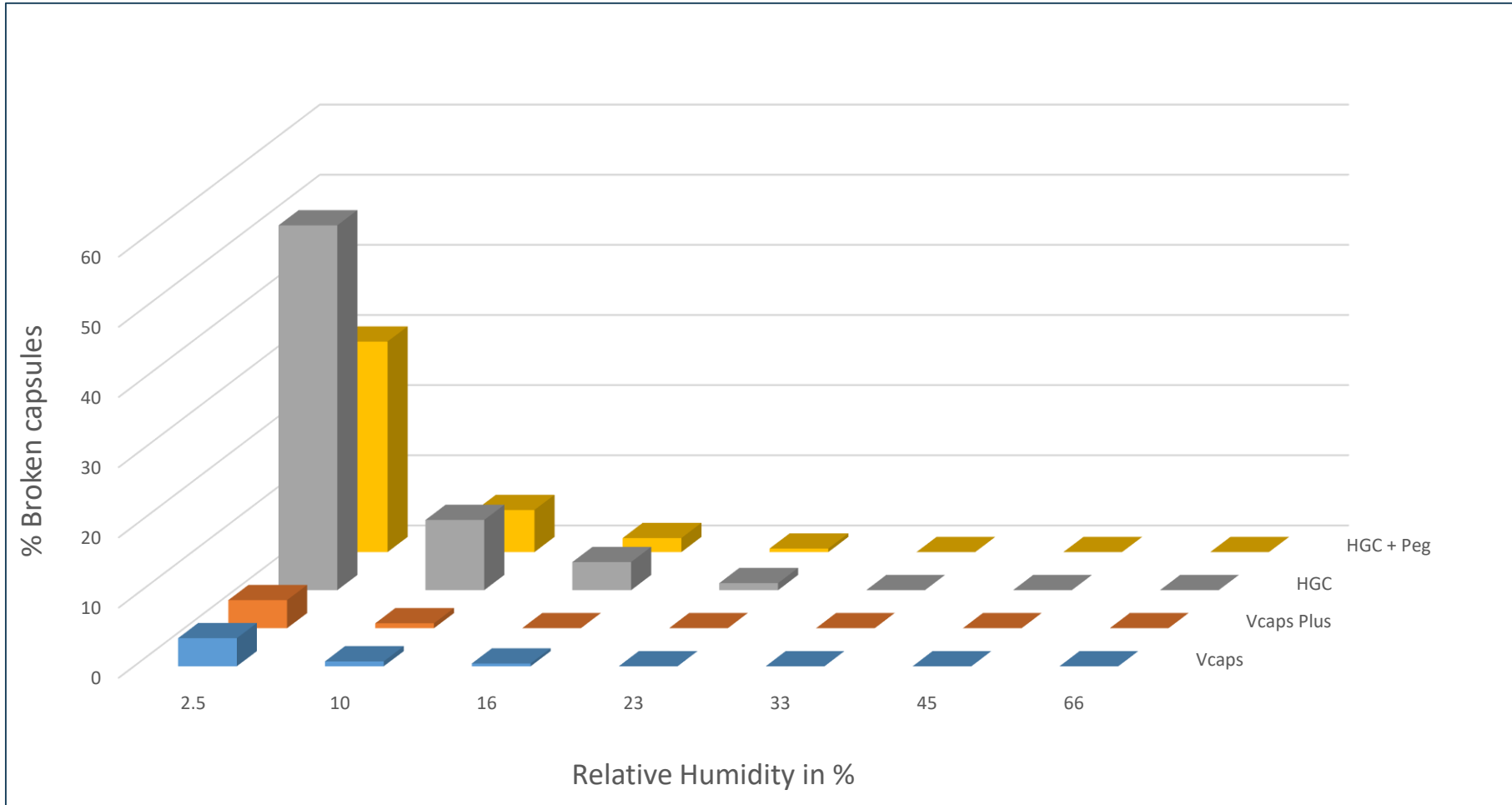
Pharma & Biotech

Gelation sorption –
desorption isotherm

Water vapor adsorption-desorption at 25°C



Capsule Mechanical Performance



Capsule interactions with environmental conditions have a decisive influence during shelf-life, packaging, deblistering and actuation phase

Capsule brittleness in function of Relative Humidity, measured by tube test on 50 capsules

LOD Customization Capabilities



Often, **capsule LOD** has to be adapted to **specific formulation requirements** (filling properties, stability)

.....

