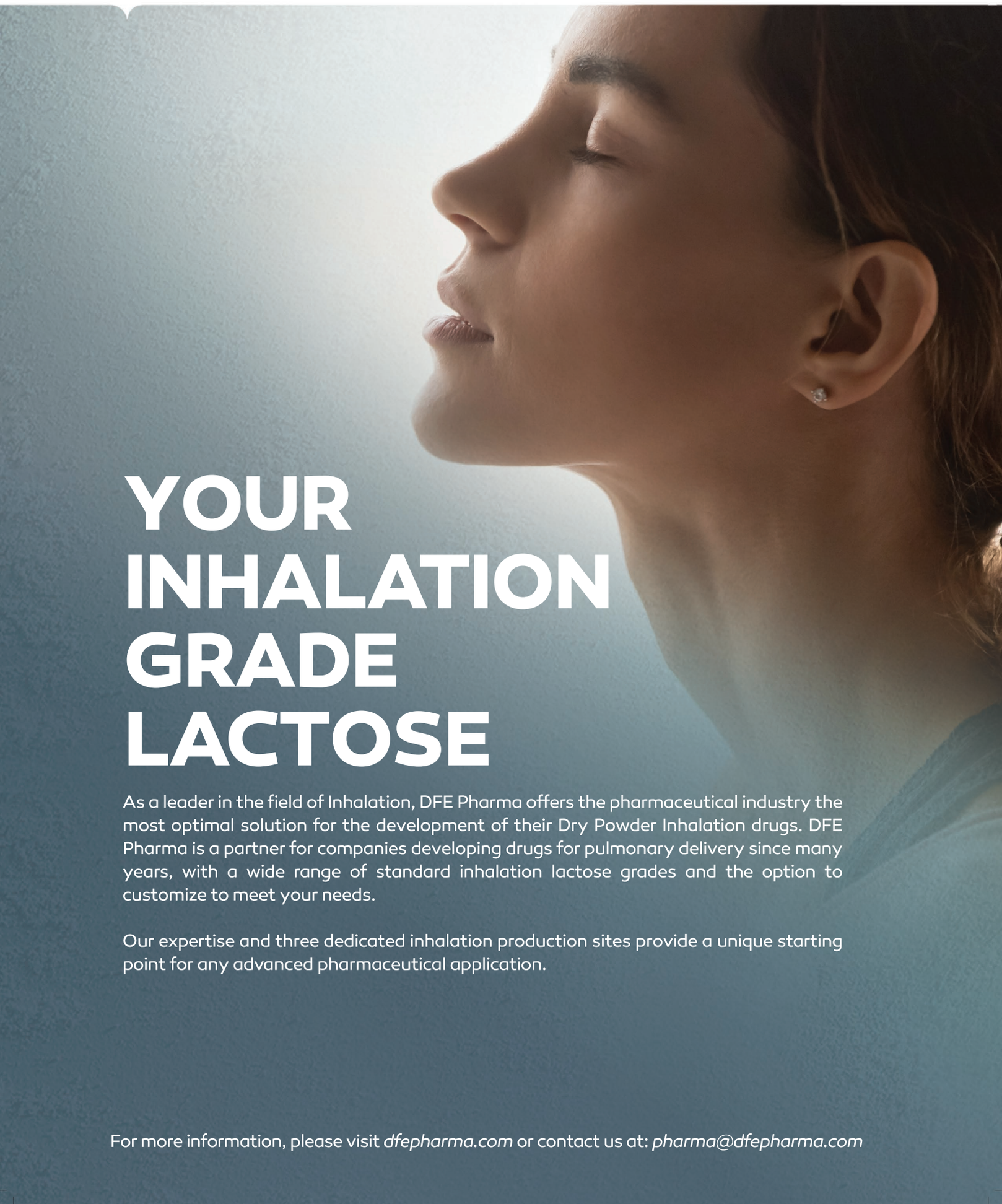
DFE pharma



YOUR INHALATION GRADE LACTOSE

As a leader in the field of Inhalation, DFE Pharma offers the pharmaceutical industry the most optimal solution for the development of their Dry Powder Inhalation drugs. DFE Pharma is a partner for companies developing drugs for pulmonary delivery since many years, with a wide range of standard inhalation lactose grades and the option to customize to meet your needs.

