CritiTech®
Pulmonary

Transforming Drugs Into Superior Treatments for Respiratory Diseases and Conditions

CritiTech®
Pulmonary

Introduction

Purcision™ Technology A Unique Platform for Respiratory Drug Development

Opportunity to Develop Inhaled Drugs Using Purcision™ Technology

CritiTech's Drug Development & Manufacturing Capabilities

CritiTech® Pulmonary

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Purcision™ Technology A Unique Platform for Respiratory Drug Development

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CritiTech's Drug Development & Manufacturing Capabilities

Management Team

CritiTech Particle Engineering Solutions has a strong and experienced management team.

Sam Campbell
Chairman

20 years at CritiTech
MBA

Matthew McClorey
President

11 years at CritiTech
JD/MBA

Jody Schrandt
Chief Operating Officer

4 years at CritiTech
MBA

Mike Baltezor, PhD
Chief Scientific Officer

10 years at CritiTech
PhD

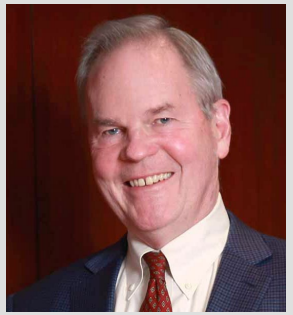
Mark Williams
Vice President
Technical Operations

8 years at CritiTech
BS

Highly Skilled & Experienced Technical Leadership Team

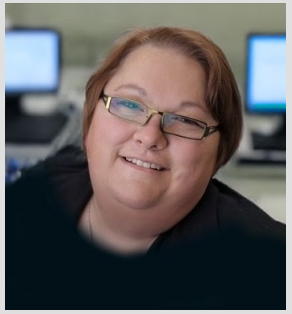
- Over 150 years of experience in the pharmaceutical industry - early-stage drug development, particle engineering, formulation, material characterization, analytical testing, method development, clinical trial management, commercial manufacturing, quality operations, regulatory, and corporate management
- Previous positions held at Sanofi-Aventis, Merck, Sandoz, Marion-Merrill Dow, Cardinal Health, Celliance, Quintiles, CareFusion, and Plastikon
- Involved in the development of >100 drugs that have been tested in the clinic and >20 drugs that have been approved by the FDA
- Collectively, members of our team have been listed as inventors on >100 patents
- Dr. Michael Baltezor, Chief Scientific Officer, is the co-inventor of Cardizem CD (>$2B in peak annual sales)

Michael Baltezor, PhD
Chief Scientific Officer



Gere diZerega, MD
Chief Medical Officer

Mark Williams
Vice President Technical Operations



Deborah Wade
Vice President Quality Operations

Jake Sittenauer
Director Drug Development Programs

Joe Farthing
Director Quality Systems & IT

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Purcision™ Technology A Unique Platform for Respiratory Drug Development

Opportunity to Develop Inhaled Drugs Using Purcision™ Technology

CritiTech's Drug Development & Manufacturing Capabilities

Purcision™ Technology is a Platform for Developing Drugs for Direct Delivery at the Site of Disease

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The Purcision™ Technology has been used to engineer, formulate and manufacture a variety of drugs that have advanced into clinical trials.

Purcision™
DIRECT TO TARGET DRUGS

Platform for Oncology Drug Development

- Taxanes
- Kinase Inhibitors
- PARP Inhibitors
- Cisplatin

Platform for Respiratory Drug Development

- Antivirals
- Antibiotics
- Respiratory Diseases (PAH, IPF, COPD, Asthma, CF)
- MCM's for Chemical Warfare Agents (Lung Treatment & Protection)

Platform for Direct-to-Site Drug Development

- Pain Management
- Wound Healing
- Topical
- Bladder Infection
- IM or SC Injections
- Nasal MCM's

Developing Inhaled Drugs is Tough

Conventional drug development and manufacturing technologies struggle to produce the right mix of particle attributes necessary for safe and effective inhaled drugs.

Problems with Inhaled Drug Development

- Insufficient drug load
- Additives (sugars, stabilizers) hinder performance
- Inconsistent material
- Poor flowability – static charge
- Inadequate delivery of drug from a DPI
- Limited retention time in the lungs
- Side effects from faster than desired systemic uptake

Purcision™ Helps Overcome Challenges Associated with Developing Inhaled Drugs

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Attributes

- Crystalline powders
- Low density
- High surface area
- 100% pure drug – no excipients
- Uniform and consistent particles
- Improved flowability

Purcision™
DIRECT TO TARGET DRUGS

Performance

- High drug load
- Long duration
- Avoid phagocytosis
- Highly stable
- Larger particles remain at the site of administration but release drug like smaller particles
- Maximizes flow from DPI

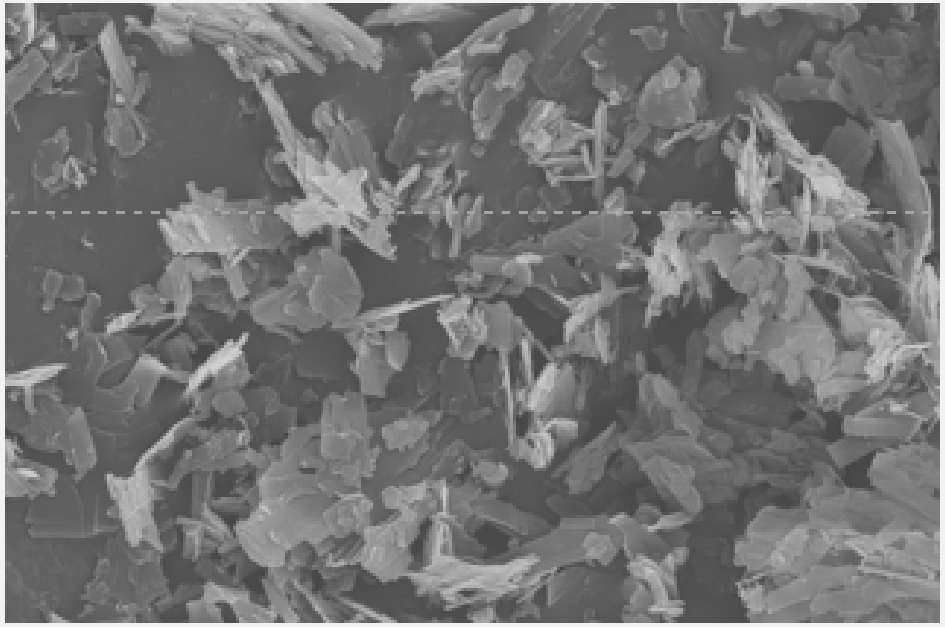
Purcision™ Creates Many Opportunities for Respiratory Drug Development

- Second chance for "shelved" drugs
- Reformulations of current IV and oral drugs
- New drugs

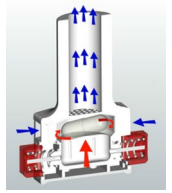
Purcision™ Particle Engineering & Production Technology

Purcision™ is a proven particle engineering technology used to develop new drugs and reformulate and repurpose existing drugs for multiple delivery systems. It is particularly effective for engineering particles for inhaled delivery.

Purcision Engineered Particles



New & Improved Drugs



Inhalation

Orals

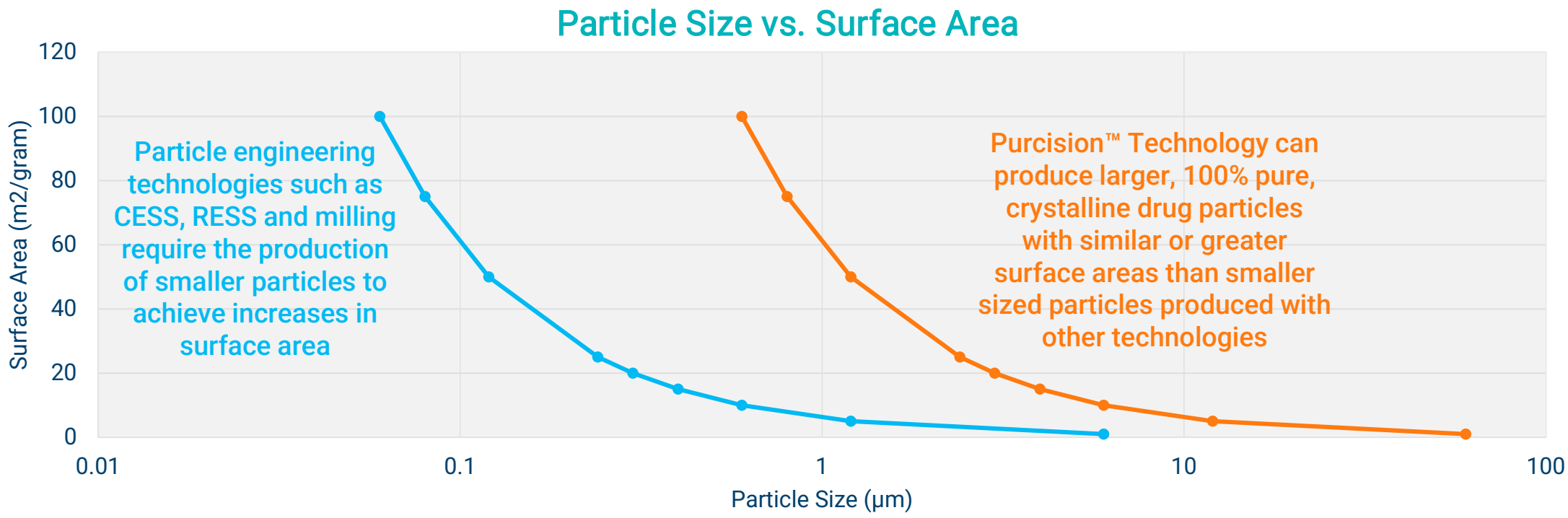
Injectables

Gels/Ointments

Controlled Concentration – Long Duration – Limited Systemic Exposure

Purcision™ Produces a Unique Particle Size to Surface Area Ratio

- Purcision™ is different from other particle engineering technologies
- Purcision™ has a unique ability to engineer large particles with surface area normally associated with much smaller particles
- Unique, disproportionate surface area to particle size ratio is optimal for delivering drug to site of disease (e.g., tumor, lung, et. al.)
- Larger, high surface area Purcision™ particles enable longer retention time at the site of disease and effective drug release
- Solid particles engineered with other technologies <1um require additives to prevent static agglomeration and improved handling



Purcision™ is an Effective Tool for Engineering Poorly Soluble Drugs

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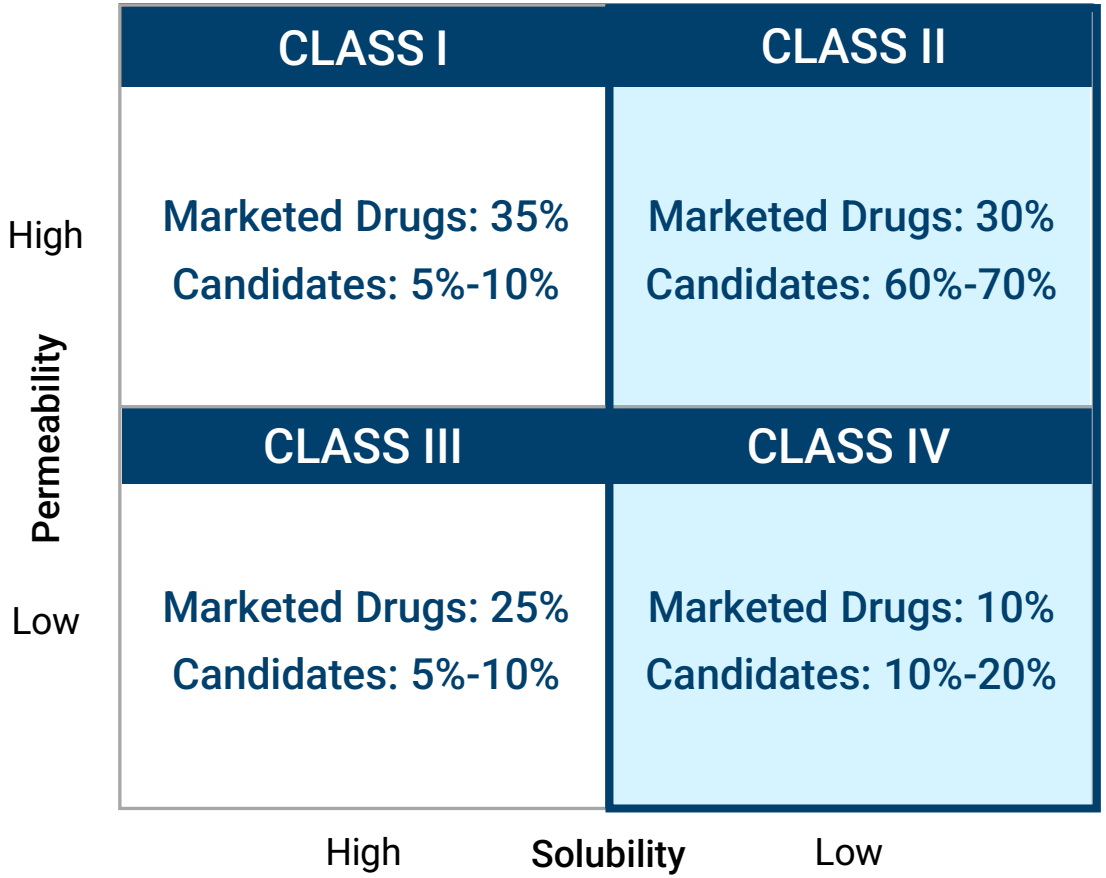
Biopharmaceutical Classification System for Drugs



Purcision™
DIRECT TO TARGET DRUGS

CritiTech's Purcision technology is best used to engineer poorly soluble, which consist of 40% of marketed drugs and 70%-90% of drug development candidates.

