

CDMO Services & Capabilities

Pre-Formulation • Formulation • Manufacturing • Fill-Finish • Analytical

**Executive
Summary**

**Pre-Formulation
Services**

**Formulation &
Manufacturing
Services**

**Fill-Finish
Services**

**Analytical
Services**

Executive
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Pre-Formulation
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Analytical
Services

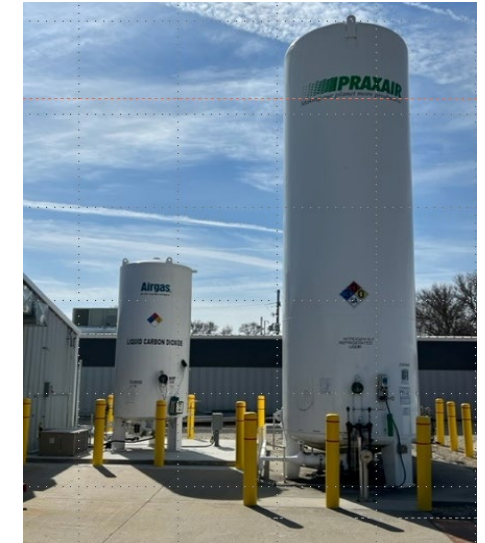
CDMO Overview

- Multi-service CDMO located in Lawrence, KS
- ~20,000 sq. ft. (R&D, Analytical, and cGMP Production)
- Proof of concept through cGMP Phase III manufacturing
 - Purcison™ Technology
 - Spray Drying Technology
- Cytotoxic, non-cytotoxic, and potent drug manufacturing
- Experience with over >220 compounds across >12 drug classes
- Engineered, formulated, and manufactured cGMP materials for numerous Phase I and Phase II clinical trials
- Clients range from “Top 15 Pharma” companies to start-ups
- Technical leadership team with >150 years of industry experience
- Committed to providing best in class customer service

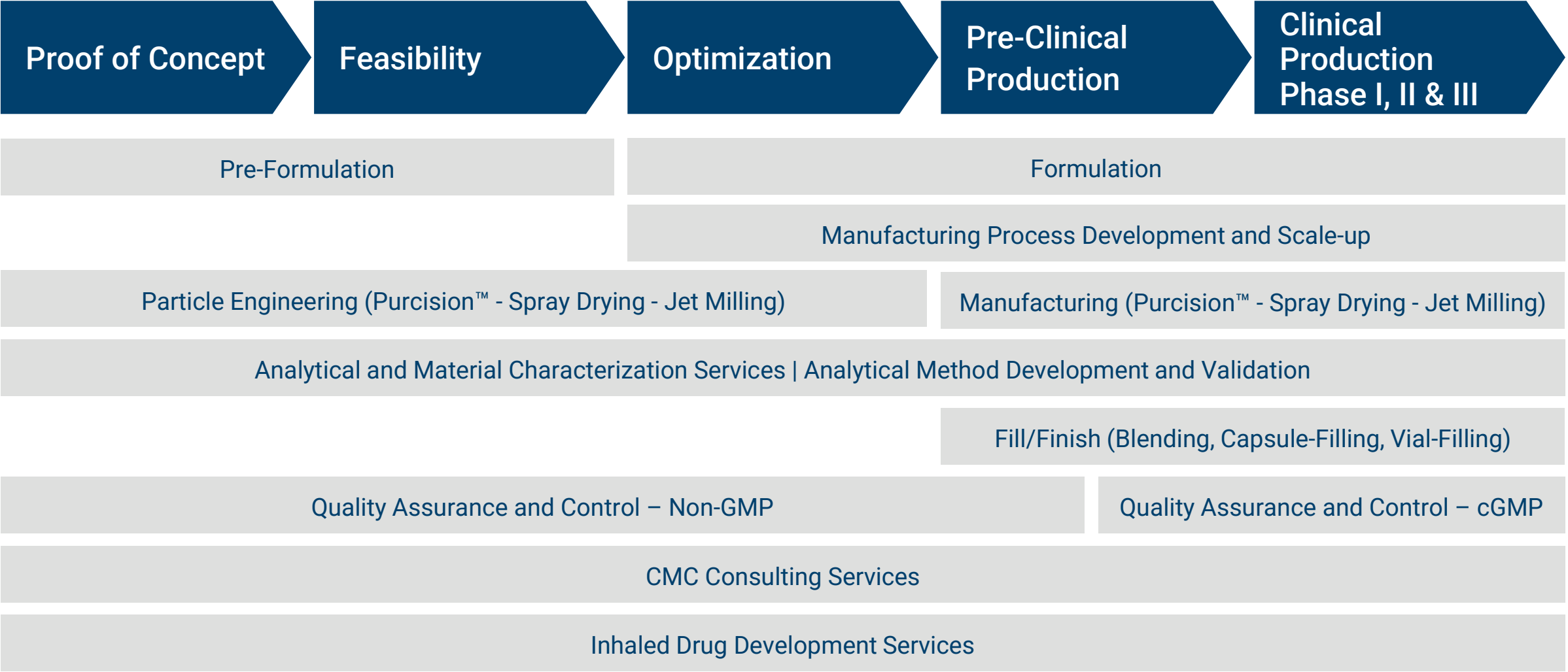


Drug Development & Manufacturing Facilities

- R&D Laboratories
- Analytical Testing Laboratories
- Separate cGMP Facilities
 - Dedicated non-cytotoxic and potent
 - Dedicated cytotoxic and potent
- Non-cGMP and cGMP Manufacturing
 - Purcison™ 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



Multi-Service CDMO



Our #1 Priority is to Help Our Customers Achieve Their Product Development Goals

Critech Particle Engineering Solutions (CT PES) uses its particle engineering technologies and expertise to help customers improve and optimize formulations, increase bioavailability, modify pharmacokinetic (PK) profile, alter dosing, and enhance the delivery of drugs.