Our expertise and three dedicated inhalation production sites provide a unique starting point for any advanced pharmaceutical application.

For more information, please visit *dfepharma.com* or contact us at: *pharma@dfepharma.com*

We are DFE Pharma

We are DFE Pharma: a global leader in excipient solutions.

We develop, produce and supply high quality excipients for use in the pharmaceutical, biopharmaceutical and nutraceutical industries. Our products are used for respiratory, oral solid dose (OSD), ophthalmic and parenteral formulations.

We work closely with pharmaceutical companies around the world, collaborating in original research, supporting their go-to-market strategies and fine-tuning our products to ensure that their medicines deliver exactly the right outcomes for patients. That makes us more than a supplier. We are recognized as a true partner to the pharmaceutical industry in helping people around the world live healthier lives.

In our more than a century of heritage, we strive for customer satisfaction from formulation development support to excipient supply. We provide our customers with our comprehensive technical expertise and support to efficiently navigate any regulatory space.

Our portfolio consists of filler/ binders (Lactose, Microcrystalline Cellulose, Starches), Co-processed excipients and superdisintegrants (Croscarmellose Sodium and Sodium Starch Glycolate) for oral solid dose, stabilizers for bio pharma applications and carriers for inhalation (Lactose).

Your medicines, our solutions. **Moving to a healthier world.**

For more information, please visit *dfepharma.com* or contact us at: *pharma@dfepharma.com*

Your Inhalation Grade Lactose

by DFE Pharma

A growing number of diseases are being treated with inhaled medicines. Many treatments now use Dry Powder Inhalers, which invariably need a high quality inhalation grade of lactose to power the formulation. Since each Dry Powder Inhaler device is different, they often need a specific grade of lactose to ensure correct product performance, particularly for highly regulated markets. Due to regulatory demands, all our inhalation grade lactose is produced in dedicated inhalation production sites.

Quality and Regulatory Support

All production sites for inhalation lactose operate under GMP standards and meet the high quality standards that are demanded by the FDA and other regulatory bodies. In addition, DFE Pharma fully supports the quality requirements demanded by our customers.

A Drug Master File is available to assist in the registration of a new formulation in the United States. For optimal control on the functionality and to comply with regulatory requirements, additional testing above the current pharmacopoeia is in place.

DFE Pharma can support you for registration of your Dry Powder Inhalation product in China: for more information, please contact our regulatory specialist.
To support our customers, an extensive list of regulatory and quality documents for Lactohale® is available at our website www.dfepharma.com.

Technical Support

The DFE Pharma Inhalation team develops pharmaceutical lactose that facilitates delivery of your active pharmaceutical ingredient to the lung.
We work closely with pharmaceutical companies to design lactose particles with the required functionality for the drug, device and filling-platform.

Research and Development

Through our own research and close co-operation with research institutes and universities, we are continuously expanding our knowledge of lactose and other excipients that can be used for inhaled delivery. Of particular interest to us is the physiochemical behaviour of lactose under conditions relevant for use as an excipient in advanced pharmaceutical applications. With this knowledge we can advise our customers on the latest scientific developments. DFE Pharma offers the following inhalation grade lactose brands:

- Lactohale®
- Respitose®

Production Capabilities

We have three production sites fully committed to the production of inhalation grade lactose within DFE Pharma, each with their unique capabilities: Veghel (the Netherlands) for production of Respitose
Borculo (the Netherlands) and Kapuni (New Zealand) for production of Lactohale®.

DFE Pharma is the only excipient supplier with three production sites on two different continents for inhalation-grade lactose, offering customers the possibility of security of supply. All three production sites have been set up to produce a consistent and high-quality inhalation grade lactose, to meet the quality needs of our customers.