Purcision Compatibility Criteria:

- Must be soluble in an organic solvent
- Must be insoluble in $scCO_2$

Source: Nikolakakis and Partheniadis, Self Emulsifying Granules and Pellets: Composition and Formation Mechanisms for Instant or Controlled Release (2017)

Purcision™ Technology Engineers Drug Particles Ideal for Direct Delivery Into the Lungs

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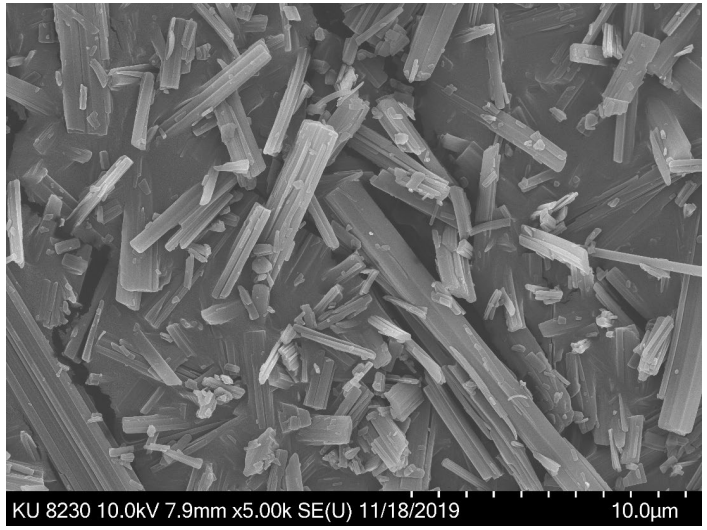
Bulk Drug



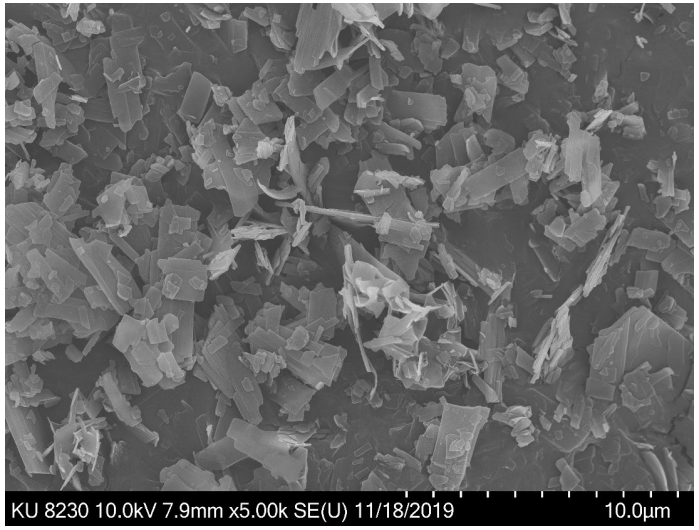
- Bulk API's are higher density solid particles with lower surface areas that limit bioavailability
- Excipients are required to achieve desired release rates

Purcision™
DIRECT TO TARGET DRUGS

Unique Competitive Advantage for Inhaled Drugs

- High Concentration
- 100% Pure Drug
- Limited Systemic Exposure
- Controlled Duration

Purcision Processed Drug

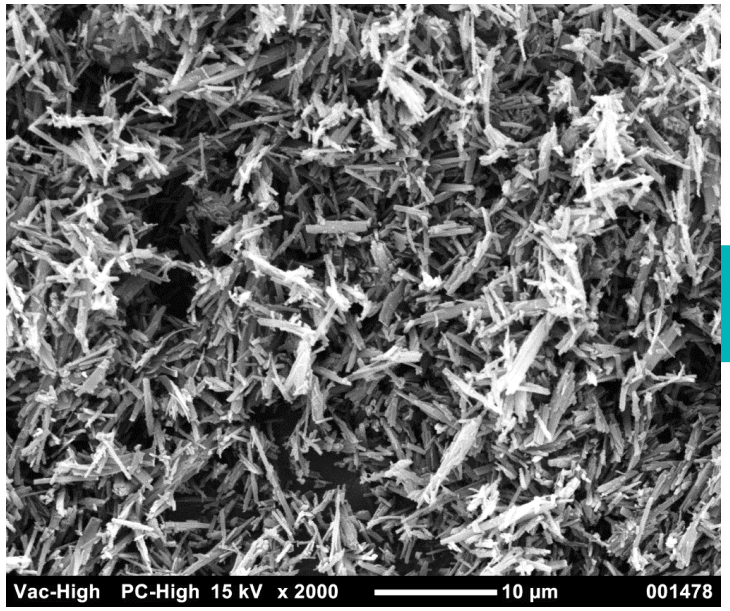


- Purcision particles are not solid and lower density with higher surface areas that improve bioavailability
- Purcision particles enable aerodynamic particle size to be much less than the physical size
- No excipients required to achieve desired release rates

Purcision™ Particles Are Ideal for Direct Delivery Into the Lungs as Dry Powder Formulations

Dry powders engineered using the Purcision technology should be delivered into the lungs at higher concentrations and release drug for a longer periods of time compared to current marketed formulations.

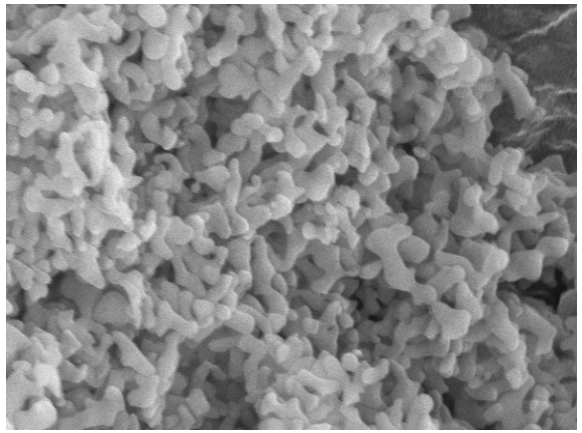
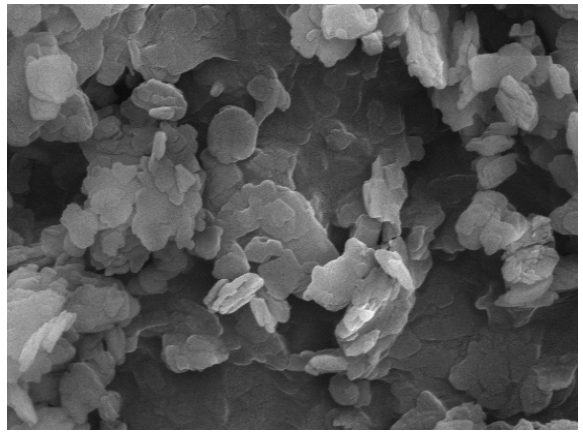
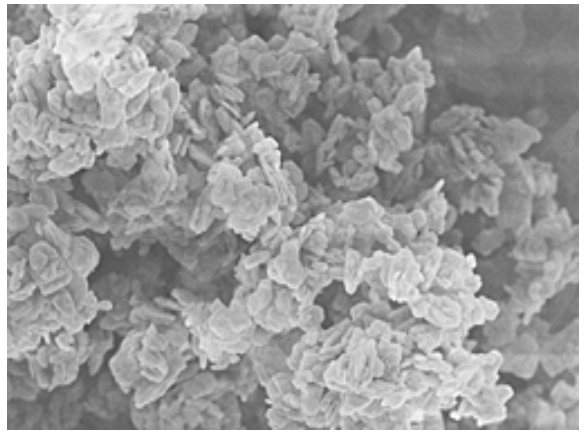
Purcision Inhaled Drugs

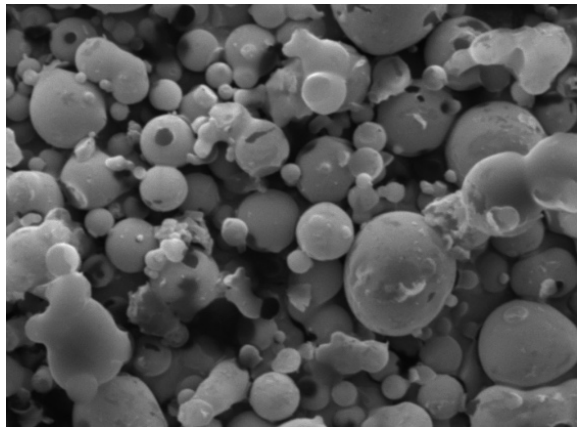
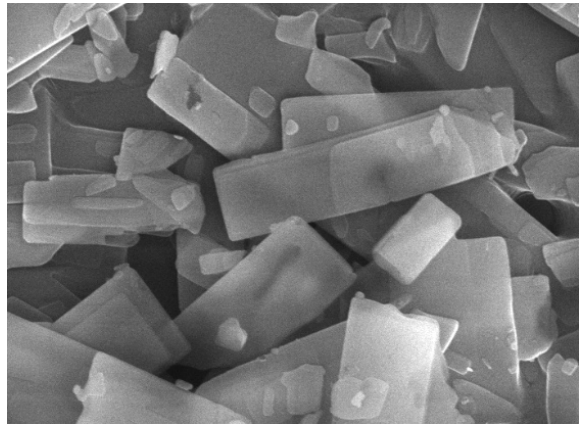
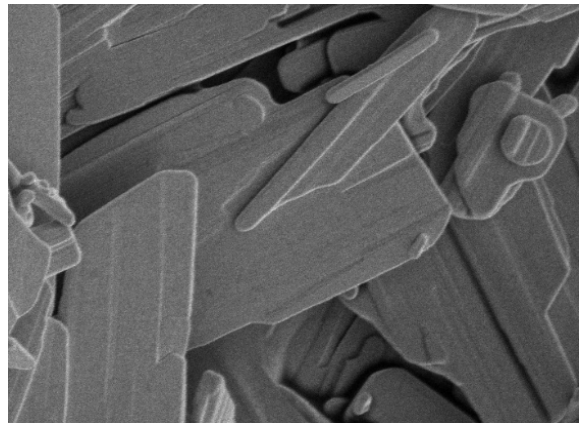
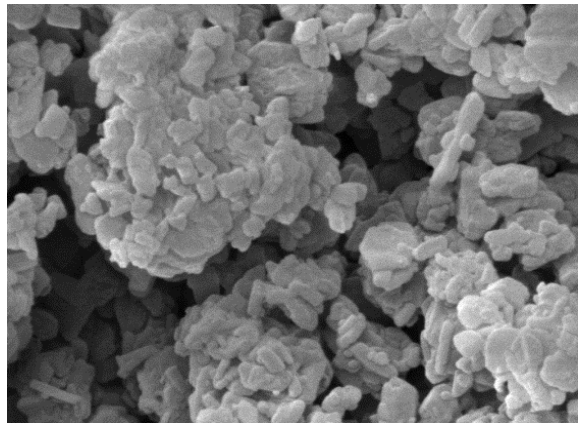


Particle Attributes	Benefits
Physical Size	Particles large enough to reduce removal from lungs by phagocytosis
Mass Median Aerodynamic Diameter (“MMAD”)	MMAD values that enable delivery to the deep regions of the lungs
Density	Less dense versus raw material which allows the aerodynamic particle size to be less than the physical particle size
Surface Area	Surface area increase versus raw material which should enable desired dissolution in the lungs

Purcision™ Size and Shape

The Purcision™ Technology can be tuned to produce various particle sizes and shapes of API (8 different drugs)

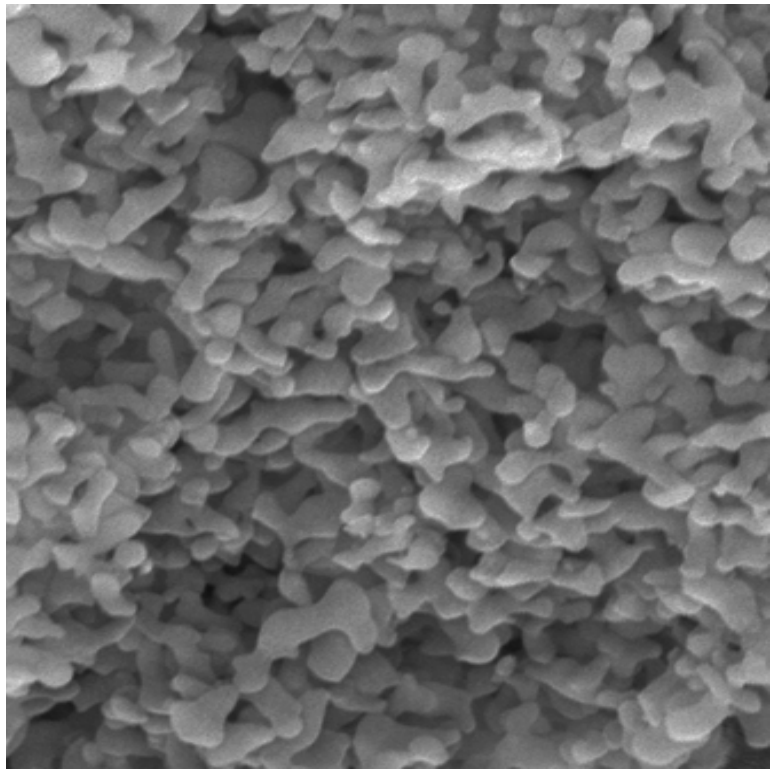




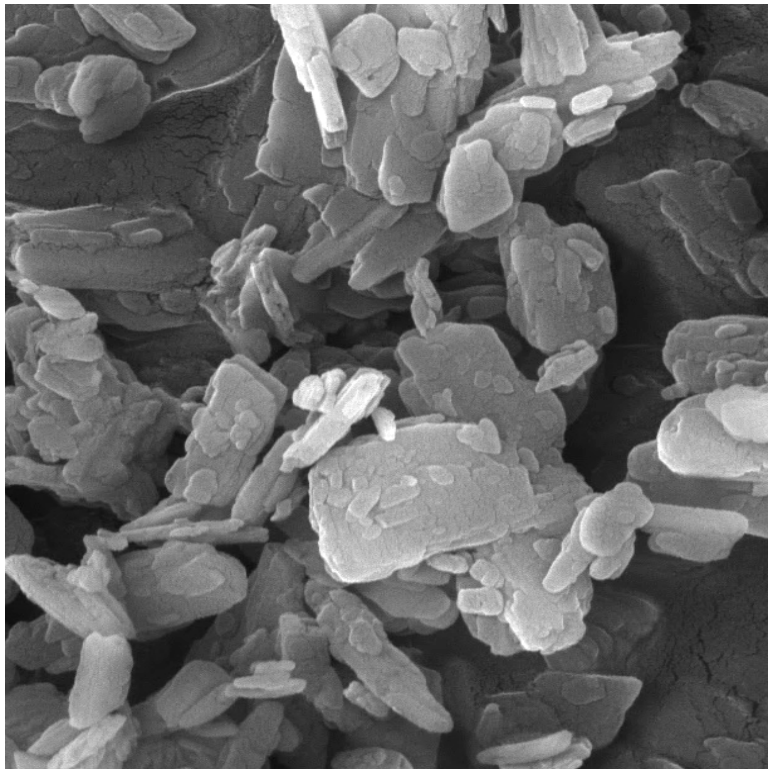
Purcision™ Morphology

The Purcision™ Technology can be tuned to produce different forms of an API (same drug - different processing conditions)