Pharmaceutical Industry Challenges

- Poor bioavailability, solubility, and absorption
- Suboptimal routes of administration
- Formulation issues (e.g., poor flowability)
- Toxicity and negative side effects
- Inadequate efficacy
- Poor patient compliance and inconvenience
- Patent expiration – lifecycle management

~70% – 90% of drugs developed by the pharmaceutical industry are poorly soluble molecules.

Source: Journal of Pharmacy and Pharmacology and Drug Delivery and Formulation Forum

Drug revenues can decrease up to 70% within several months of patent expiration.

Source: EvaluatePharma and Dolcera

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)



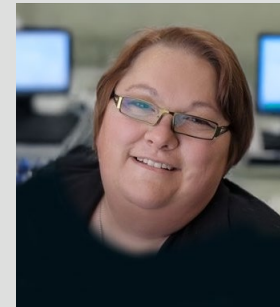
Michael Baltezor, PhD
Chief Scientific
Officer



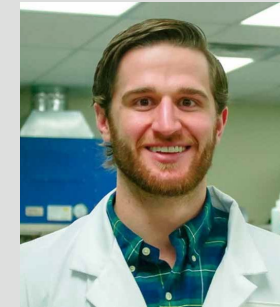
Gere diZerega, MD
Chief Medical
Officer



Mark Williams
Vice President
Technical Operations



Deborah Wade
Vice President
Quality Operations



Jake Sittenauer
Director Drug
Development Programs



Joe Farthing
Director Quality
Systems & IT

Differentiated Services



Purcison™ Technology

- Proprietary technology for formulating drugs for delivery direct to site
- Great tool for development of inhaled powders & injectable suspensions
- Opportunities for patent protection



Cytotoxic Manufacturing

- Years of experience producing cytotoxic materials
- GMP cytotoxic manufacturing
- GMP Purcison™ and spray drying



Particle Engineering

- Purcison™, spray drying, jet milling
- Let the best technology win
- Inhaled drug development is strong area of expertise



Best in Class Customer Service

- Every customer matters
- Fast response times
- High-quality deliverables
- Transparency regarding projects
- Honesty and integrity



Formulation

- Strong early-stage drug development and formulation expertise
- Numerous drugs formulated for the clinic



Can Do Culture

- Problem solvers
- Strong work ethic
- Work as a team
- Get it done right!

Best in Class Customer Service

CT PES's customers are very pleased with the quality of service they receive. As a result, they are expanding the amount of business they are doing with CT PES.

"Delighted to be working with you and the great team at CT-PES. Anticipate many good things to come from our partnership..."

CEO, Respiratory
Pharmaceutical Company

"There is no end to the Thanks You's that (we have) for you and the entire team at Critech! At a critical moment for (us), you enabled our program to keep moving forward! We cannot thank you enough!!!"

CEO, Pharmaceutical Company

"I am extremely impressed with the level of customer focus your team has! Wish all the vendors were at your level."

VP, CMC, Pharmaceutical
Company

"Exciting times ahead for Critech. I've been very impressed with the interaction for the project...."

Senior Director, Global Inhalation
R&D, Top 15 Pharma

"A big thank you to you and your team for all the hard work on this project. We appreciate the quick turnarounds throughout the process and your thorough updates."

Product Development Lead,
Medical Dermatology Company

Best in Class Customer Service

CT PES's customers are very pleased with the quality of service they receive. As a result, they are expanding the amount of business they are doing with CT PES.

"Thank you for your hospitality and the hard work your people put in to make this a successful effort. Your skills and work ethic are exemplary and unique."

Consultant, Global Specialty
Materials Company

"Thank you again for working with us to bring these documents to completion so quickly. And of course we are thrilled with the successes we've seen thus far on our compound. We look forward to a long collaboration!"

CEO, Pharmaceutical Company

"I found everyone at your organization to be helpful, knowledgeable and customer-focused."

Executive Director, Formulation
R&D, Biopharmaceutical
Company

"You guys are awesome... We look forward to hearing if you can work your magic."

Program Leader,
Pharmaceutical Company

"Thanks so much for putting this together so quickly and for being a terrific partner in this process."

CEO, Pharmaceutical Company

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Summary

Pre-Formulation
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Pre-Formulation Services

The formulation of poorly soluble drugs during early-stage development and animal studies can be challenging. Critech provides pre-formulation services to help our clients develop the right formulation early in the drug development process, saving valuable time and money.

**Drug Substance
Characterization**

**Solubility
Screening**

**Excipient
Screening**

**Formulation
Techniques**

**Formulation
Stability**

Pre-Formulation Services

Drug Substance Characterization

- Full range of testing including XRPD, DSC, SEM, particle size distribution and early HPLC method development

Solubility Screening

- Water and pH solubility profiling including testing solubility in several organic solvents that can be used with our spray drying and Purcison™ particle engineering technologies
- Solvent screens typically include propylene glycol, PEG 400, ethanol, methanol, acetone, dichloromethane, DMSO, dimethyl formamide (DMF) and tetrahydrofuran (THF)

Excipient Screening

- Evaluation of cyclodextrin complexation, surfactants, and self-emulsifying drug delivery excipients
- Examples of cyclodextrin excipients include hydroxypropyl, Betadex and Betadex Sulfobutyl Ether Sodium.
- Surfactants and self emulsifying drug delivery excipients include polysorbate 80, Kolliphor HS15, low molecular weight PVP and Polyoxymers 188 plus and several others
- Only excipients that are on the FDA approved excipients list for the intended route of delivery are evaluated.