For more information, please visit *dfepharma.com* or contact us at: *pharma@dfepharma.com*

Packaging of **Inhalation Lactose**

The packaging of the inhalation products we offer, is important to guarantee the quality and stability of the material. In the table below, the standard packaging options for Lactohale® and Respitose® are listed. Additional packaging options might be available on request.

Storage

We recommend to store inhalation lactose in the closed original packaging under normal warehouse conditions.

Packaging overview Respitose® and Lactohale®

Packaging attributes	Cardboard Box NL	Cardboard Box NZ	HDPE Box	HDPE Drum
Length (cm)	38	36	38.9	38.9
Width (cm)	28	32	32.8	32.8
Height (cm)	45	42	71.4	71.4

Product	Weight				Re-test date
Lactohale® 100	20 kg	-	-	-	3 years
Lactohale® 200	20 kg	-	-	-	3 years
Lactohale® 201	20 kg	-	-	-	3 years
Lactohale® 206	20 kg	-	-	-	3 years
Lactohale® ML001	-	20 kg	-	-	3 years
Lactohale® 800	-	20 kg	-	-	3 years
Lactohale® 210	15 kg	-	-	-	3 years
Lactohale® 220	15 kg	-	-	-	3 years
Lactohale® 230	10 kg	-	-	-	3 years
Lactohale® 300	12.5 kg	-	-	-	12 months
Lactohale® 400	20 kg	-	-	-	12 months
Respitose® ML001	-	-	-	50 kg	3 years
Respitose® ML003	-	-	-	40 kg	3 years
Respitose® SV001	-	-	-	50 kg	3 years
Respitose® SV003	-	-	-	50 kg	3 years
Respitose® SV010	-	-	-	50 kg	3 years
Respitose® SV014	-	-	-	50 kg	3 years

Lactose-by-Design

Dry Powder Inhalation Formulations

A dry powder inhaler formulation should contain drug particles with an aerodynamic particle size of less than 5 µm for an optimal pulmonary delivery. Due to the high surface area to mass ratio of the particulates, the powdered drug is highly cohesive. Therefore a larger carrier, such as lactose, is applied to de-agglomerate the drug particles and optimize the deposition of the drug in the lung. In addition, the use of a lactose carrier has the added benefit of making the formulation manageable on an industrial scale by boosting the amount of powder in each dose. Summarizing, both the filling of a device and the deposition of the drug in the lung are strongly influenced by the quality of the carrier.

Role of Lactose in inhaled Formulations

Lactose is one of the few excipients that have been accepted by all authorities to be used in inhaled formulations. The properties of the inhalation lactose are chosen based on the different parameters, like the device (flow of lactose), filling platform (flow of lactose), type of drug and how it is processed and the required drug release (fine lactose particles). In practice, this means that DFE Pharma can deliver customized inhalation lactose to meet the specific requirements of their customers.

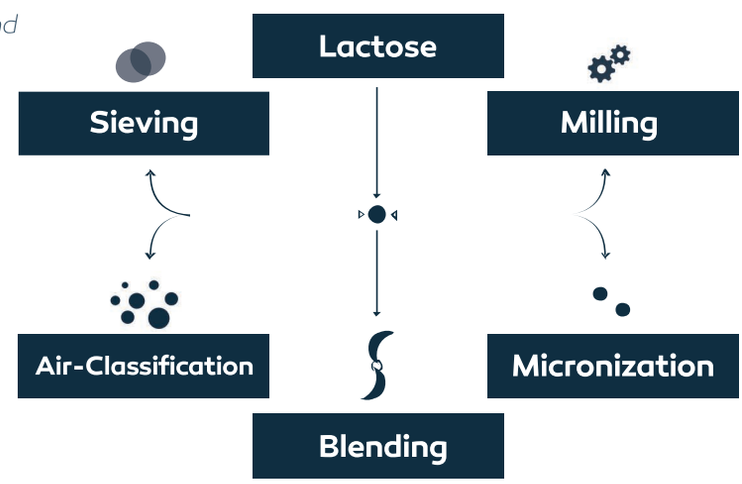
Inhalation lactose is a naturally occurring disaccharide, which is extensively purified to meet the strict requirements for use in an inhaled application. To obtain different functionalities for the inhalation formulation the lactose is further processed by techniques such as sieving, milling, micronization or air-classification.[1]