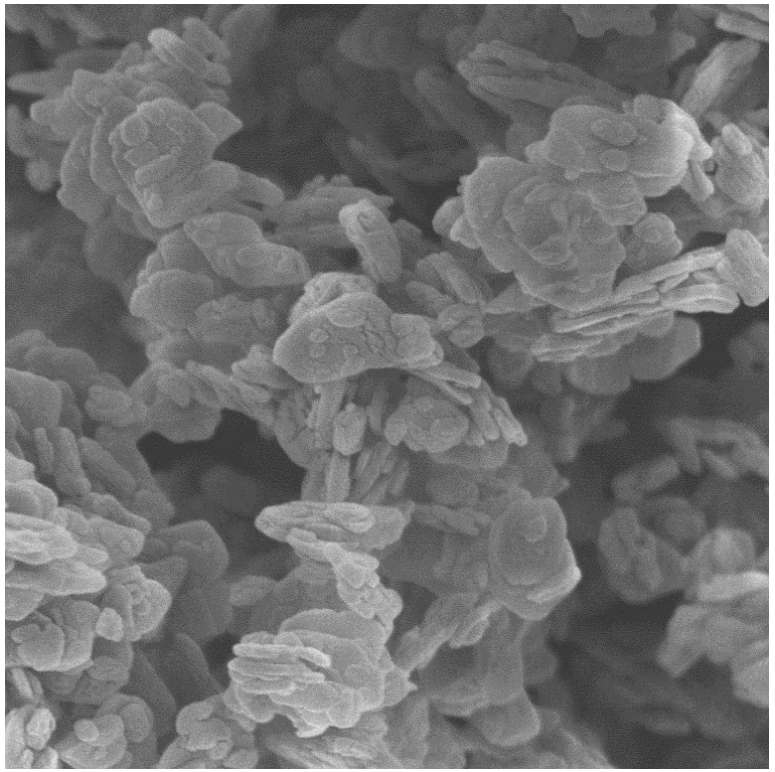
Amorphous



Co-crystal



Crystalline

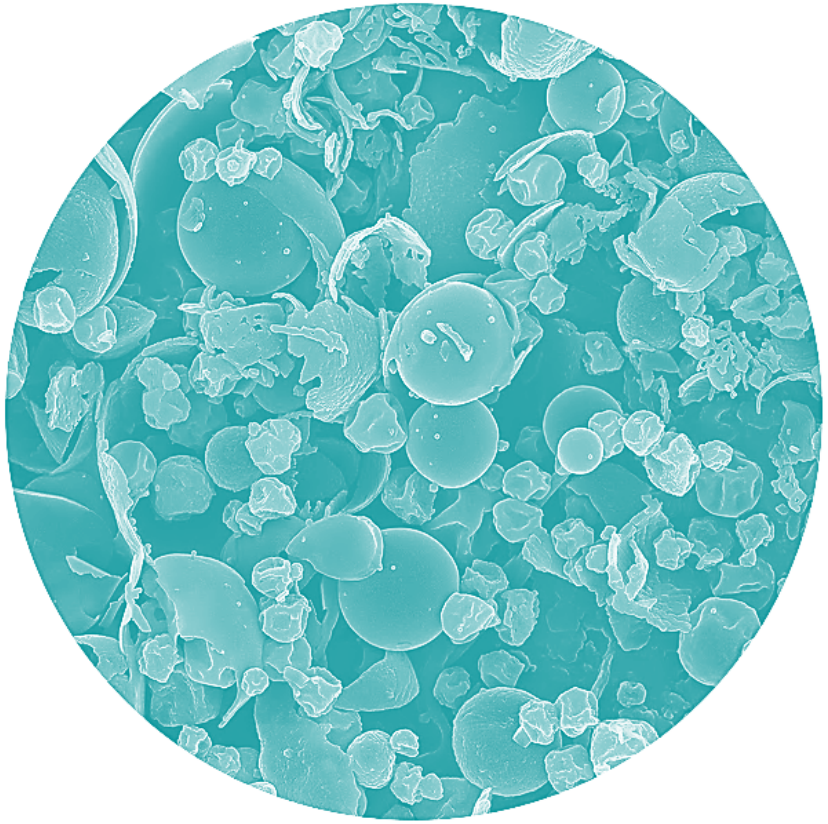


Benefits of the Purcision™ Technology

- **Improves dissolution, pharmacokinetics and stability** of poorly-soluble drugs
- Enables multiple routes of delivery but is **excellent for local, targeted administration**
- **Low bulk-density, high surface area particles** result in **increased drug load and residence time** – especially useful for delivery into the lungs or nasal cavity
- **Pure drug** – no excipients required – especially useful when the amount of drug dosed is limited by available space (e.g. intratumoral injection) or by route of delivery (e.g. inhalation)
- Reformulates existing drugs and **provides patent protection** on improved formulations
- Much **better control over physical particle attributes** compared to conventional micronization technologies

Potential Benefits of Purcision™ Inhaled Drugs

- Higher drug concentration and longer duration of action in the lungs compared to systemic standard of care treatments
- Improved safety – lower and adjustable systemic exposure
- More efficient dosing – lower dose can achieve effective concentration of drug in the lung
- Low COGS
- Purcision powders do not require “cold-chain”
- Fast and easy administration using a dry powder inhaler
- Improved shelf-life, temperature tolerance, and transportability compared to IV formulations
- Reformulates existing drugs and provides patent protection on improved formulations



Purcision™ Manufacturing

- **Commercial-scale** and **fully-validated cGMP equipment**
- Used to manufacture drugs for numerous clinical trials
- Low cost - high yields typically > 90% (much more efficient compared to spray drying)
- Minimal induction of electrostatic charges
- Milligrams to 100’s of kilograms
- **Excellent reproducibility** from POC to commercial production
- Virtually **eliminates residual solvents** – no secondary drying necessary

Purcision™ Equipment

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POC and Development Units – RC612 and RC612B

- Supercritical fluid carbon dioxide: catch production arrangement
- Milligram to gram quantities of 200mg to 50g

cGMP Manufacturing Units – cFPC-411A (Cytotoxic) and cFPC-411B (Non-cytotoxic)

- Supercritical fluid carbon dioxide: continuous manufacturing arrangement
- Proven capability of producing cGMP Phase II clinical trial materials
- Production capacity of ~75 g/hr./system (drug dependent)

CT PES can process OEL ≥0.03 µg/m3 compounds & DEA schedule compounds II-V

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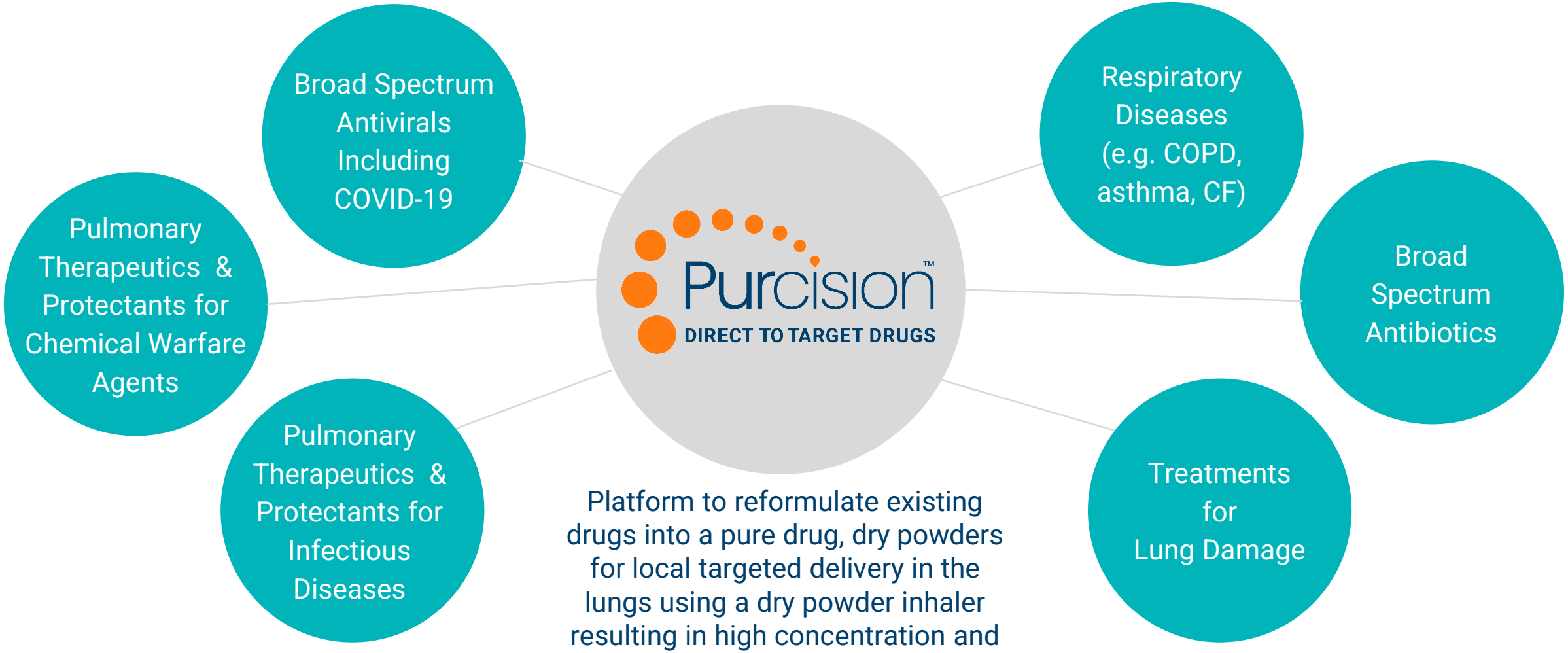
Opportunity to Develop Inhaled Drugs Using Purcision™ Technology

CritiTech's Drug Development & Manufacturing Capabilities

Purcision™ Technology is a Platform for Respiratory Drug Development



Platform to reformulate existing drugs into a pure drug, dry powders for local targeted delivery in the lungs using a dry powder inhaler resulting in high concentration and long duration of action.

Purcision™ Respiratory Drug Development Strategies

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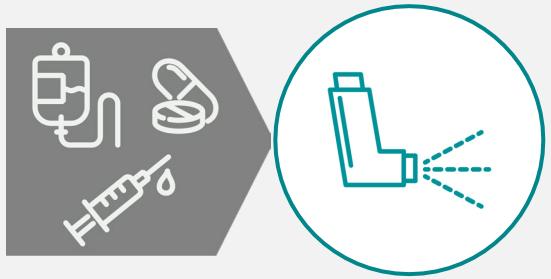

Reformulate Oral and IV Drugs for Inhaled Delivery

- Enable new route of administration
- Increase concentration in lungs
- Increase duration of action in lungs
- Decrease side effects associated with systemic drugs (e.g. oral and IV)

Reformulate "Off-Patent" Drugs
505(b)(2)

Reformulate Branded Drugs

Target Markets and Initial Purcision™ Respiratory Drug Development Candidates

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Target Market	Global Market Size (2027)	Drug Development Candidates	Owner	Current Formulation	2022 Sales
Idiopathic Pulmonary Fibrosis (IPF)	$13.4B	Ofev® (nintedanib)	Boehringer Ingelheim	Oral	EUR 3.2B
		Niclosamide	Generic	Oral	NA
Pulmonary Arterial Hypertension (PAH)	$11.7B	Uptravi® (selexipag)	Janssen	Oral, IV	~$550M
		Niclosamide	Generic	Oral	NA
Antivirals	$74.8B	Niclosamide	Generic	Oral	NA
Antibiotics	$49.6B	Ciprofloxacin	Generic	Oral and IV	~$256M
		Vancomycin	Generic	IV	~$477M
COPD/Asthma	$42B	Singulair®	Merck (Generic)	Oral	~$393M
		Roflumilast	Generic	Oral	~$440M
		Niclosamide	Generic	Oral	NA
Cystic Fibrosis (CF)	$31.9B	Trikafta®, Orkambi®, Klaydeco®, Symdeko®	Vertex	Oral	~$8.9B
		Niclosamide	Generic	Oral	NA

Top Initial Respiratory Drug Development Candidates

Drug Development Candidates Under Evaluation

Purcision™ Respiratory Drug Development Pipeline

Opportunities for Drug Development Collaborations and Investment

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Purcision™ Technology is a **platform that can re-engineer existing drugs into dry powder formulations for local, targeted delivery in the lungs using a dry powder** inhaler resulting in higher concentrations and long duration compared to systemic standard of care.

Drug	Current Use	Current Administration	Use of Purcision Reformulation for Pulmonary Delivery	Formulation Development	Animal POC	Human Studies Phase I/II
Paclitaxel	Solid Tumors	IV	NSCLC (Direct Intratumoral Injection)	Partnered		
	Solid Tumors	IV	NSCLC (Nebulized Suspension)	Partnered (IND Approved)		
Niclosamide	Treatment for Parasites	Oral	• Severe Asthma, COPD, IPF, PAH, CF • Broad Spectrum Antiviral	Partnered		
Ciprofloxacin	Antibiotic	IV, Oral	Antibiotic	Testing w/ Potential Partner		
Fluticasone	COPD, Asthma	DPI	COPD, Asthma			
Nintedanib	Pulmonary Fibrosis	Oral	Pulmonary Fibrosis			
Singulair®	COPD, Asthma	Oral	COPD, Asthma			
Roflumilast	COPD	Oral	COPD			
Remdesivir	Antiviral	IV	Antiviral			

Purcision™ Technology is a Unique and Effective Tool for Developing Respiratory Drugs

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The Purcision technology is an effective tool for producing drug particles that are ideal for inhaled delivery. Based on animal trials conducted at Lovelace Biomedical, drugs processed with Purcision technology were delivered into the lungs at **higher concentrations and for longer periods of time** compared to current marketed formulations.

Drug	Method of Delivery	High Concentration in Lungs	Long Duration (Sustained Delivery) in Lungs	Systemic Exposure	PK Profile of New Purcision Formulation	New Route of Administration
Paclitaxel (Cancer Drug)	Nebulizer	✓	✓	Very Low	Better than IV	Yes
Fluticasone (Asthma/COPD)	DPI	✓	✓	Low	Better than Current Inhaled Formulation	No
Ciprofloxacin (Antibiotic)	DPI	✓	✓	Similar to IV	Better than IV	Yes

Purcision™ Technology is an Effective Tool for Reformulating Drugs for Respiratory Delivery

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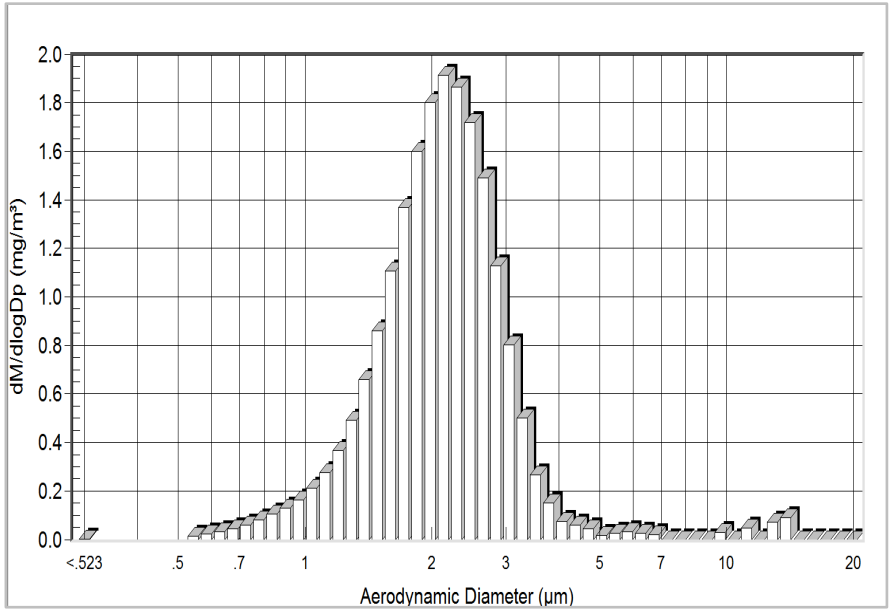
Particle Size	Purcision Paclitaxel	Purcision Ciprofloxacin	Purcision Fluticasone Propionate
MMAD	1.8µm – 2.3µm	2.1µm	2.1um – 2.3µm
GSD	1.9µm – 2.0µm	1.5µm	1.55µm – 1.66µm

Note: Powders aerosolized using rotating brush generator.