To find out best range, **water activity** measures can be performed in-house

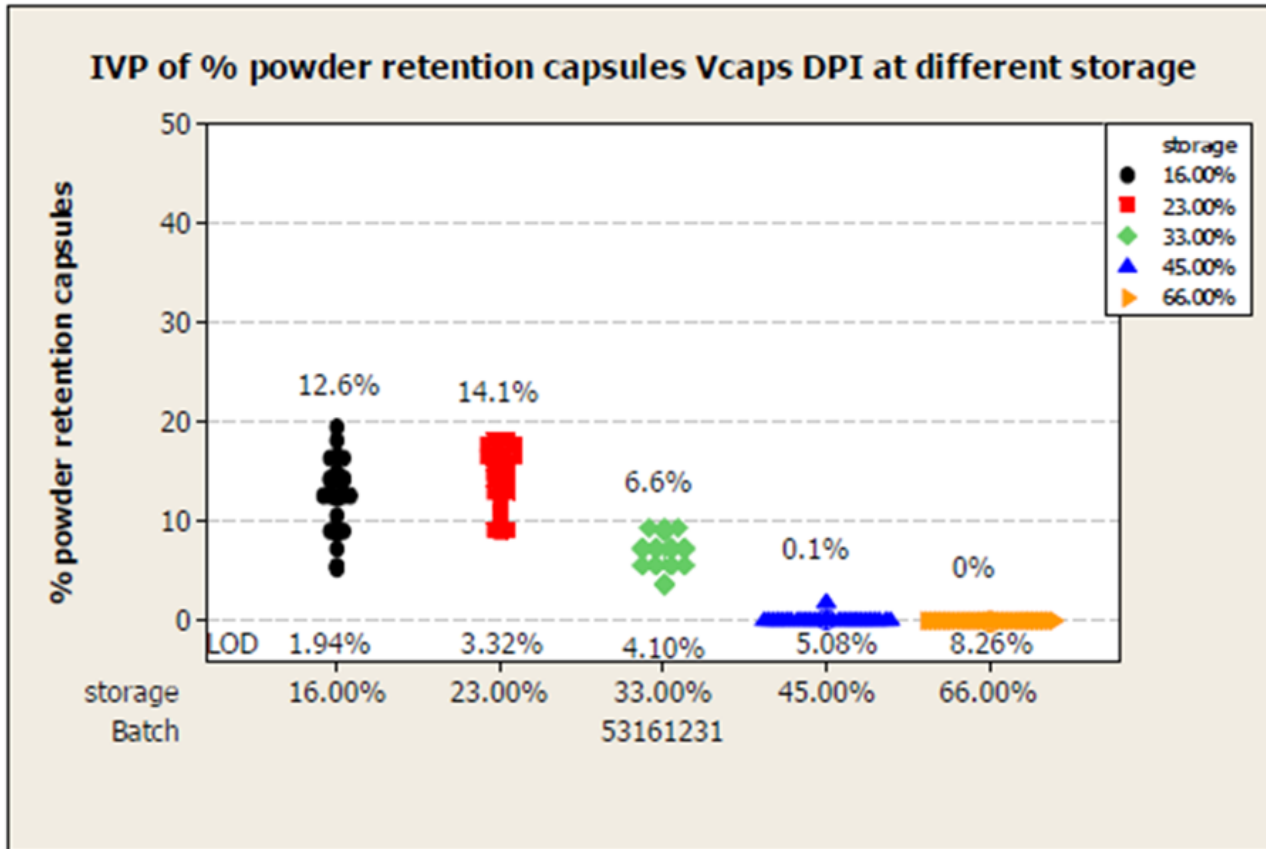
.....

We deliver **LOD range** customization

LOD Customization for Optimal Performance

Capsugel®

Lonza
Pharma & Biotech



Powder retention and water content of HPMC capsules (Vcaps DPI) filled with 25.0 ± 1 mg 150 mesh lactose at different RH conditions (n=20)

Conclusion:

- Powder retention increased with decrease of LOD > Static effect
- Low LOD can be a solution for specific situations, but lower is not always better
- Water Activity measure allows to define the best compromise.