The technical publications of DFE Pharma show how the different physical properties of inhalation lactose can be controlled by blending a fine fraction with a coarse fraction, i.e. the fines content in inhalation grade lactose. [2] The choice of fines is a critical decision point in the development of a DPI formulation. The detailed knowledge of the experts of DFE Pharma can support customers to predict various physical parameters of the lactose for inhalation out of fine and coarse lactose fraction.

More technical information can be found on our website www.dfepharma.com

[1] Steckel, H; Markefka, P; teWierik, H; Kammelar, R; 2004, Functionality testing of inhalation grade lactose. Eur. J. Pharm. Biopharm. 57: 495-505

[2] Kinnunen, H.; Hebbink, H.; Peters, H.; Huck, D.; Makein, L.; Price, P.; Extrinsic lactose fines improve dry powder inhaler formulation performance of a cohesive batch of budesonide via agglomerate formation and consequential co-deposition; 2015 Int J Pharmaceutics 478, 53-59



Lactohale®

Lactohale® is our high-quality inhalation grade lactose that can be optimized and customized to meet the specific need of customer. Strict and highly consistent particle size control during the production, combined with particle size measuring techniques form the basis for the success of Lactohale®.

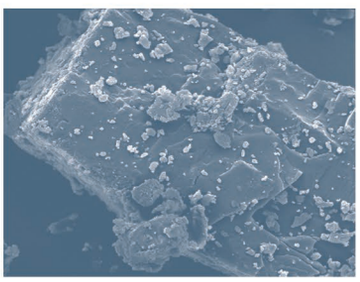
While most customers start their development with the standard Lactohale® grades, many convert to customization to fine-tune the performance of their formulation. In close collaboration, the flow properties can be matched to the correct fines content for an optimal product performance.

In the final processing step all Lactohale® products are blended in order to ensure that the batch is homogeneous. The resulting customized Lactohale® grade with their specific particle size profiles is unique for each customer.

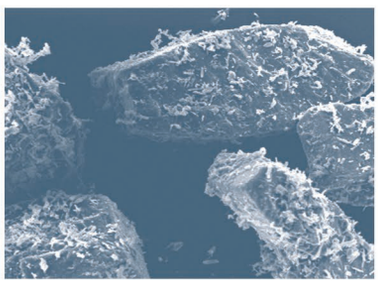
Lactohale® Inhalation lactose is produced in a dedicated inhalation lactose production sites in Borculo (the Netherlands) and in Kapuni (New Zealand). Both plants were designed to meet the strict quality requirements that are demanded by the FDA and supply to commercialized end-product in regulated markets. We look forward to collaborate closely with pharmaceutical companies to develop, produce and deliver lactose with the required functionality.

Please, contact your sales representative for more information.

Crystals of alpha monohydrate



Milled alpha monohydrate lactose.



Example of an adhesive mixture of Lactohale® and salbutamolsulphate.

Lactohale® products overview

Packaging attributes	Type of lactose	Production Location	Particle Size Distribution (Sympatec) D10 (µm)	D50 (µm)	D90 (µm)	Typical values Tapped Density	Poured Density	Carr's Index
Lactohale® 300	Fine	Borculo (NL)		< 5	≤10	520	260	>25%
Lactohale® 230	Fine	Borculo (NL)	1.0 - 3.0	<10	<30	500	310	>25%
Lactohale® 220	Fine	Borculo (NL)	1.5 - 3.0	11 - 15	25 - 40	660	370	>25%
Lactohale® 210	Fine	Borculo (NL)	2.0 - 3.5	14 - 19	35 - 50	680	400	>25%
Lactohale® 201	Fine	Borculo (NL)	3 - 6	20 - 25	50 - 60	700	500	>25%
Lactohale® 400	Anhydrous	Borculo (NL)	5 - 10	80 - 120	230 - 330	920	650	>29%
Lactohale® ML001	Coarse	Kapuni (NZ)	3-7	37 - 61	124 -194	880	570	>25%
Lactohale® 206	Coarse	Borculo (NL)	20 - 50	75 - 95	115 -170	870	720	17%
Lactohale® 200	Coarse	Borculo (NL)	5 - 15	50 - 100	120 - 160	940	650	>25%
Lactohale® 800	Coarse	Kapuni (NZ)	5 - 15	50 - 100	120 - 160	940	650	>25%
Lactohale® 100	Coarse	Borculo (NL)	45-65	125-145	200 - 250	840	690	19%