Ciprofloxacin Particle Size Distribution

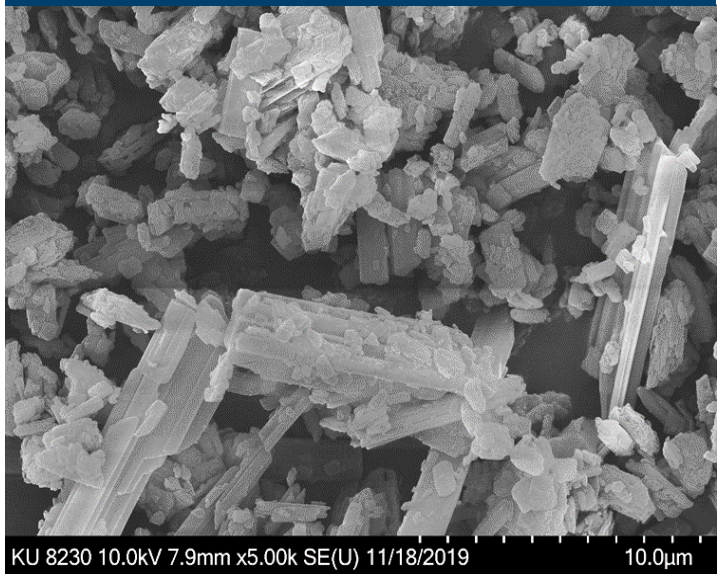
- Purcision technology has been used to reformulate numerous drugs including paclitaxel, ciprofloxacin and fluticasone – all with **agglomerated, high-surface area, low bulk density particles that are ideal for pulmonary delivery**
- The aerodynamic particle size (MMAD) of drugs reformulated with the Purcision technology are very consistent and right in the “sweet spot” for pulmonary delivery

LOVELACE BIOMEDICAL

Purcision™ Technology Enables Novel Inhaled Formulations of Paclitaxel

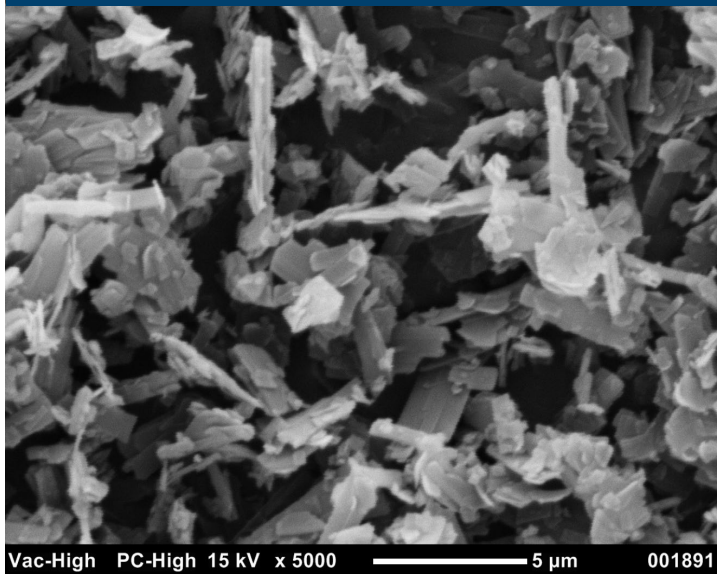
- Studies of Purcision Paclitaxel particles were conducted using an inhaled nebulized suspension in rats
- Inhalation of the Purcision Paclitaxel dry powders could also be viable since the MMAD is suitable for use in a dry powder inhaler
- NanOlogy is conducting clinical studies using Purcision Paclitaxel particles using direct injection into tumors

Raw Paclitaxel



D_{v10}[1]	1.33 µm
D_{v50}[1]	4.17 µm
D_{v90}[1]	20.6 µm
Surface Area	m2/g
Bulk Density	g/cm³

Purcision Paclitaxel



D_{v10}[1]	0.778 µm
D_{v50}[1]	3.22 µm
D_{v90}[1]	9.51 µm
MMAD[2]	1.8 – 2.3 µm
Surface Area	20.3 m^2/g
Bulk Density	0.085 g/cm³

1. Particle size distribution by volume where particle size shown is for 10%, 50% and 90% of the population of particles.
2. MMAD = Mass Median Aerodynamic Particle Diameter.

Purcision™ Inhaled Paclitaxel – PK Rat Inhalation Studies

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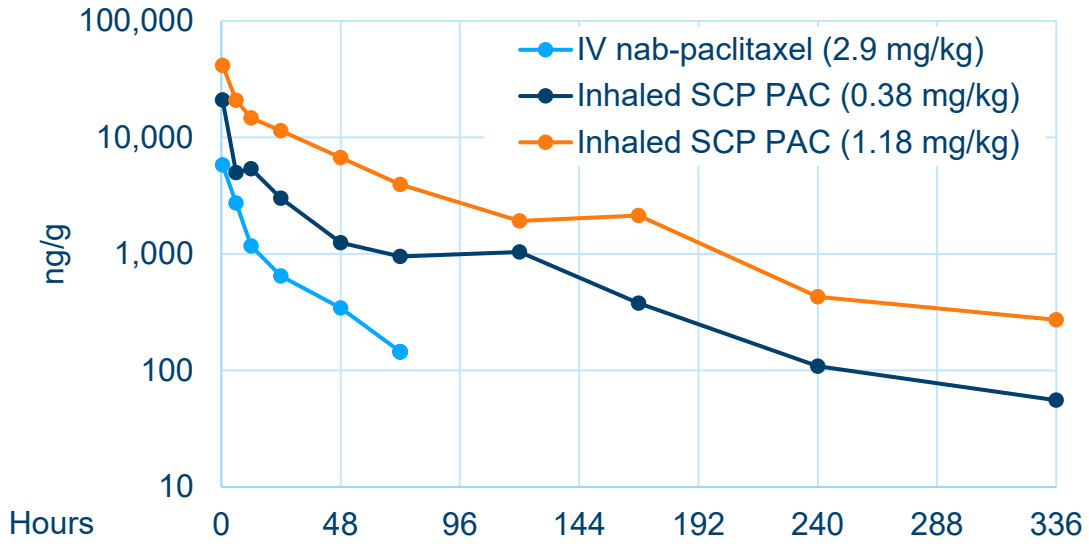
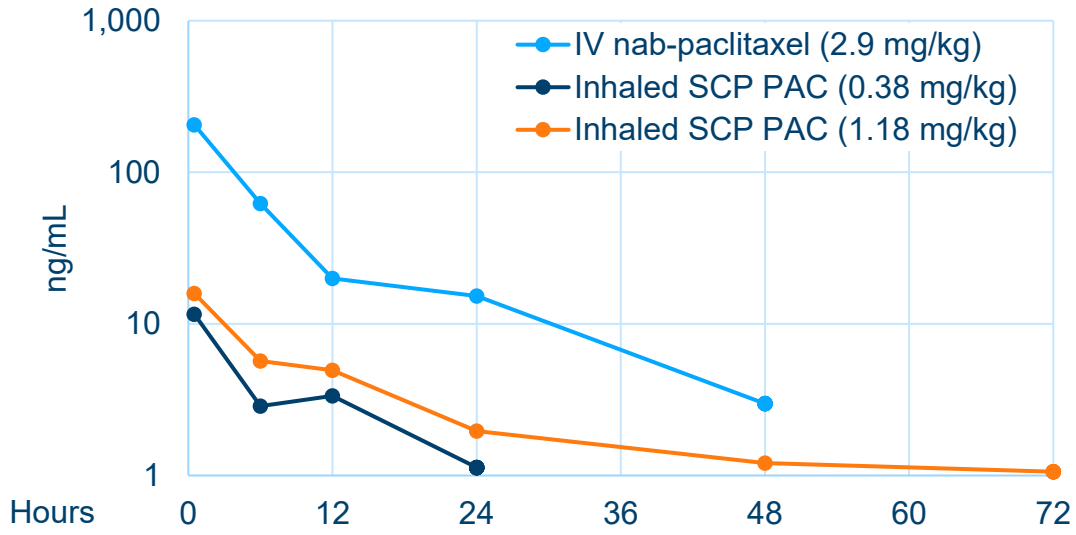
Paclitaxel Levels in Lung



Paclitaxel Levels in Plasma



- Purcision Inhaled Paclitaxel achieves high concentration and long duration in the lungs
- Lung half-life for Purcision Inhaled Paclitaxel was 56 hours vs 19.9 hours for IV nab-paclitaxel (Abraxane®)
- Much lower systemic exposure of Purcision paclitaxel compared to the IV route of delivery

LOVELACE BIOMEDICAL

Purcision™ Technology Enables a Novel Dry Powder Formulation of Ciprofloxacin

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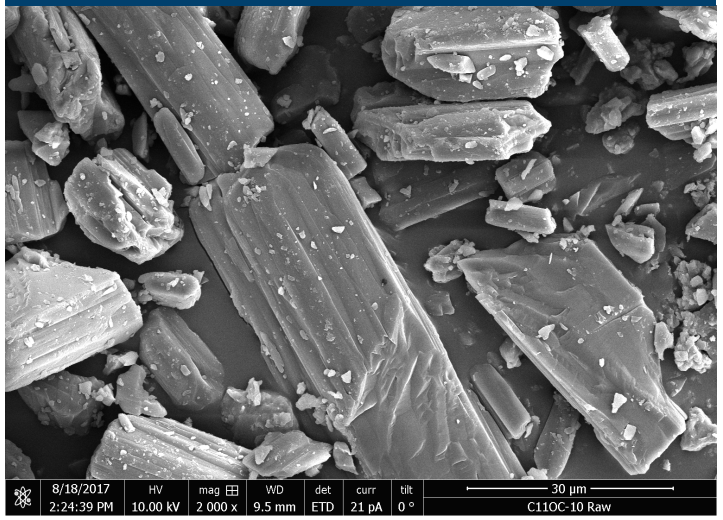
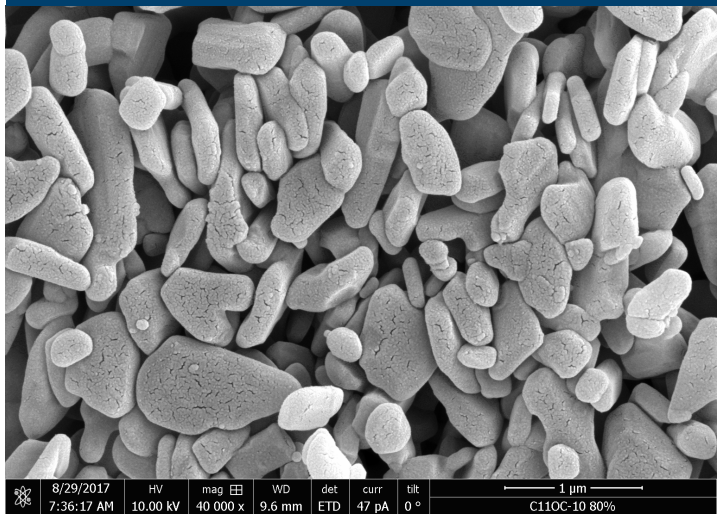
- Purcision technology produced ciprofloxacin particles that are much smaller, possess a greater surface area, and are more consistent and uniform than the raw material
- Pure drug – no excipients
- The aerodynamic particle size of the Purcision Inhaled Ciprofloxacin particles is between 2 to 3 microns – ideal for pulmonary delivery
- Engineered new polymorph of ciprofloxacin freebase

Raw Ciprofloxacin



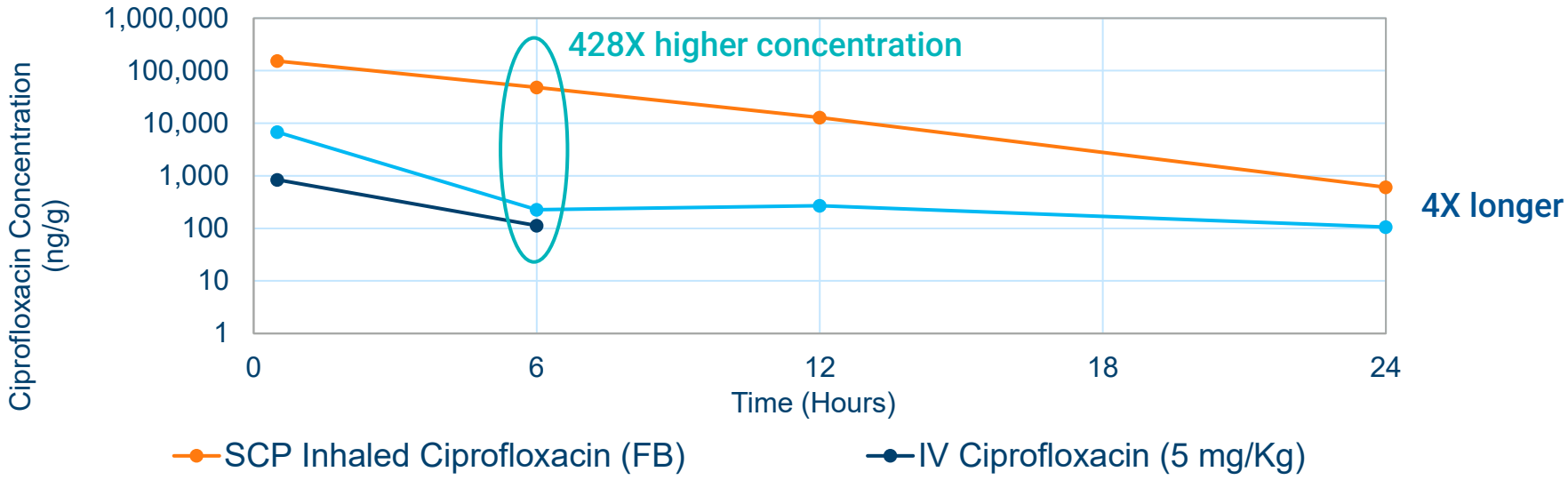
D_v10	6.05 µm
D_v50	22.7 µm
D_v90	56.0 µm

Purcision Inhaled Ciprofloxacin



D_v10	0.72 µm
D_v50	1.74 µm
D_v90	13.0 µm
MMAD	2.1 µm
Surface Area	21.4 m^2/g

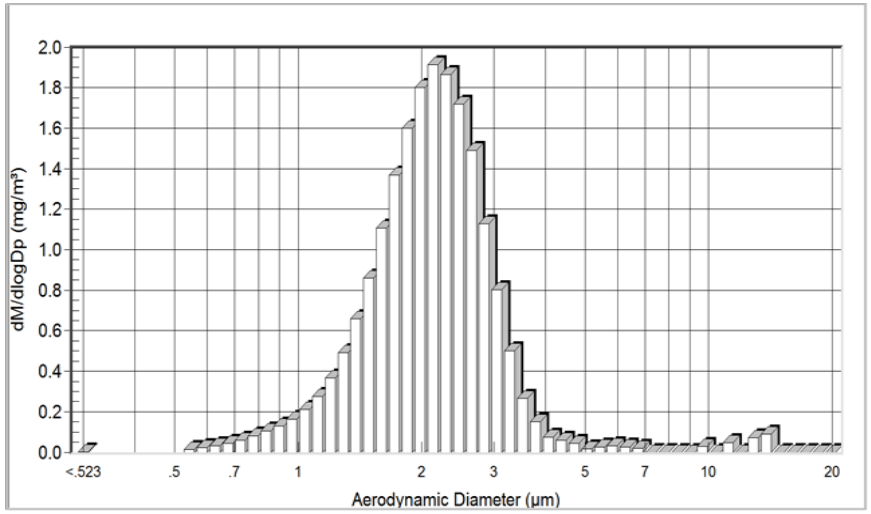
Purcision™ Inhaled Ciprofloxacin – PK Rat Inhalation Studies



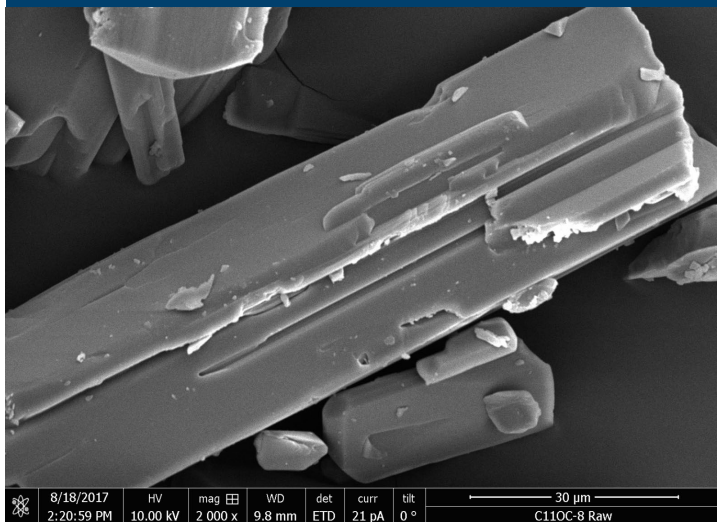
- Purcision Inhaled Ciprofloxacin (Free Base) is delivered into the lungs at a much **higher concentration (428X higher)** and for a **longer residence time (4X longer)** compared to the marketed IV formulation of ciprofloxacin
- Purcision Inhaled **Ciprofloxacin HCl particles were too soluble** and delivered drug into the lungs which quickly diffused into the systemic circulation (blue line above)
- The Purcision Inhaled Ciprofloxacin was dosed at 3mg/Kg versus 5mg/Kg for the marketed IV formulation of ciprofloxacin

Purcision™ Technology Enables a Novel Dry Powder Formulation of Fluticasone Propionate

- Fluticasone Propionate Purcision particles were produced which were much smaller, possessed a greater surface area, and were more uniform than the raw material.
- The MMAD of the Purcision Inhaled Fluticasone particles was between 2 to 3 microns – ideal for pulmonary delivery. A typical aerodynamic particle size distribution plot is shown below.