Powder Retention – Visual aspect

Internal Lubrication Impact



Capsules filled with lactose blend for DPI applications, closed, shaken, then opened, emptied and assembled.

Consistency of internal lubrication process drives optimal consistent performance.

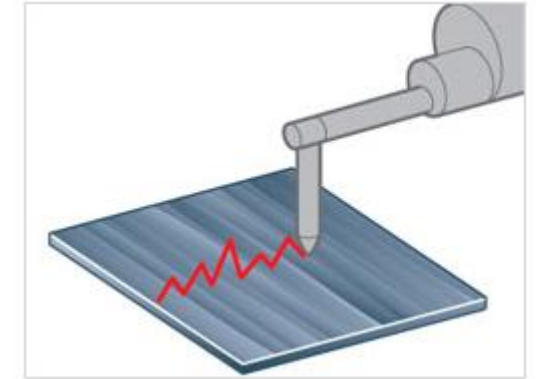
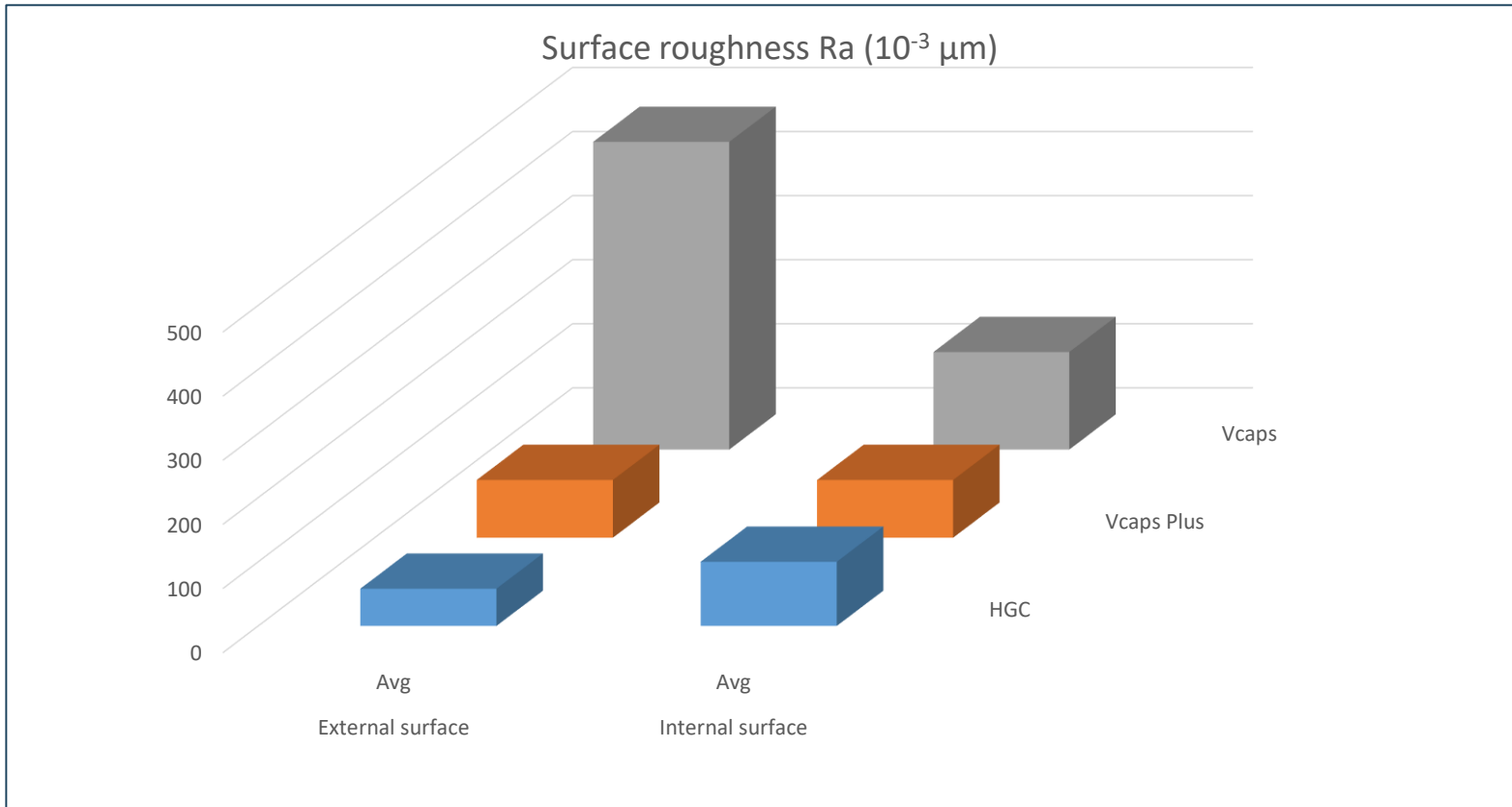
Capsule Surface Approach