Pre-Formulation Services

Formulation Techniques

- Formulations developed with Purcison™ Technology, spray drying and air jet milling
- Preparation of solutions/suspensions for injection or oral gavage in animals
- Preparation of powder formulations for inhalation, filling into capsules or for topical applications

Formulation Stability

- Assay drug content for newly developed formulations
- UV or HPLC methods that comply with early-stage requirements
- Accelerated stability testing at selected conditions and time frames to match development plan needs

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Formulation and Manufacturing Services



Spray Drying

Jet Milling

Critech formulates and produces materials for pre-clinical and clinical studies using the technology that best suits our clients' needs

Formulation and Manufacturing Services



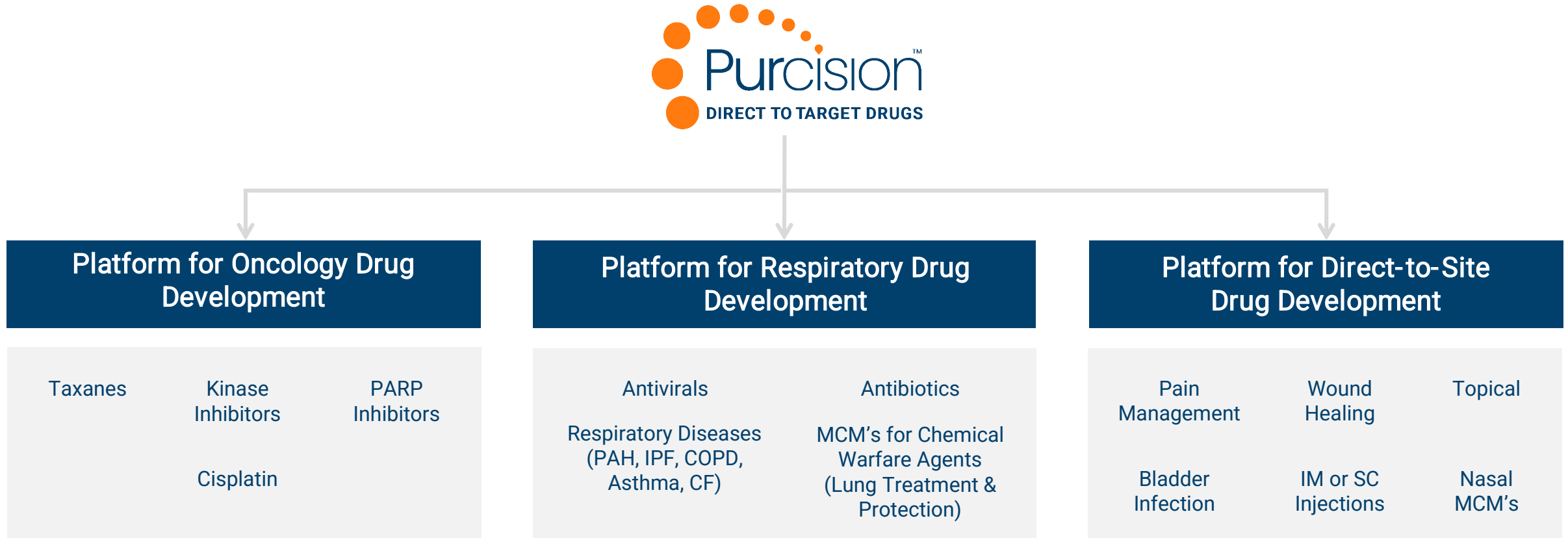
Spray Drying

Jet Milling

Critech formulates and produces materials for pre-clinical and clinical studies
using the technology that best suits our clients' needs

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

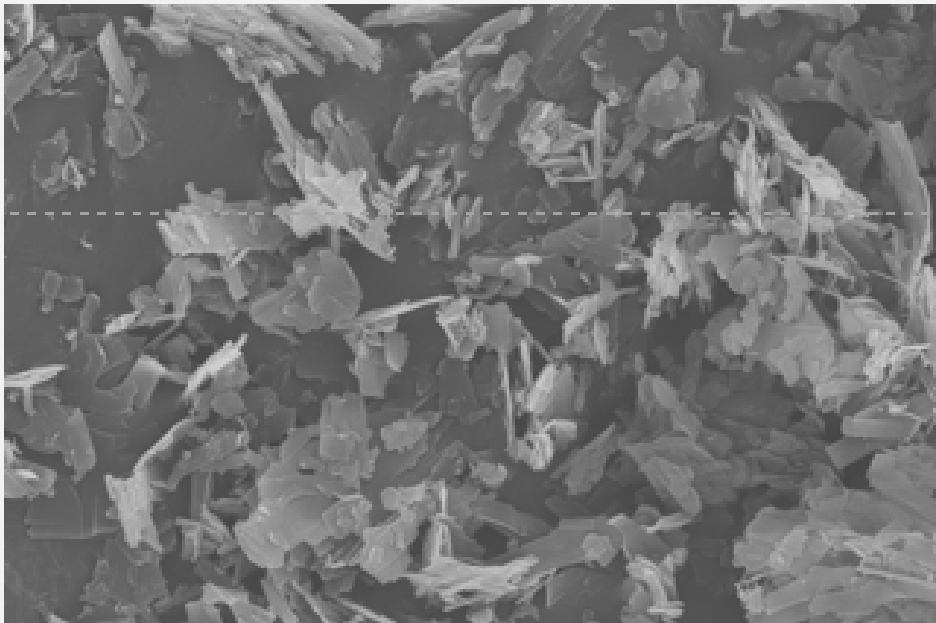
The Purcison™ Technology has been used to engineer, formulate and manufacture a variety of drugs that have advanced into clinical trials.