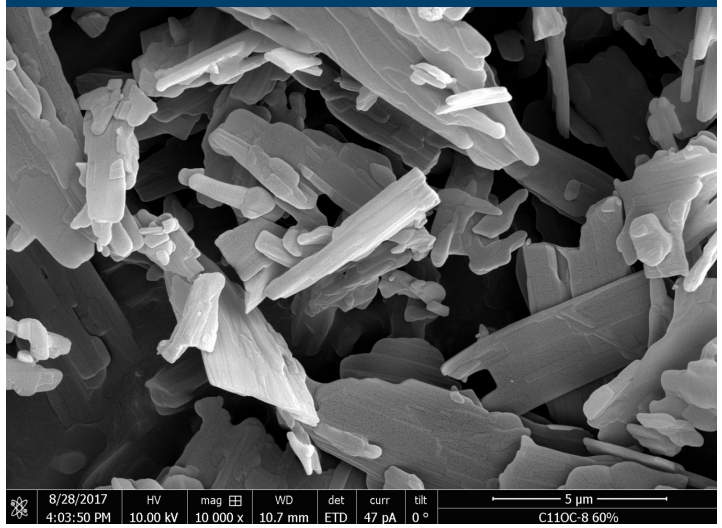


Raw Fluticasone Propionate



D_v10	10.9 µm
D_v50	39.0 µm
D_v90	74.4 µm
Surface Area	4.11 m²/g

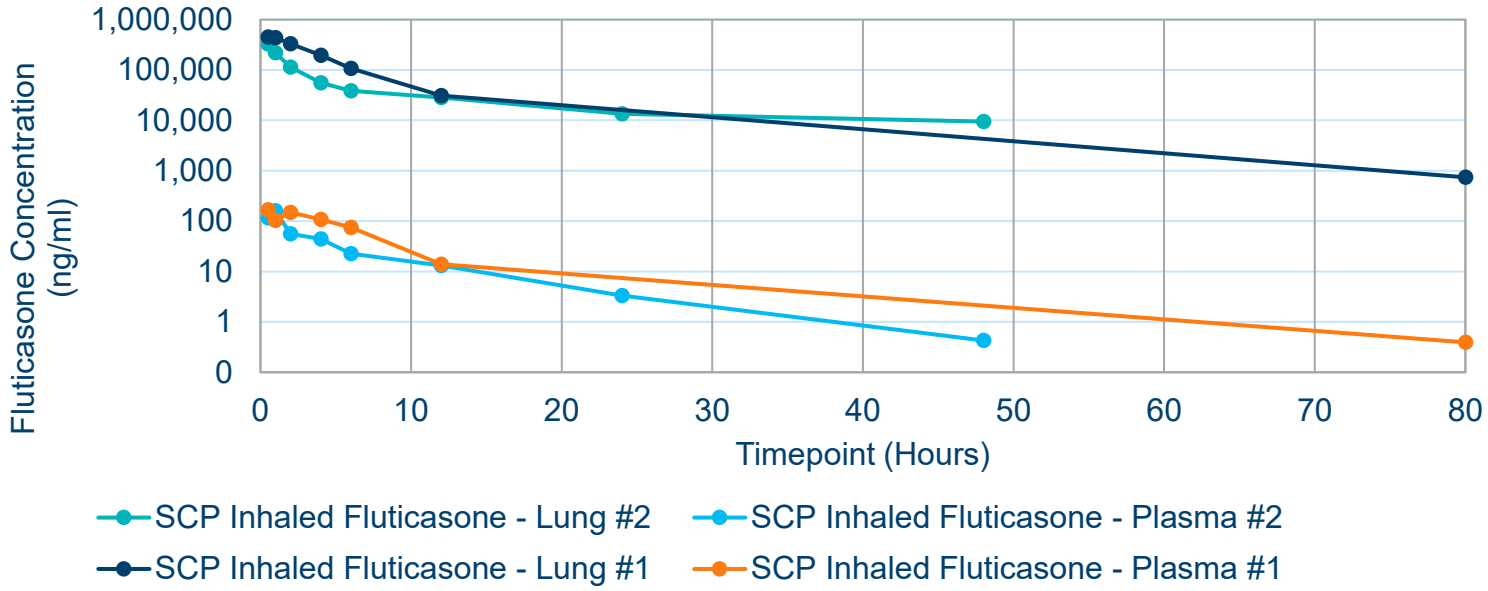
Purcision Fluticasone Propionate



D_v10	0.89 µm
D_v50	3.62 µm
D_v90	9.28 µm
MMAD	2.1-2.3 µm
Surface Area	13.7 m²/g
Bulk Density	0.082 g/cm³

32

Purcision™ Inhaled Fluticasone Propionate – PK Rat Inhalation Studies



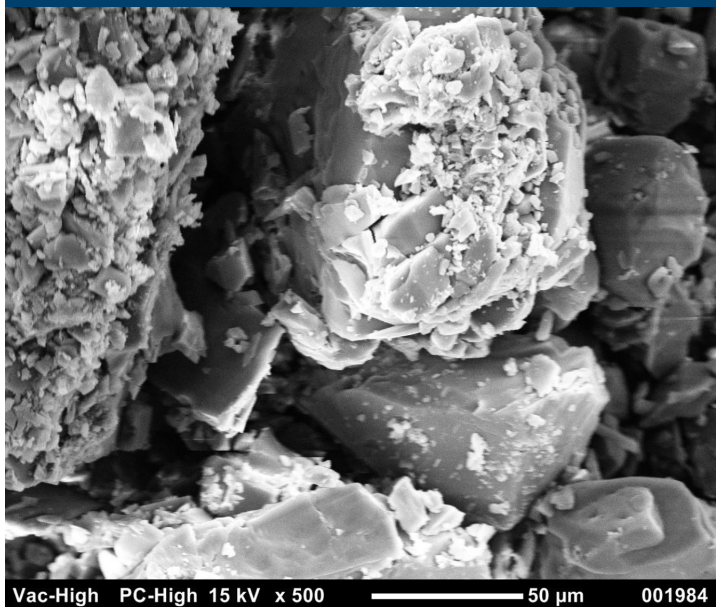
- Purcision Inhaled Fluticasone is delivered into the lungs at **high concentrations** and for **long residence times** with minimal systemic exposure.
- The Purcision Inhaled Fluticasone concentration and duration in the lungs are expected to be greater than the current marketed formulation of fluticasone.
- The study was conducted twice and the results demonstrate the consistency of the delivery of fluticasone to the lungs

Purcision™ Technology Enables a Novel Dry Powder Formulation of Montelukast (Singulair®)

- This sample (SC16) is one of many successful engineering runs of Purcision Inhaled Montelukast. The Purcision technology produces more uniform particles and a profound change in surface area and bulk density compared to the raw material.
- Purcision Inhaled Montelukast should achieve therapeutic lung concentrations for a longer duration while limiting systemic exposure.
- The goal is for Purcision Inhaled Montelukast to provide better patient safety and the elimination of the black box warning for neuropsychiatric events associated with oral Montelukast.

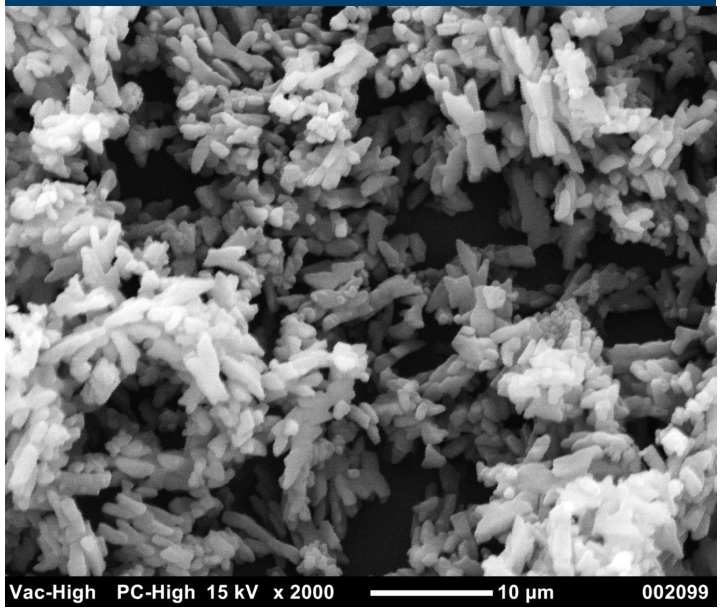
1. Physical particle size distribution by volume where particle size shown is for 10%, 50% and 90% of the population of particles.

Raw Montelukast



D_{v10}[1]	7.04 µm
D_{v50}[1]	32.1 µm
D_{v90}[1]	94.8 µm
Surface Area	2.48 m2/g
Bulk Density	0.491 g/cm³

Purcision Montelukast – SC16

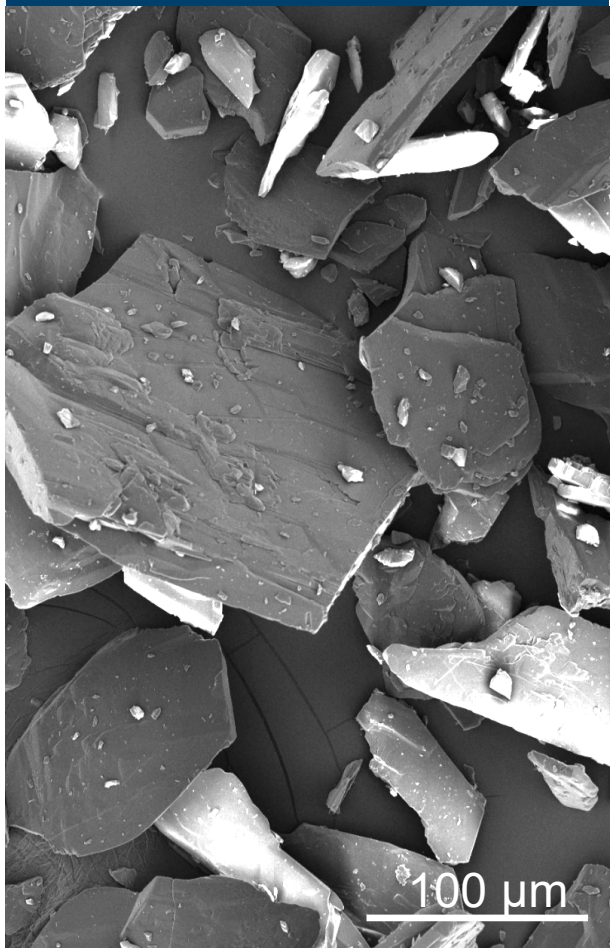


D_{v10}[1]	2.14 µm
D_{v50}[1]	5.06 µm
D_{v90}[1]	9.46 µm
Surface Area	13.88 m^2/g
Bulk Density	0.066 g/cm³

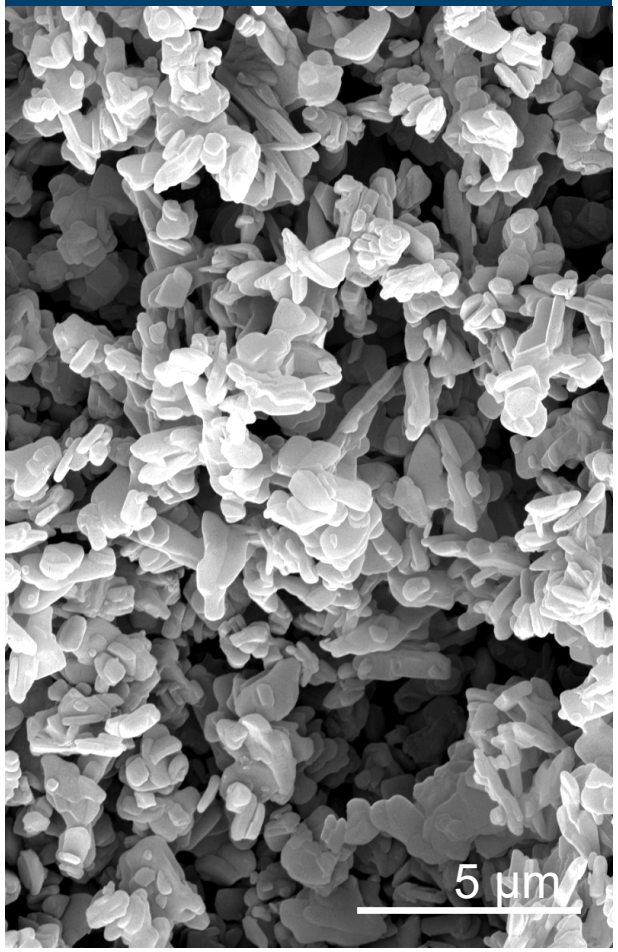
Purcision™ Technology Enables a Novel Dry Powder Formulation of Nintedanib (Ofev®)