External and Internal surfaces

Capsugel®

Lonza

Pharma & Biotech

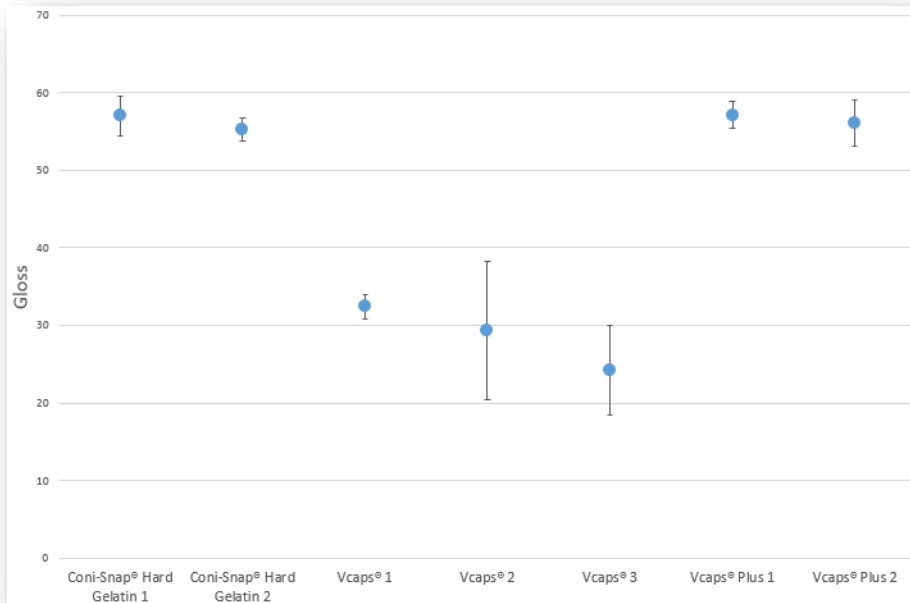
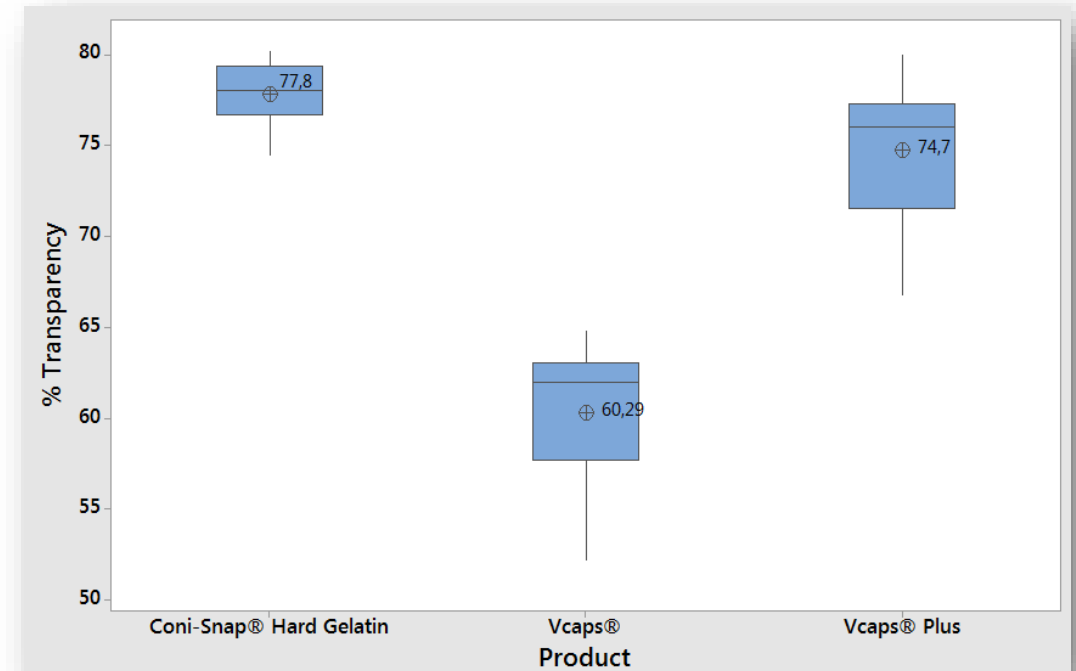