NL | The Netherlands NZ | New Zealand

Respitose®

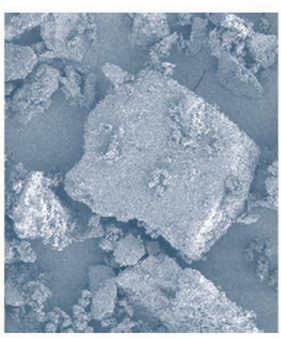
Respitose® Inhalation lactose is a highly consistent product with excellent control of particle size. The offering can be divided in either sieved crystalline lactose grades with tomahawk-shaped articles (Respitose® SV) or milled lactose grades with irregular shaped particles (Respitose® ML).

Respitose® product range include unique lactose grades with good flow and strict control of particle size. Global customers especially favor the standard Respitose® SV003 product because of its unique particle size profile.

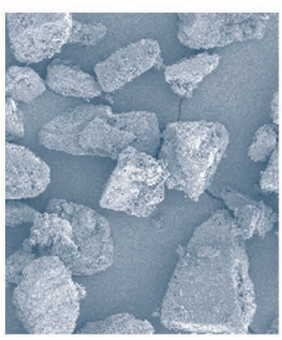
Respitose® Inhalation lactose is produced under GMP conditions at a dedicated inhalation lactose production site in Veghel, the Netherlands. The plant was designed to meet the strict quality requirements that are demanded by the FDA.

Combination of different Respitose® standard grades provide customers a tool to achieve optimal performance for their Dry Powder Inhalation formulation.

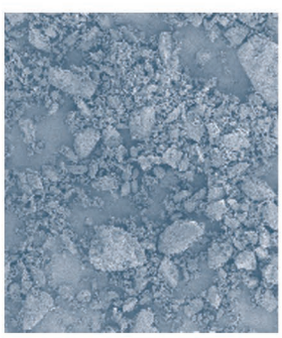
Please, contact your sales representative for more information.



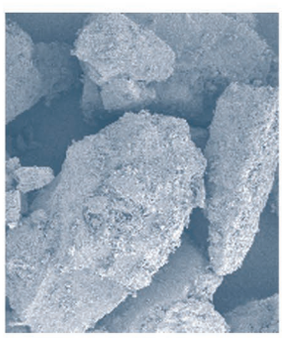
Respitose® ML001



Respitose® SV003



Respitose® ML003



Respitose® SV010

Respitose® standard products overview

Packaging attributes	Type of lactose	Production Location	Particle Size Distribution (Sympatec)			Typical values		
			D10 (µm)	D50 (µm)	D90 (µm)	Tapped Density	Poured Density	Carr's Index
Respitose® ML003	Milled	Veghel (NL)	1-6	20-50	65-140	850	560	>25%
Respitose® ML001	Milled	Veghel (NL)	3-7	37-61	124-194	880	570	>25%
Respitose® SV003	Sieved	Veghel (NL)	19-43	53-66	75-106	780	630	19%
Respitose® SV010	Sieved	Veghel (NL)	35-65	95-125	160-190	830	690	17%
Respitose® SV001	Sieved	Veghel (NL)	120-160	210-250	290-350	810	700	14%
Respitose® SV014	Sieved	Veghel (NL)	245	365	545	810	720	12%

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by DFE Pharma

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