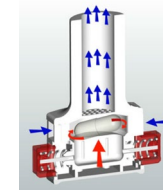
Purcison™ Particle Engineering & Production Technology

Purcison™ 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.

Purcison Engineered Particles



New & Improved Drugs



Inhalation



Orals



Injectables

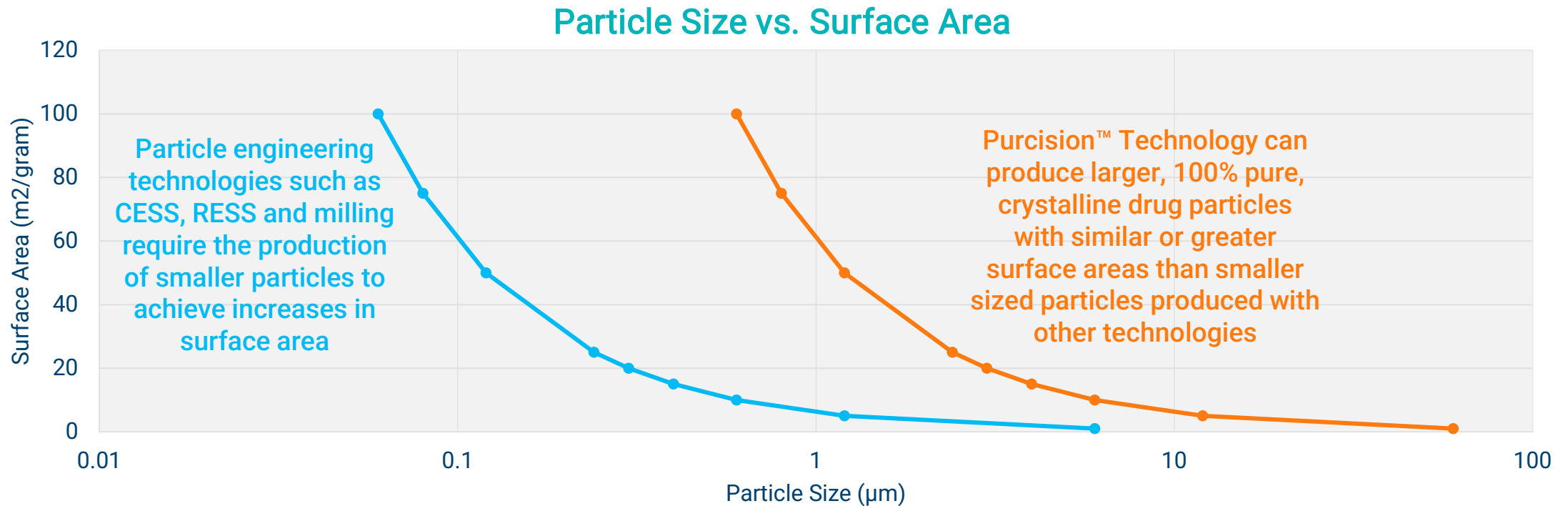


Gels/Ointments

**Controlled Concentration – Long Duration –
Limited Systemic Exposure**

Purcison™ Produces a Unique Particle Size to Surface Area Ratio

- Purcison™ is different from other particle engineering technologies
- Purcison™ 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 Purcison™ particles enable longer retention time at the site of disease and effective drug release
- Solid particles engineered with other technologies <1μm require additives to prevent static agglomeration and improved handling



Purcison™ is an Effective Tool for Engineering Poorly Soluble Drugs

Biopharmaceutical Classification System for Drugs

Permeability	High	Low
	CLASS I	CLASS II
Solubility	High	Marketed Drugs: 35% Candidates: 5%-10%
	Low	Marketed Drugs: 30% Candidates: 60%-70%
Permeability	High	Low
	CLASS III	CLASS IV
Solubility	High	Marketed Drugs: 25% Candidates: 5%-10%
	Low	Marketed Drugs: 10% Candidates: 10%-20%



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

Purcison Compatibility Criteria:

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

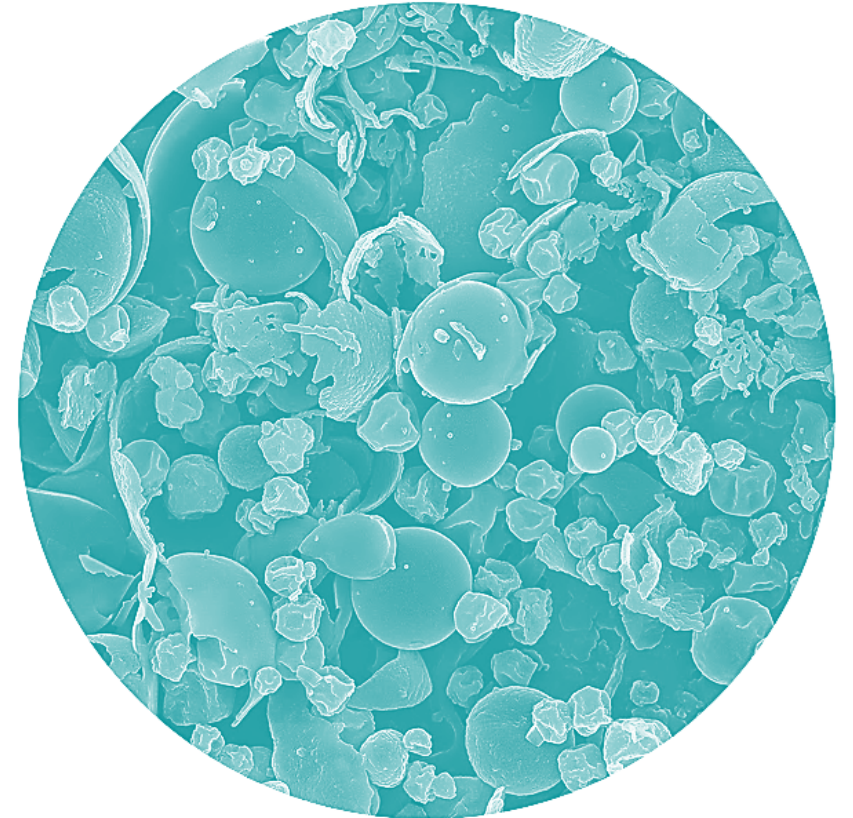
Benefits of the Purcison™ Technology

- 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



Purcison™ Particle Characteristics

- Small Physical Particle Size DV_{50} (Volume) = ~ 0.5 to $5\mu\text{m}$
- High Specific Surface Area = $>20\text{m}^2/\text{g}$
- Low Bulk Density = $<0.1\text{g}/\text{cm}^3$
- Uniquely shaped and structured particles in a narrow size range
- Particles are pure drug – no excipients necessary but can add them if desired
- Particles are normally crystalline but can sometimes be different polymorphs or amorphous if desired