Ra is the average roughness of a surface.

Transparency & Glossiness Data

Transparency :

Capsule transparency is measured using spectrometer and is given by the percentage of light transmission at 650nm length wave. Sample size: 10 capsules



Glossiness :

A gloss meter Novo-Curve from Electrometer was used for the capsule measurement. Measurements performed on 10 capsules.

Performance With Different Inhalation Devices

Capsugel®

Lonza

Pharma & Biotech



RS01 (Plastiapex)



Capsuhale
(RPC – Formatec)



Handihaler®
(Boehringer Ingelheim)



Twister™ (Aptar)



Rotahaler (Cipla)

	Puncturing ⁽¹⁾		
Capsules conditioning	23%RH	33%RH	45%RH
RS01	Good for HPMC capsules	Good for HPMC capsules	Good for HPMC, PEG & gelatin capsules
Capsuhale	Good for HPMC & PEG capsules	Good for HPMC & PEG capsules, acceptable for gelatin capsules	Good for HPMC, PEG & gelatin capsules
Handihaler	Good for HPMC capsules acceptable for other capsules	Good for HPMC & PEG capsules, acceptable for gelatin capsules	Good for HPMC, PEG & gelatin capsules

(1) Puncturing: 15 capsules were tested and observed after use for absence of particle; when a minor particle is missing for a few capsules only, the test is rated “acceptable”

	Opening ⁽¹⁾		
Capsules conditioning	23%RH	33%RH	45%RH
Twister	Good for HPMC & Gelatin capsules, acceptable for PEG capsules	Good for HPMC, PEG & gelatin capsules	Good for HPMC, PEG & gelatin capsules
Rotahaler	Good for HPMC, PEG & gelatin capsules	Good for HPMC, PEG & gelatin capsules	Good for HPMC, PEG & gelatin capsules

(1) Opening: : 15 capsules were tested and observed after use; when a minor part of the capsule is missing (capsule partly broken when opening) for a few capsules only, the test is rated “acceptable”

CONCLUSIONS:

- Capsugel® capsules are adapting to a broad spectrum of device solutions
- Industry choice of device and capsules for DPI will be driven by the moisture sensitivity of the formulation
- Preferences in the targeted population to select between puncturing or opening devices

Capsule Filling Machine Evaluation

Capsugel® capsules have been tested on a broad range of capsule filling machines and exhibit excellent machinability performances. Some of the brands include:

- Bosch
- IMA Group
- Harro Hofliger
- MG2
- Capsugel® filling machines

Our Technical Service Engineers can offer you their experience and knowledge in optimizing and setting up the triangle machine/capsule/powder according to your needs.