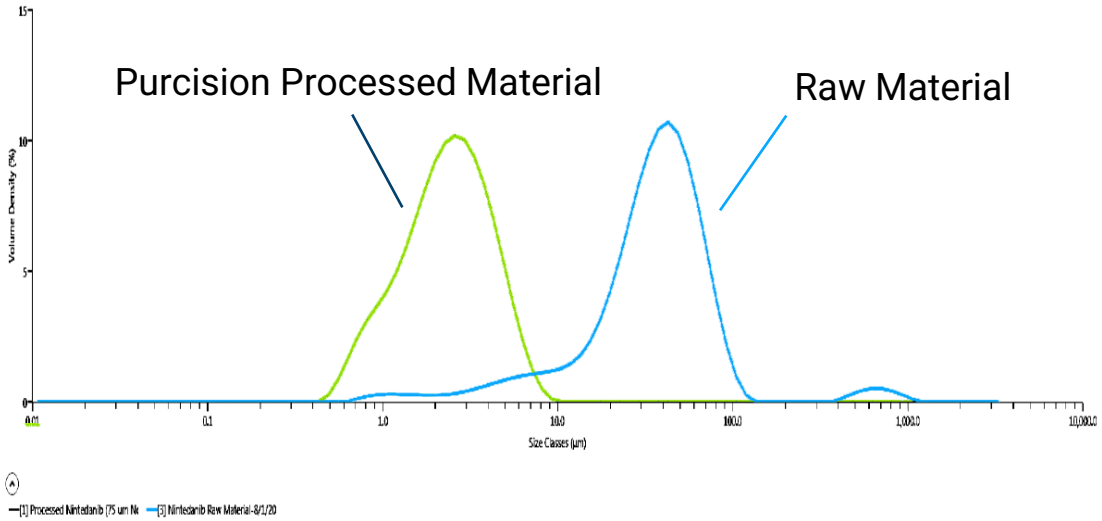
CritiTech Pulmonary

Raw Nintedanib



Purcision Nintedanib

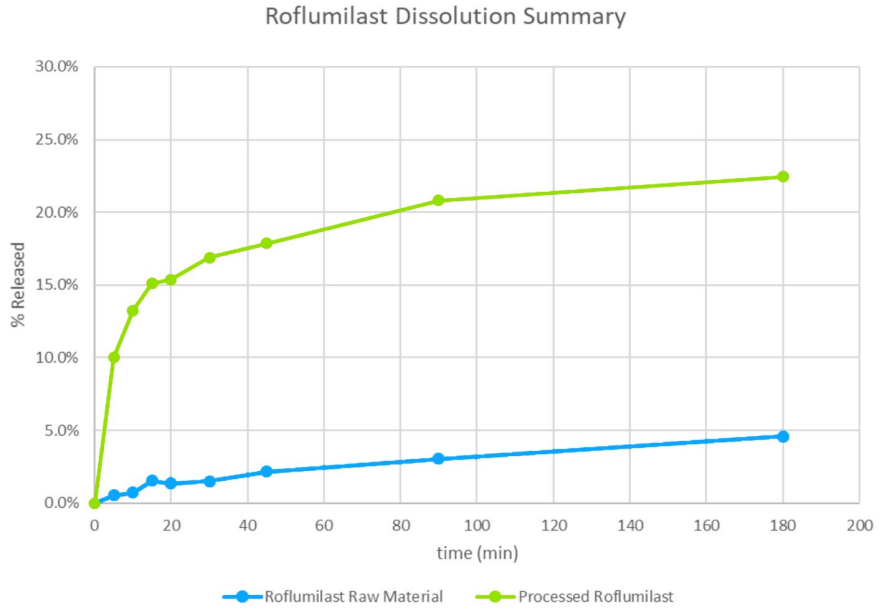




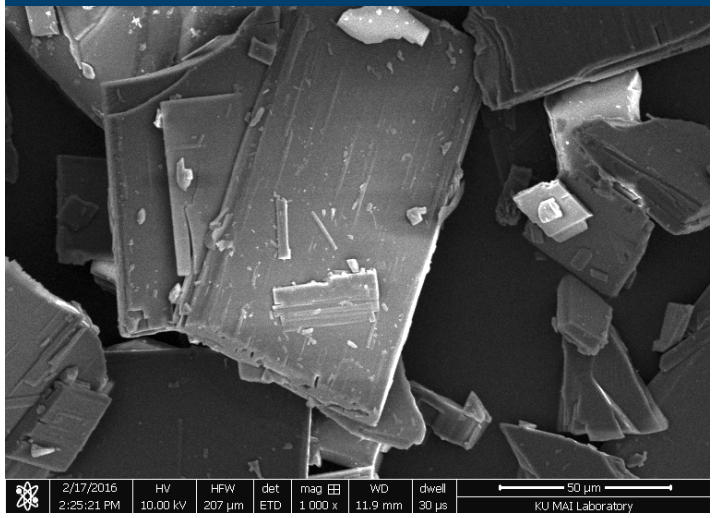
Characteristic	Raw	Purcision	% Change
Dv10	10.5 µm	0.99 µm	-91%
Dv50	36.8 µm	2.36 µm	-94%
Dv90	70.2 µm	4.70 µm	-93%
Surface Area	4.11 m^2/g	20.14 m^2/g	+389%

Purcision™ Technology Enables a Novel Dry Powder Formulation on Roflumilast

- The development work for Purcision Roflumilast is still in process.
- Purcision created particles of Roflumilast are extremely thin - nearly transparent particles.
- Purcision Inhaled Roflumilast substantially improved the rate of dissolution in water

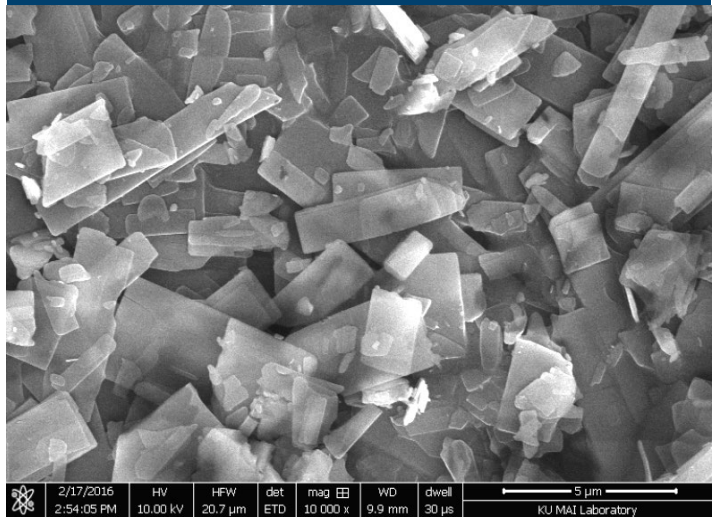


Raw Roflumilast



D_{v10}[1]	7.98 µm
D_{v50}1	19.5 µm
D_{v90}[1]	36.8 µm
Surface Area	3.40 m²/g
Bulk Density	0.349 g/cm³

Purcision Roflumilast



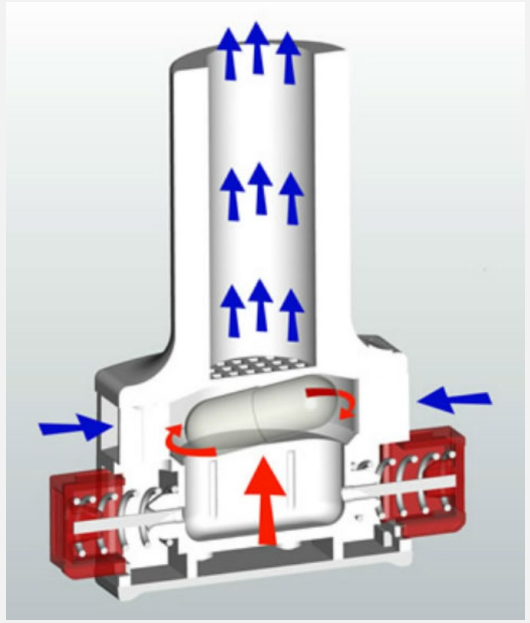
D_{v10}[1]	1.64 µm
D_{v50}1	4.92 µm
D_{v90}[1]	11.21 µm
Surface Area	13.80 m²/g
Bulk Density	0.047 g/cm³

1. Particle size distribution by volume where particle size shown is for 10%, 50% and 90% of the population of particles..

Example of Delivery of Purcision™ Powders with a Dry Powder Inhaler

Purcision Fluticasone particle characterization studies showed excellent flowability and a large percentage of the drug delivered from a DPI even though the particles and formulation have not been optimized.

Plastiape RS01 (Generic DPI)



iPHARMA

NGI Analysis of Purcision-Processed Fluticasone

	MMAD (um)	GSD	FPF % < 5 um	% Drug Delivered
Run 1	3.5	1.6	79%	74%
Run 2	3.7	1.6	73%	80%
Run3	3.7	1.6	74%	73%
Average	3.63	1.6	75.3%	75.6%

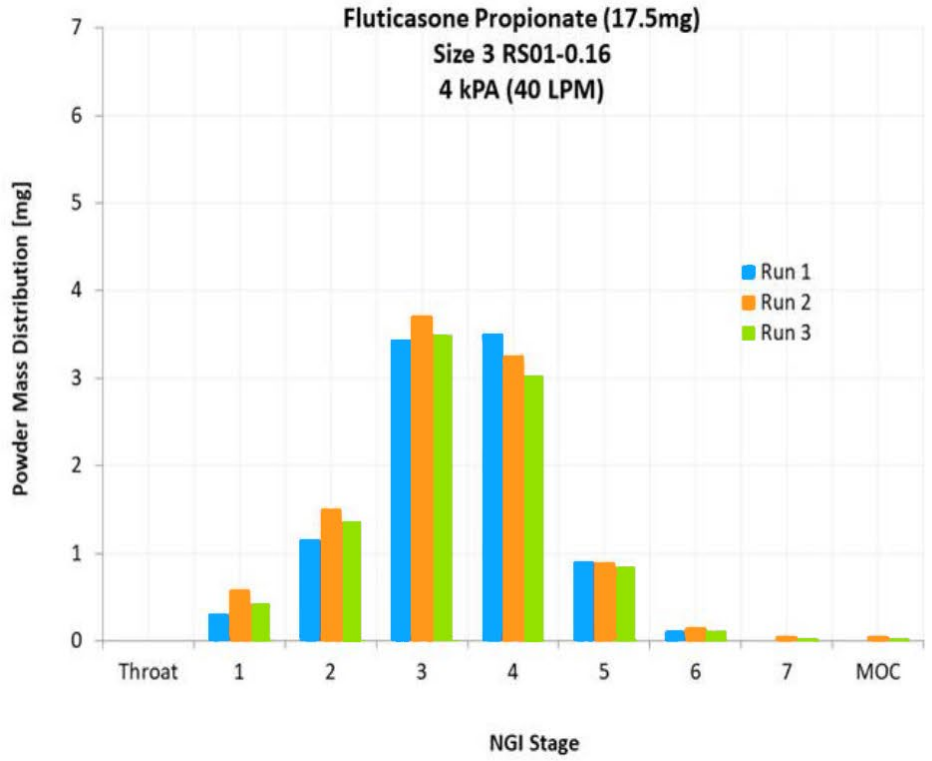
Purcision Fluticasone delivers ~75% of the drug in a capsule versus ~30% with some of the fluticasone products on the market

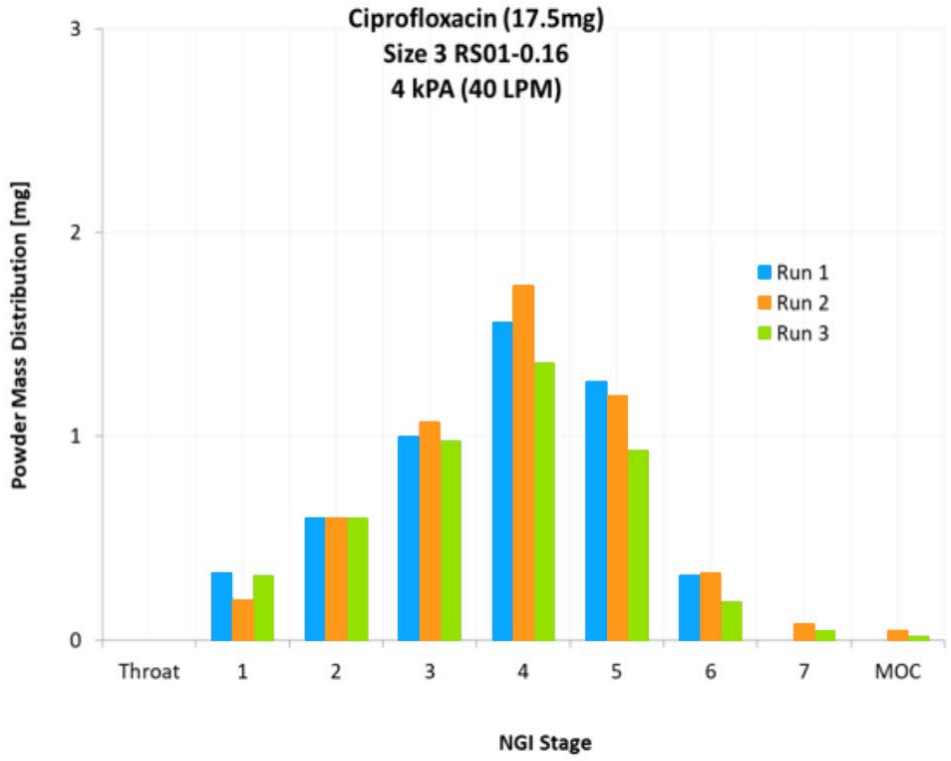
Examples of Delivery of Purcision™ Powders with a Platstiape DPI

CritiTech Pulmonary

iPharma tested the mass distribution of Purcision Fluticasone and Purcision Ciprofloxacin powders from the DPI. The results were **very consistent over multiple runs**.

iPHARMA



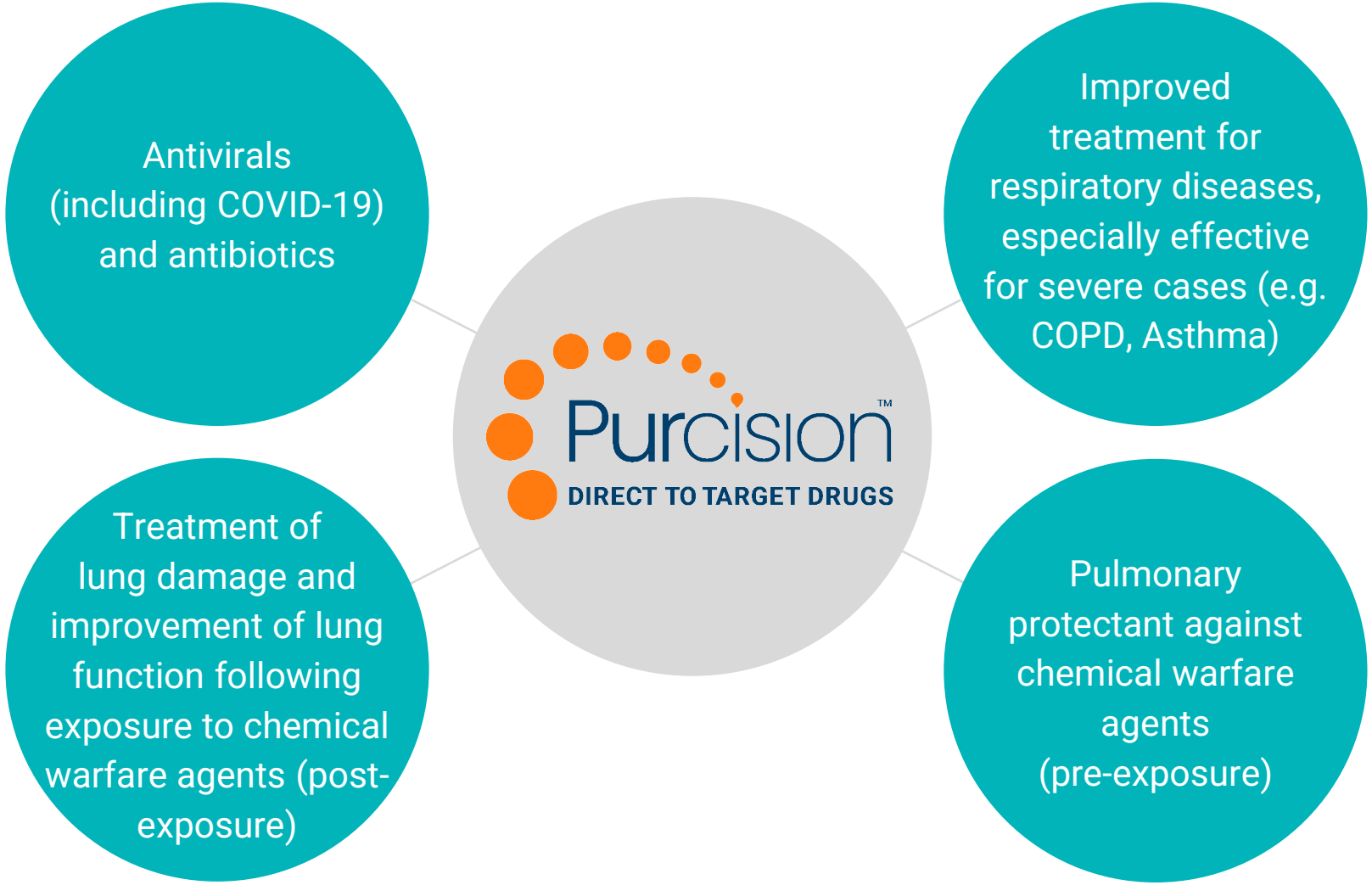


Opportunity to Develop Purcision™ Inhaled Niclosamide as Multi-Purpose Respiratory Drug

CritiTech Pulmonary

Purcision Inhaled Niclosamide, under development by Aeon Respire, has the potential to be used for multiple indications. It should be particularly useful for treating **lung infections, lung injury and respiratory distress**.