- Particles designed to be larger, easier to manipulate particles with the surface area and drug release characteristics of much smaller submicron particles – an alternative to other micronization technologies without added excipients



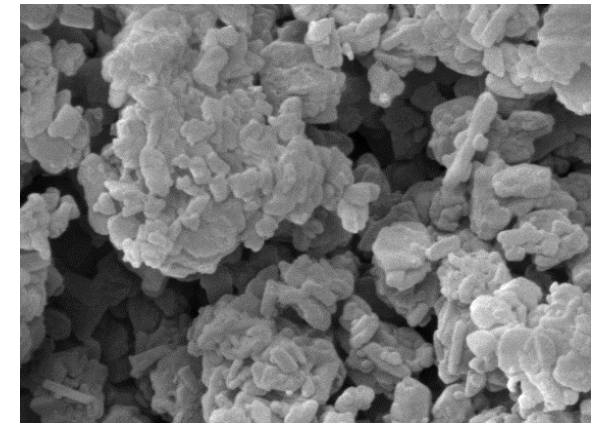
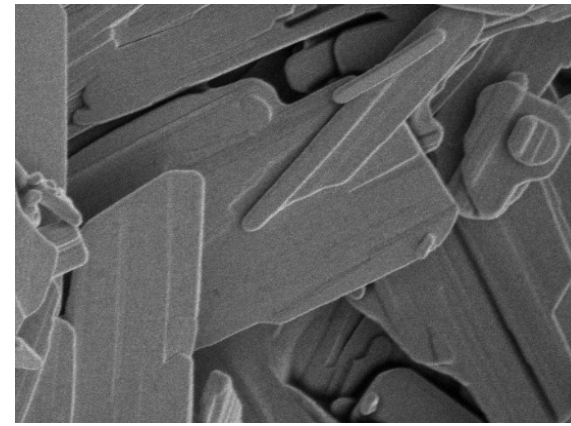
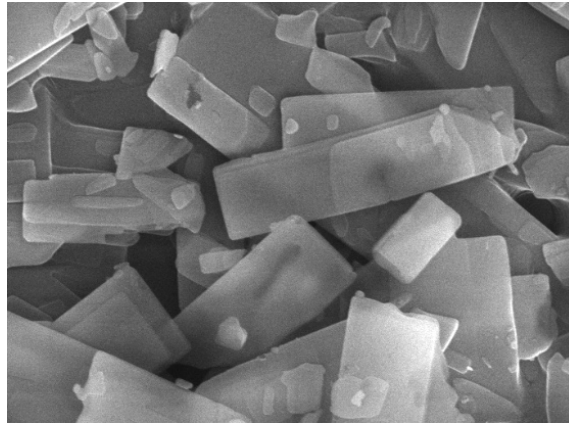
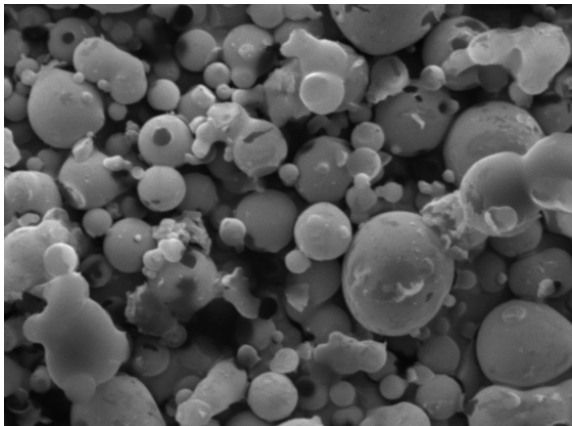
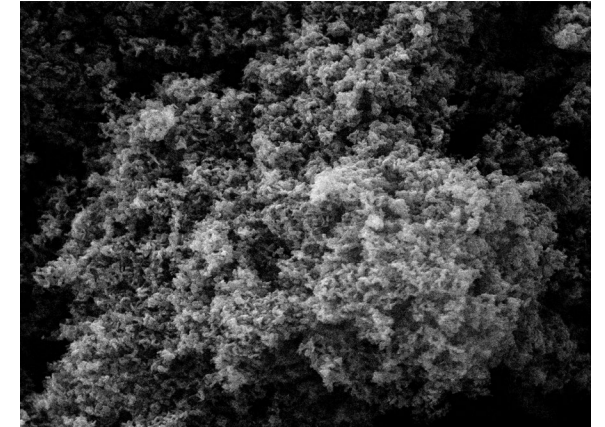
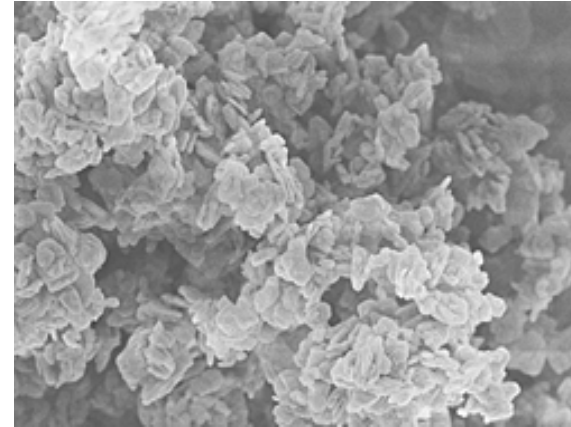
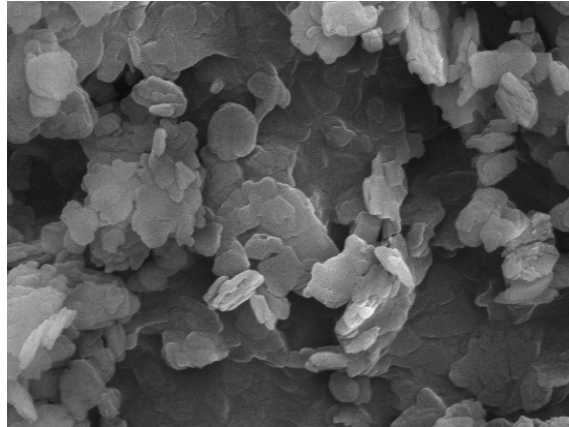
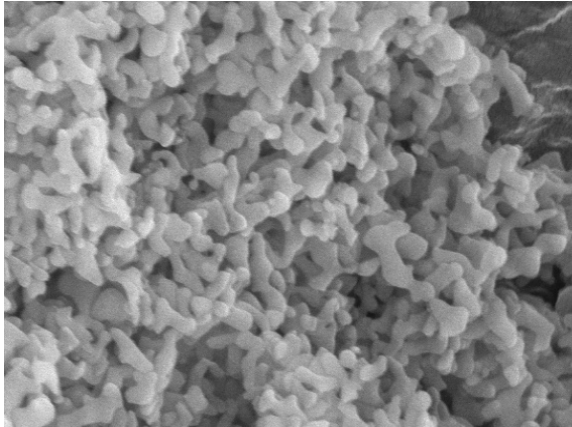
Critech can modify particle characteristics such as size, shape, and polymorph by adjusting the properties of the feed solution and operating parameters in the Purcison™ systems