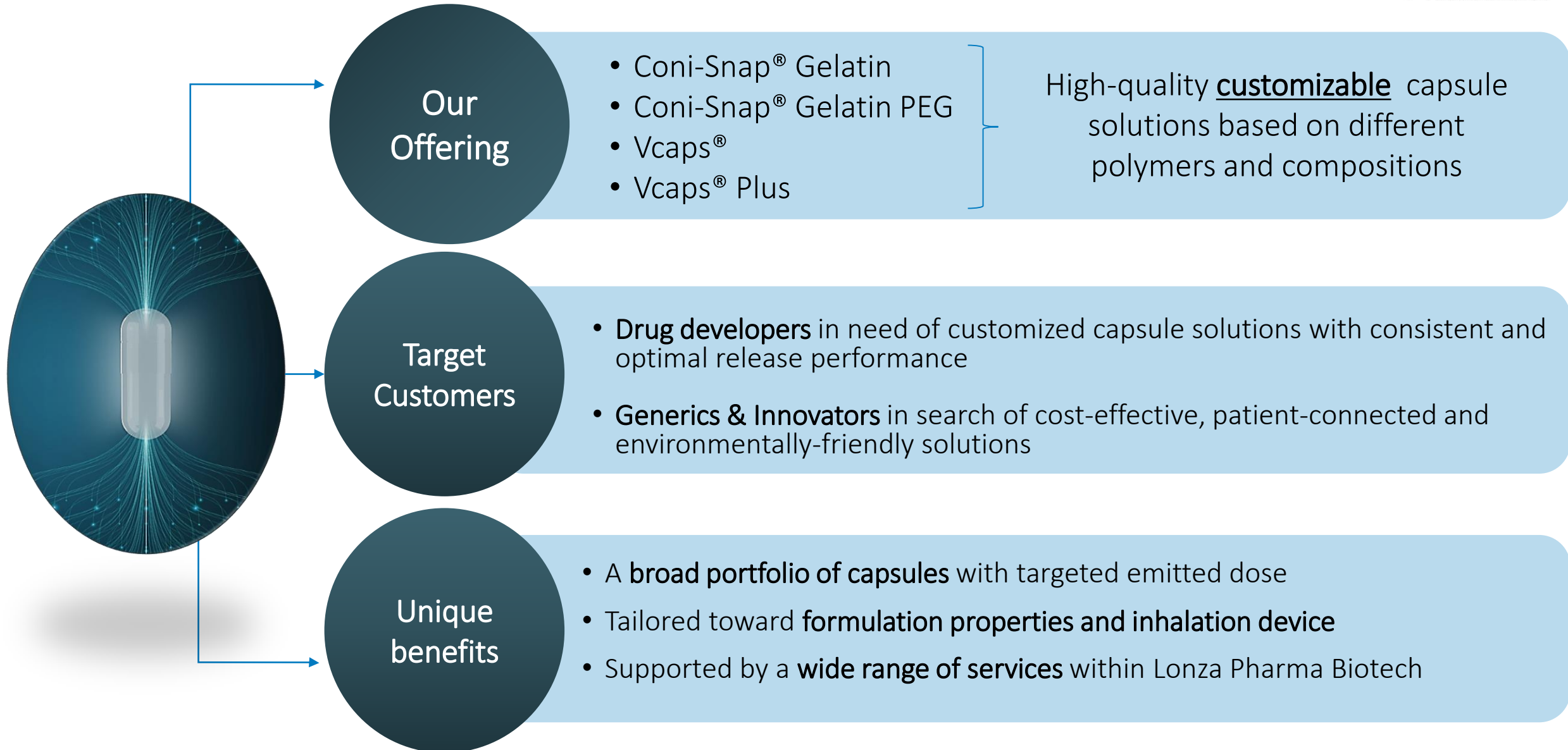


Capsugel® Zephyr™ Summary and Availability

Capsugel® DPI Portfolio - May 2019



Capsugel® Zephyr™ in a Nutshell...



Sample Availability



R&D Bottles



Caddies



Cartons

Consult your Lonza representative for ordering information

Review and follow all product safety instructions. The statements made in these materials have not been evaluated by the U.S. Food and Drug Administration or any other regulatory authority. Lonza's products are not intended for use to diagnose, treat, cure or prevent any disease. All information in this presentation corresponds to Lonza's knowledge on the subject at the date of publication, but Lonza makes no warranty as to its accuracy or completeness and Lonza assumes no obligation to update it. All information in this presentation is intended for use by recipients experienced and knowledgeable in the field, who are capable of and responsible for independently determining the suitability and to ensure their compliance with applicable law. Proper use of this information is the sole responsibility of the recipient. Republication of this information or related statements is prohibited. Information provided in this presentation by Lonza is not intended and should not be construed as a license to operate under or a recommendation to infringe any patent or other intellectual property right. All trademarks belong to Lonza or its affiliates or to their respective third parties and are used here only for informational purposes. Copyrighted material has been produced with permissions or under license, all other materials © 2019 Lonza.

Questions?



Capsugel®

Lonza

Pharma & Biotech