Æon Respire
OPENING AIRWAYS TO IMPROVE HEALTH



Purcision™ Technology Enables a Novel Dry Powder Formulation of Niclosamide

CritiTech Pulmonary

Purcision Inhaled Niclosamide should be delivered into the lungs at **controlled concentrations** and for **longer duration** than other formulations of niclosamide providing superior bronchodilation, reduced inflammation, mucin hypersecretion and oxidative stress.

Niclosamide

- **Oral** formulations do not deliver enough drug to the lungs
- **IV** formulations can be toxic at higher concentrations and do not deliver enough drug to the lungs
- **Inhaled** formulations must deliver a gradual, efficacious level of drug to the lungs and keep systemic concentrations low

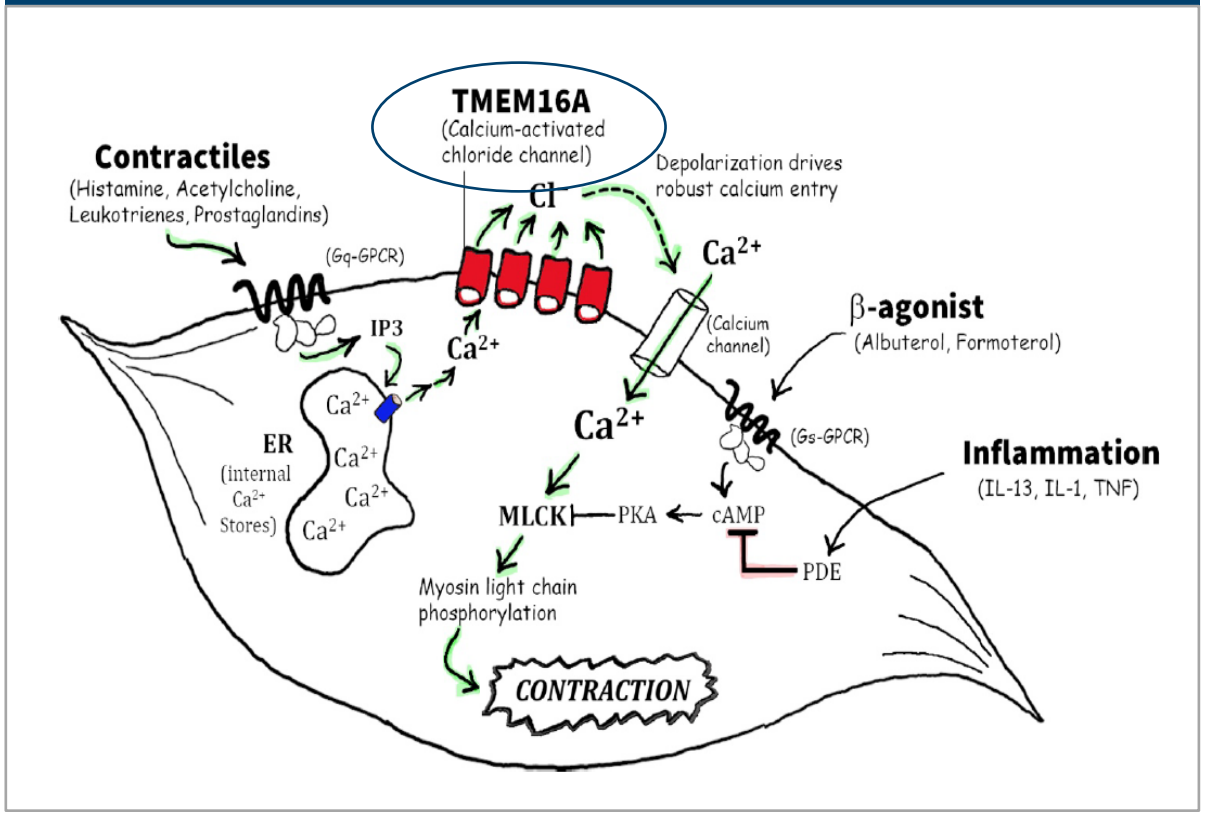
Purcision Inhaled Niclosamide

- Inhaled formulation of niclosamide enabled by CritiTech's Purcision technology should inhibit TMEM16A better than other formulations
- Purcision Inhaled Niclosamide is **pure drug** that will be delivered into the lungs at **controlled concentrations for a long duration while keeping the blood concentrations below toxic levels**

Purcision™ Technology Enables a Novel Dry Powder Formulation of Niclosamide

- TMEM16A is a calcium activated chloride channel expressed in epithelial cells, smooth muscle cells, endothelial cells and fibroblasts in the lung.
- Niclosamide is a potent inhibitor of TMEM16A
- **Niclosamide inhibits TMEM16A which acts as a calcium control valve to regulate airway tone, inflammation, mucus production and oxidative stress.**
- Niclosamide inhibits TMEM16A to block multiple viruses which hijack the calcium response in epithelial cells to aid in their infectivity.

By inhibiting TMEM16A, Purcision Inhaled Niclosamide offers a new approach and potential breakthrough for treating lung diseases, infection and injury.



Opportunity to Develop Purcision™ Inhaled Niclosamide as a Treatment for Respiratory Diseases

CritiTech Pulmonary

Purcision Inhaled Niclosamide has the potential to provide better outcomes for patients suffering from respiratory diseases

Unmet Need in Respiratory Diseases

- Inhaled steroids don't relax smooth muscle and lose effectiveness in severe disease requiring high doses with side effects
- ß-agonists effectiveness are limited by overuse and inflammation
- Unlike ß-agonists, TMEM16A blockade is not compromised by overuse or inflammation
- Anti-muscarinics and leukotriene inhibitors only block single pathways and don't directly affect mucus

Purcision Inhaled Niclosamide has the potential to provide better outcomes for patients suffering from respiratory diseases

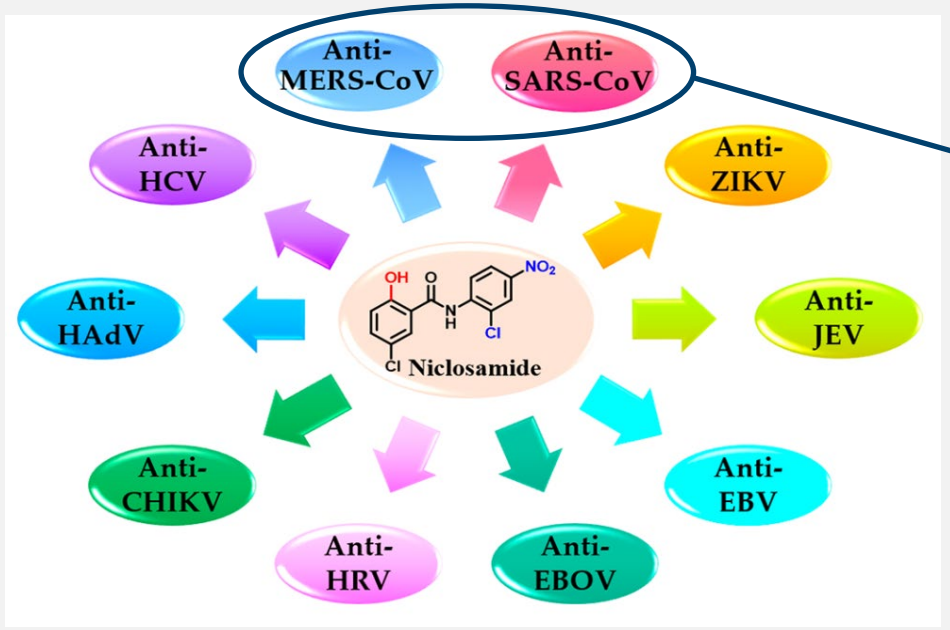
Moderate to Severe Asthma	• Directly treats the core phenotype • Advantages compared to ß-agonists
COPD	• Superior bronchodilation • Blocks mucus associated with chronic bronchitis
Idiopathic Pulmonary Fibrosis	• Alleviates fibrosis in models • Blocks fibrotic signaling and activation
Pulmonary Arterial Hypertension	• Relaxes vascular smooth muscle • Inhibits VSM cell proliferation
Cystic Fibrosis	• Blocks driver of excess mucus

Opportunity to Develop Purcision™ Inhaled Niclosamide as a Multi-purpose Inhaled Antiviral

CritiTech Pulmonary

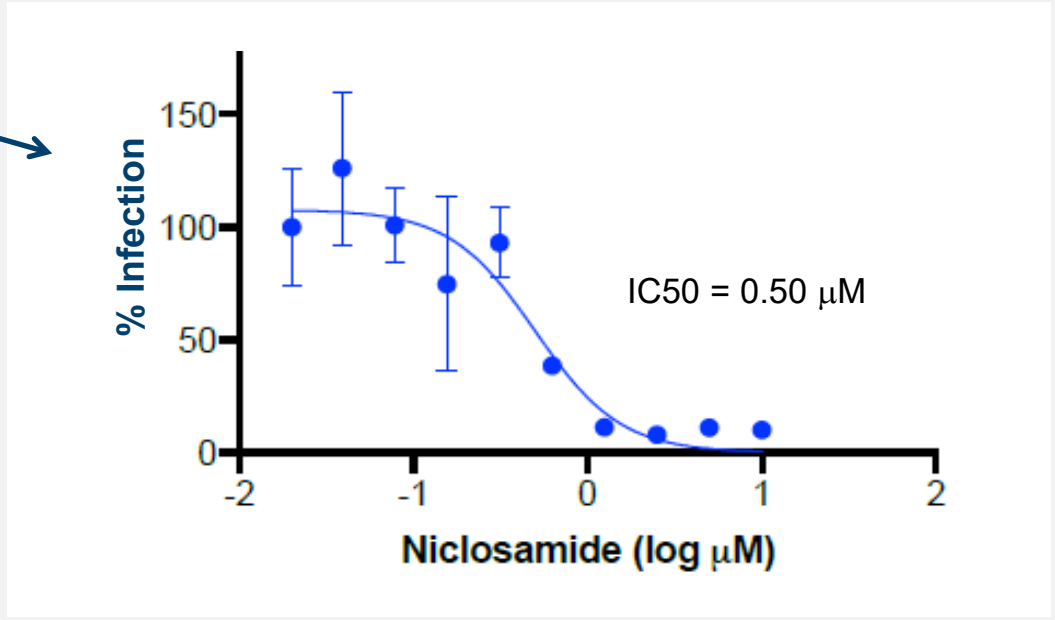
Niclosamide is a broad-spectrum antiviral that inhibits many enveloped RNA viruses, including coronaviruses (CoV). Purcision Inhaled Niclosamide would enable direct delivery into the lungs resulting in high concentration and long duration. The Purcision technology could also be used to reformulate niclosamide for other routes of delivery.

Initial Focus is on Airborne Viruses



TMEM16A-mediated calcium signaling is a new kind of target for combating viral infections

Niclosamide Inhibition of SARS-CoV-2 Infection of Calu-3 Lung Epithelial Cells*

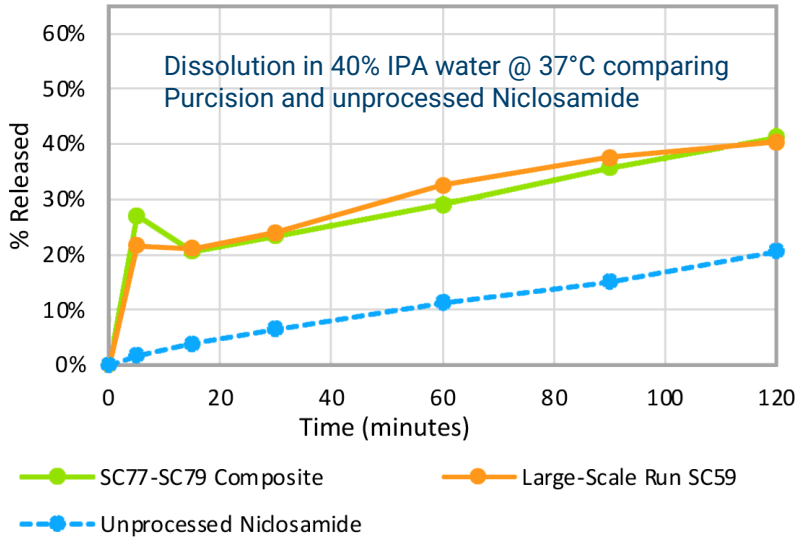


*Data generated by Aeon Respire.

Purcision™ Technology Enables a Novel Dry Powder Formulation of Niclosamide

CritiTech Pulmonary

Niclosamide is very poorly soluble which limits oral absorption. Blood levels from the traditional oral dose are very low. The intent of the Purcision Inhaled Niclosamide powder is to dissolve slowly in the lungs creating an efficacious level of drug with limited systemic exposure.

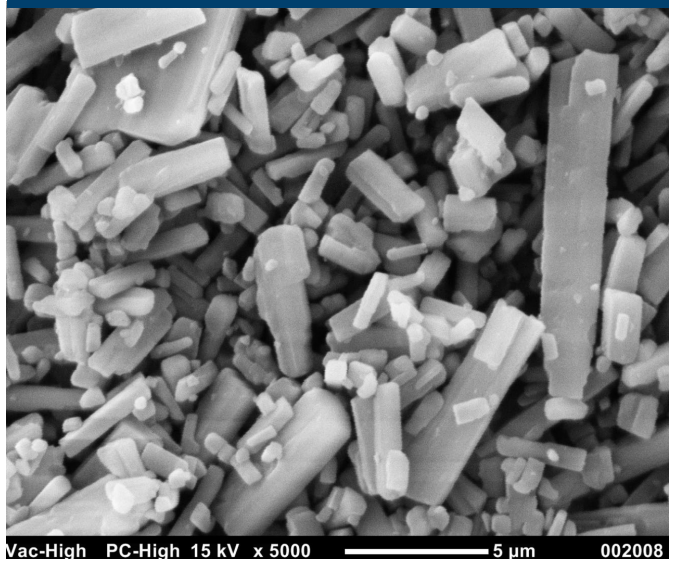


1. Particle size distribution by volume where particle size shown is for 10%, 50% and 90% of the population of particles.
2. MMAD = Mass Median Aerodynamic Particle Diameter.