- Solvent selection
- API concentration
- Temperature
- Pressure
- Solution/feed flow rate
- scCO2 flow rate
- Ultrasonic energy
- Nozzle configuration



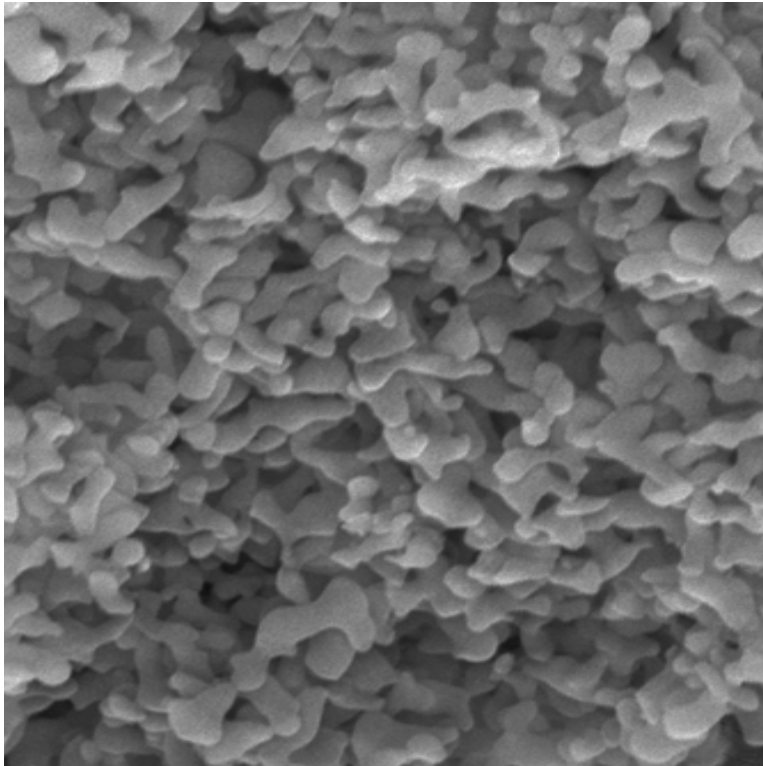
Purcison™ Size and Shape

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

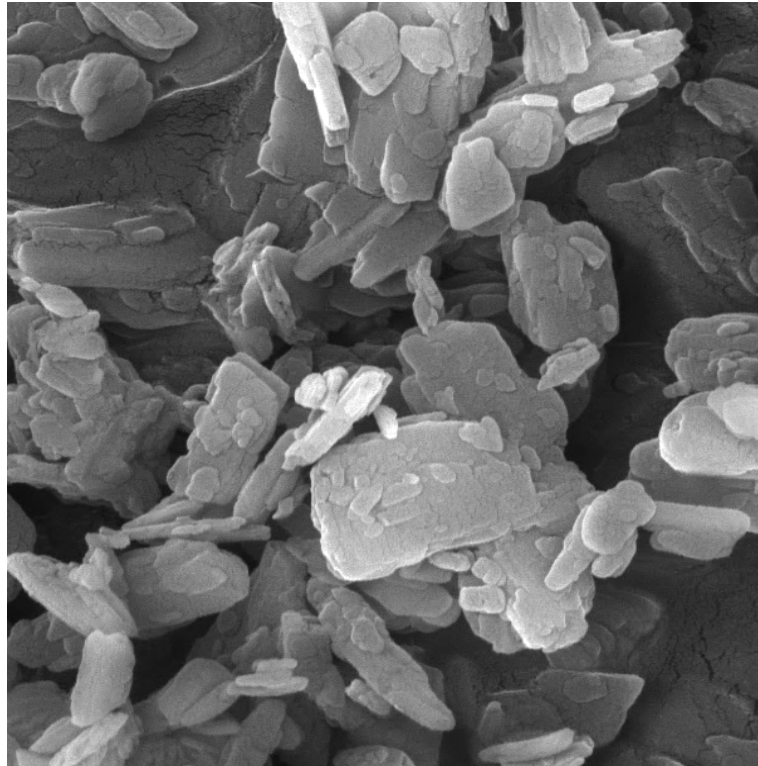


The Purcison™ Technology can be tuned to produce different forms of an API (same drug - different processing conditions)

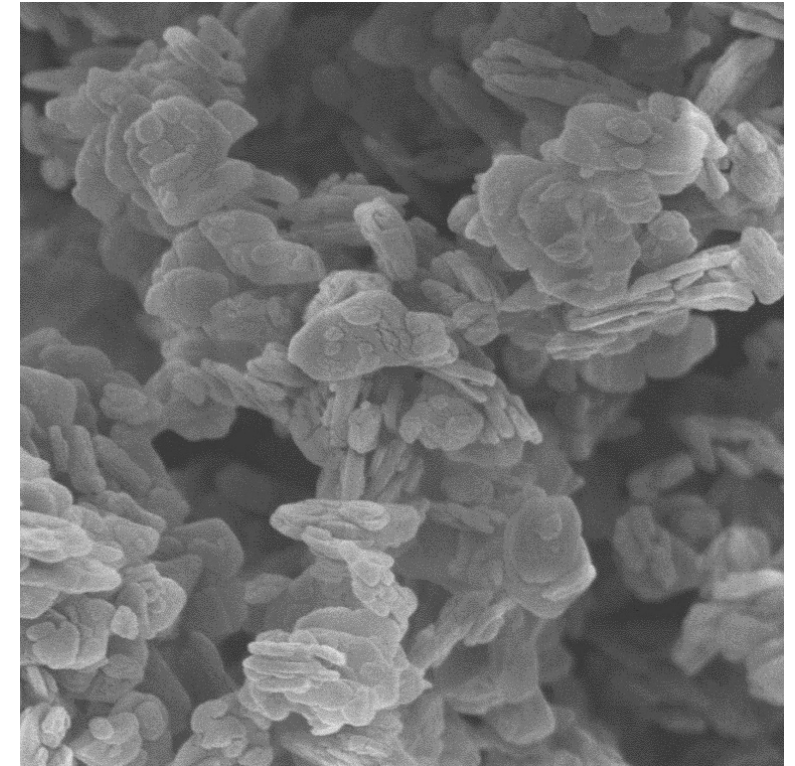
Amorphous



Co-crystal

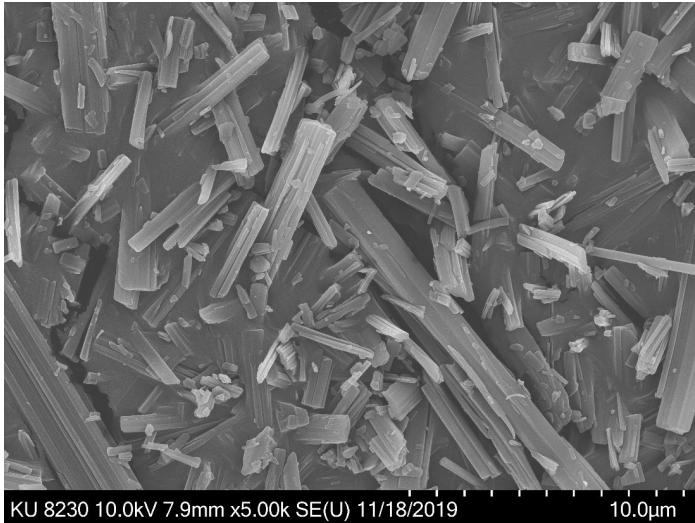


Crystalline



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

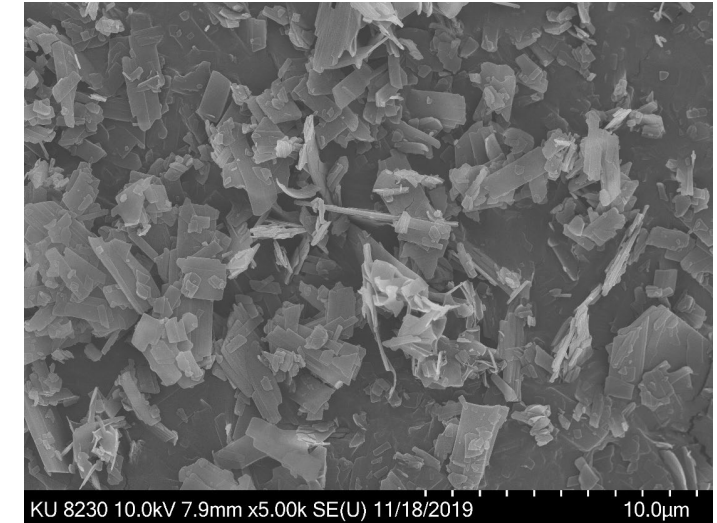
Bulk Drug



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



Purcison Processed Drug



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

Purcison[™] Helps Overcome Challenges Associated with Developing Inhaled Drugs

Attributes

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



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

Purcison[™] Creates Many Opportunities for Respiratory Drug Development



Second chance for
“shelved” drugs



Reformulations of current
IV and oral drugs



New drugs

Purcison™ 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



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 $\geq 0.03 \mu\text{g}/\text{m}^3$
compounds & DEA schedule compounds II-V