Raw Niclosamide

D_{v10}[1]	7.75 µm
D_{v50}[1]	21.1 µm
D_{v90}[1]	38.8 µm
MMAD[2]	15.9 µm
Surface Area	1.36 m2/g
Bulk Density	0.45 g/cm³

Purcision Niclosamide



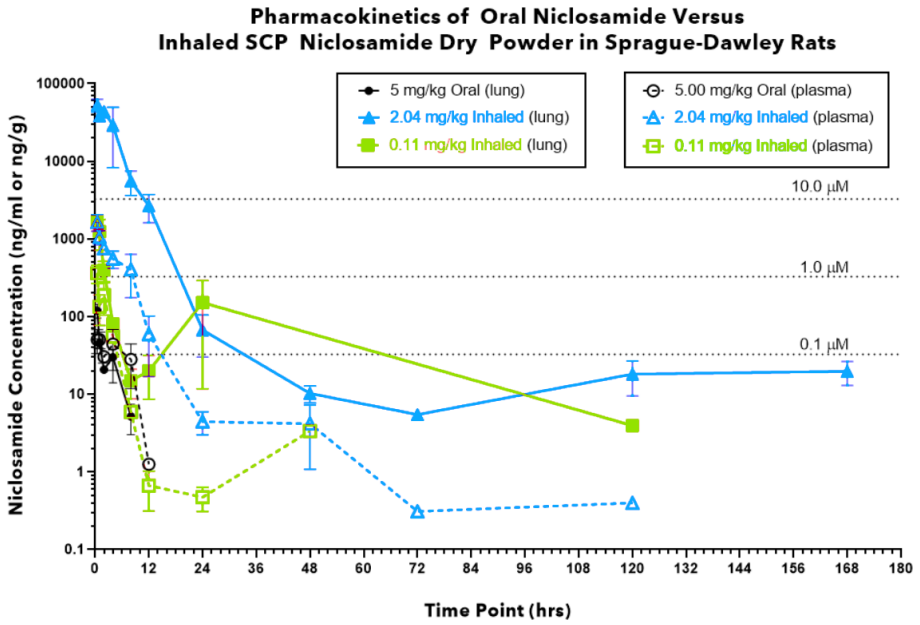
D_{v10}[1]	1.09 µm
D_{v50}[1]	4.77 µm
D_{v90}[1]	13.7 µm
MMAD[2]	3.38 µm
Surface Area	3.49 m^2/g
Bulk Density	0.085 g/cm³

Purcision™ Niclosamide Rat Pharmacokinetic Studies

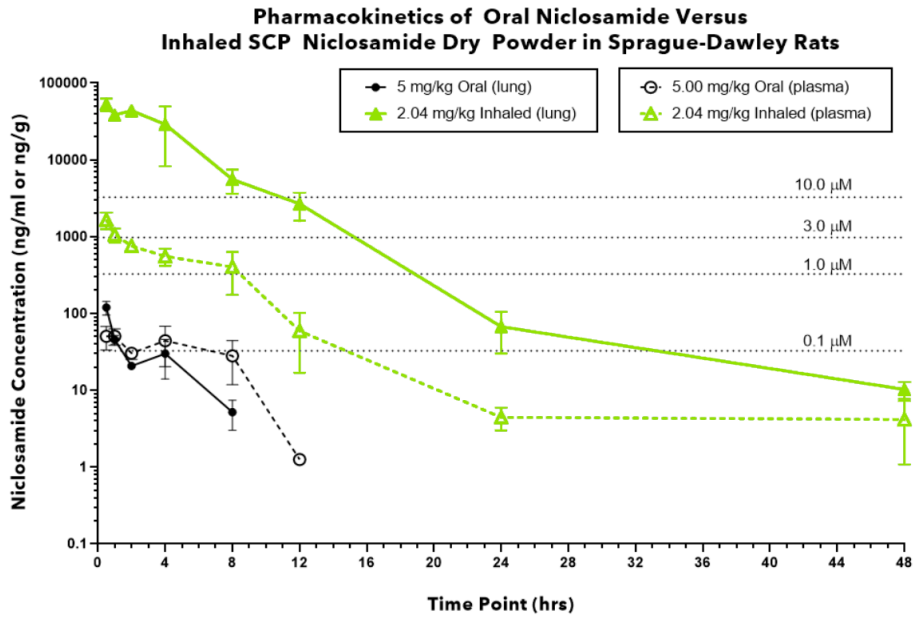
CritiTech Pulmonary

Two dose levels of Purcision inhaled Niclosamide (2.04 and 0.11mg/Kg) were compared to an oral solution dose of 5mg/Kg of Niclosamide.

The results for the lung tissue and plasma levels



The results comparing the 2.04mg/Kg inhaled dose to the 5mg/Kg oral dose for the initial 48 hours



- **High concentration** and **long duration** of Purcision inhaled Niclosamide in the lungs. A lung concentration of greater than 0.1µM after 24 hours suggests that **once daily dosing would be possible**.
- The dose normalized AUC for the inhaled 2.04mg/Kg dose compared to the oral 5mg/Kg solution showed a **2,750-fold increase in lung exposure by the inhaled route**.

LOVELACE BIOMEDICAL

Aeon Respire's Purcision Inhaled Niclosamide Versus TFF Pharmaceuticals' Inhaled Niclosamide

CritiTech Pulmonary

TFF PHARMACEUTICALS

- API = 1.67%
- Completed Phase I clinical trial for Covid-19
- 2x/day dosing – 6 capsules each dose
- Still scaling-up manufacturing

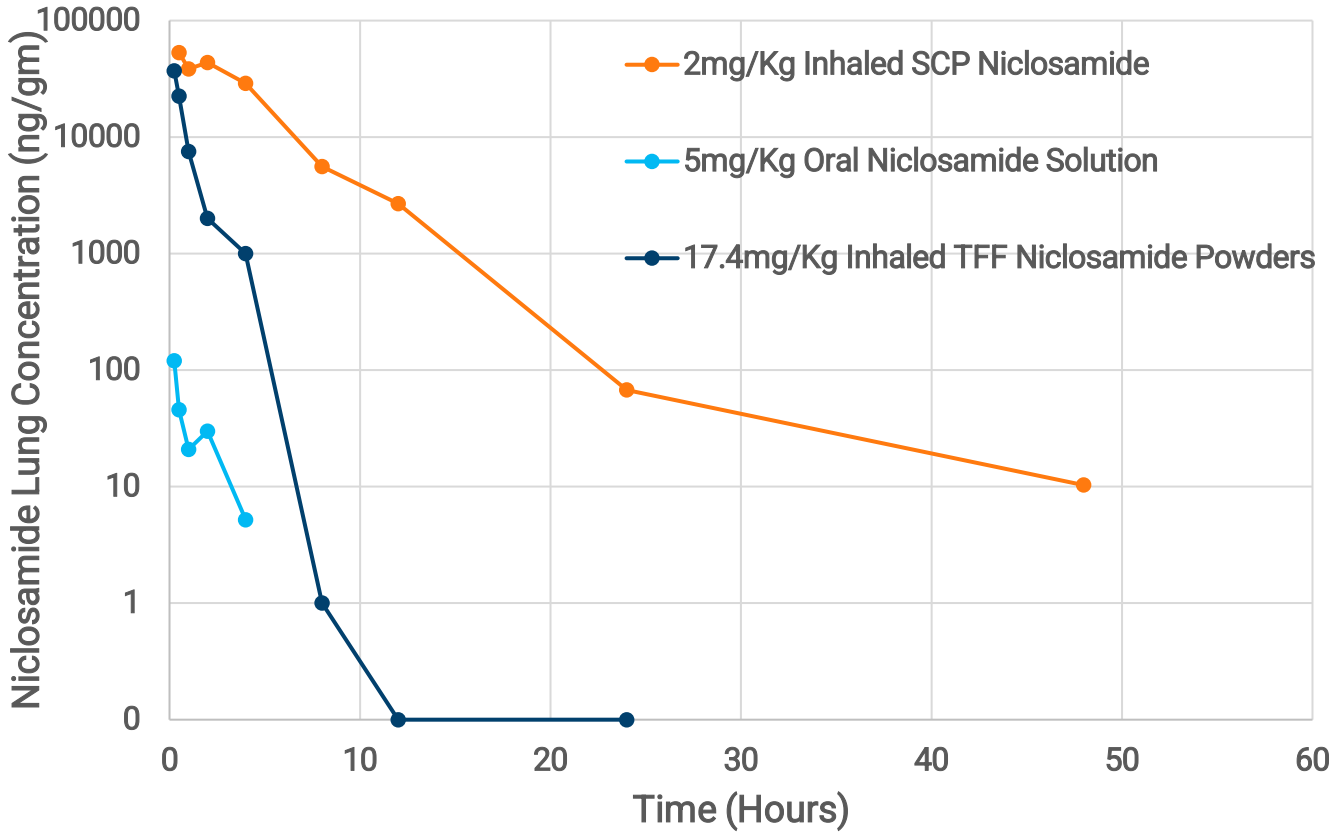
Æon Respire, Inc.

- 100% pure drug
- Much longer retention time
- 1x/day dosing – 1 capsule per dose
- Commercial-scale manufacturing
- Best PK results of any formulation of niclosamide

Aeon Respire's Purcision Inhaled Niclosamide Versus TFF Pharmaceuticals' Inhaled Niclosamide

- Purcision® Inhaled Niclosamide (dry powder) is 100% pure drug. 2mg/Kg dosed in rats suggests that once daily dosing in humans is very possible.
- TFF inhaled niclosamide (dry powder) is 1.67% API. 17.4 mg/Kg of TFF inhaled niclosamide dosed in hamsters dissolves very quickly in the lungs. Dosing in humans would be expected to be at least twice per day.
- Allometric scaling from the 2mg/Kg inhaled dose of Purcision® Niclosamide in rats predicts a human dose of approximately 19.7mg/day. The projected inhaled dose for TFF niclosamide is over 500mg given twice daily or over 1000mg/day.

Comparison of Pharmacokinetic Results
SCP Nicolsamide (Sprague-Dawley rats)
TFF Niclosamide Syrian golden hamsters)*



* From M.O. Jara *et. al.*, Niclosamide Inhalation Powder Made by Thin Film Freezing: Pharmacokinetic and Toxicology Studies in Rats and Hamsters. *bioRxiv*, 2021.2001.2026.428293(2021)

CritiTech®
Pulmonary

Introduction

Purcision™ Technology A Unique Platform for Respiratory Drug Development

Opportunity to Develop Inhaled Drugs Using Purcision™ Technology

CritiTech's Drug Development & Manufacturing Capabilities

Summary of Drug Development and Manufacturing Experience

- Clinical-stage, pharmaceutical drug developer and manufacturer located in Lawrence, KS
- Experience with >200 compounds across >10 drug classes
- Developed & manufactured several drug products that have completed or in the process of completing numerous Phase I/II clinical trials
- Extensive patent portfolio: >100 patents (e.g. composition of matter, formulation, method of administration, manufacturing processes and equipment, et. al.) used to support partners' drug development programs
- Technical leadership team with >150 years of drug development and manufacturing experience

Pharmaceutical Drug Development, Manufacturing & Program Management Capabilities

CritiTech Pulmonary

CritiTech has experience executing drug development programs and managing cross-functional drug development teams from discovery through clinical trial manufacturing.

Early-Stage Development → Formulation & Preclinical → Phase I → Phase II → Phase III → FDA Review

Phyton Biotech
US BIOTEST
iPHARMA
LOVELACE BIOMEDICAL
TEXAS
NanOlogy
KCAS
CardinalHealth™
PTL Particle Technology Labs
eurofins
Latham BIOPHARM GROUP
THE UNIVERSITY OF IOWA PHARMACEUTICALS
KU THE UNIVERSITY OF KANSAS
Catalent
MRIGlobal
DavosPharma
charles river
Æon Respire, Inc.
Sterigenics A Sotera Health company

Drug Development & Manufacturing Facilities

- R&D Laboratories
- Analytical Testing Laboratories
- Separate cGMP Facilities
  - Dedicated non-cytotoxic and potent
  - Dedicated cytotoxic and potent
- Non-cGMP and cGMP Manufacturing
  - Purcision™ Technology
  - Spray Drying
  - Fill/Finish (blending, capsule filing, vial filling)
  - Schedule drugs II-V
  - Potent Drugs
  - Grams to 100’s of kilograms
  - POC to commercial manufacturing







Material Characterization and Analytical Services

CritiTech provides a broad range analytical services to support our clients drug development projects from proof-of-concept through cGMP production. Our testing data and documentation is reviewed by experienced technical and quality staff to ensure it can be used to support regulatory filings.

- Analytical Method Development
- Analytical Validation Studies
- Particle Size Analysis
  - Laser Diffraction – Liquid and Dry Powder Dispersion
  - Laser Obscuration
- Aerodynamic Particle Size Analysis
  - Next Generation Impactor (NGI)
- Sorptometry – BET Surface Area
- Bulk and Tapped Density of Powders
- Physical Chemical Properties
  - LogP, LogD, pKa, and pH Dependent Solubility
- Calorimetry
  - DSC
- X-Ray Powder Diffraction
- Identification
  - FTIR
- Imaging
  - Optical Microscopy with Digital Image Analysis
  - Scanning Electron Microscopy (EDX)
  - Transmission Electron Microscopy (EDX)
- Moisture Determination
  - Karl Fischer Titration
  - Loss on Drying
- Quantification and Purity
  - UPLC/HPLC (ELSD, UV, & PDA)
  - UV/Vis Spectroscopy
  - GC (FID & ECD)
- Residual Solvent Determination
  - Gas Chromatography
  - HPLC
  - UV/Vis Spectroscopy
- Dissolution
  - USP Apparatus 1 and 2
- Potentiometric Titration
- Optical Activity
  - Polarimetry
- ICH Stability
  - Analytical Testing In-House
  - Storage Outsourced

Example of Clinical-Stage Drug Development & Manufacturing Experience

CritiTech has developed and manufactured oncology drug products with its Purcision™ Technology that are licensed to a partner, NanOlogy. CritiTech is a part owner of NanOlogy.

NanOlogy

Local Injection

Intraperitoneal
Intracystic
Intratumoral
Intravesicular

Inhalation

Topical

Advantages

- No Drug-Related SAE's
- High, Sustained, Local Concentration
- Continuous Tumor Kill
- Stimulation of Immune System

Example of Clinical-Stage Drug Development & Manufacturing Experience

CritiTech has developed and manufactured oncology drug products that have completed or are in the process of completing numerous Phase I/II clinical trials.

Product	Indication	Route of Delivery	Preclinical	Phase I	Phase II	Phase III
NanoPac® (Injectable Suspension)	Locally Advanced Pancreatic Adenocarcinoma	Intratumoral				
	Mucinous Cystic Pancreatic Neoplasms	Intracystic				
	Peritoneal Malignancies/Ovarian Cancer	Intraperitoneal				
	Prostate Cancer	Intratumoral				
	Non-Small Cell Lung Cancer	Direct Injection				
NanoPac® (Topical)	Cutaneous Metastasis	Topical				
NanoPac® (Inhalation)	Non-Small Cell Lung Cancer	Inhalation				
NanoDoce® (Injectable Suspension)	High-Risk Non-Muscle Invasive Bladder Cancer	Resection Bed Injection Intravesical Instillation				
	Muscle Invasive Bladder Cancer	Resection Bed Injection Intravesical Instillation				
	Renal Cell Carcinoma	Intratumoral				

CritiTech®
Pulmonary

Let’s connect

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