Purcison™ Drug Development & Manufacturing



Compatibility Testing

- Is the drug soluble in CO₂?
- Is the drug soluble in an organic solvent?
- Is there an ability to modify particle size, shape and/or morphology?

POC Testing

- Baseline data collected
- Drug processed using up to 8 different operating parameters
- Analytical data collected on processed drug (particle size, surface area, SEM, etc.)
- Production of material for client evaluation

Optimization

- Refine processing conditions to achieve desired product profile
- Assist with formulation development
- Evaluate reproducibility and scalability
- Produce pre-clinical supplies

Pre-Clinical & Clinical Production

- Production of material for pre-clinical studies through Phase III clinical trials
- cGMP production environment
- Documentation to support regulatory filings
- Assist with scale-up

Critech Particle Engineering Solutions has a standard process for developing and manufacturing drugs using its Purcison™ Technology, from basic compatibility testing through cGMP Phase III drug production.

Formulation and Manufacturing Services



Spray Drying

Jet Milling

Critech Can Formulate and Produce Materials for Pre-clinical and Clinical Studies
Using the Technology that Best Suits Our Clients Needs

Spray Drying Benefits

- Bioavailability enhancement of poorly soluble drugs (BCS Class II and IV)
- Modified release rates of highly and poorly soluble compounds
- Enables improved pharmacokinetics and multiple routes of delivery
- Development of multiple formulations with grams of API
- Scalable and reproducible
- Can be utilized as an LCM tool for a reformulated and improved 2nd generation product
- Conditions from Buchi B-290 or Mobile Minor systems can be transferred to Critech



Spray Drying Capabilities

- Spray-dried dispersions - API + polymer/excipients
- Spray-dried powders - API alone
- Spray dry from aqueous or organic solvent systems
- Applicable to large molecules (e.g. proteins, peptides, mRNA)
- Critech's single pass nitrogen systems are especially advantageous for oxygen sensitive and hygroscopic compounds
- Non-potent API (dedicated rooms, equipment, and air handling system)
- Non-cytotoxic API (dedicated rooms, equipment, and air handling system)
- Potent API (dedicated rooms, equipment, and air handling system)
- Cytotoxic API (dedicated building, equipment, and air handling system)
- Milligrams to hundreds of kilograms production scale
- Fully validated cGMP equipment



Spray Drying Equipment

Critech can process cytotoxic and potent compounds (OEL $\geq 0.03 \mu\text{g}/\text{m}^3$) & DEA schedule compounds II-V

	Buchi B-290	Critech SD30	Critech SD100	Anhydro MS75	Anhydro MS150
Nominal process gas flow	40 kg/hr.	120 kg/hr.	120 kg/hr.	75 kg/hr.	150 kg/hr.
Water evaporation capacity	1.0 L/hr.	3.5 L/hr.	3.5 L/hr.	3 L/hr.	14 L/hr.
Maximum drying gas temperature	220 °C	215 °C	215 °C	200 °C	350 °C
Approximate production scale	0.25-10 g	10-250 g/hr.	10-250 g/hr.	10-200 g/hr.	50-2,000 g/hr.
Aqueous processing	✓	✓	✓	✓	✓
Multiple nozzle configurations	✓	✓	✓	✓	✓
Volatile solvent compatible	✓	✓	✓	✓	✓
Non-Cytotoxic	✓	✓		✓	✓
Cytotoxic	✓		✓		

POC and Development System – Buchi B-290

Critech's Buchi B-290

Nominal Process Nitrogen Flow	40 kg/hr.
Water Evaporation Capacity	1.0 L/hr.
Approximate Batch Scale	0.25-10 g
Aqueous Processing	✓
Volatile Solvent Compatible	✓
Multiple Nozzle Configurations	✓



cGMP Spray Drying Manufacturing – SD30

The Critech SD30 Spray Drying System provides scaled-up cGMP production from the Buchi B-290. The SD30 consistently reproduces material produced on the Buchi B-290.

Critech's SD30

Nominal Process Nitrogen Flow	120 kg/hr.
Water Evaporation Capacity	3.5 L/hr.
Approximate Production Scale	10-250 g/hour
Typical Mean Particle Size	1-50 μm
Aqueous Processing	✓
Volatile Solvent Compatible	✓
Multiple Nozzle Configurations	✓



cGMP Spray Drying Manufacturing – SD100

The Critech SD100 Spray Drying System provides scaled-up cGMP production from the Buchi B-290.

Critech's SD100

Nominal Process Nitrogen Flow	120 kg/hr.
Water Evaporation Capacity	3.5 L/hr.
Approximate Production Scale	215 °C
Typical Mean Particle Size	10-250 g/hr.
Aqueous Processing	✓
Volatile Solvent Compatible	✓
Multiple Nozzle Configurations	✓
Cytotoxic	✓



cGMP SD Manufacturing – Anhydro MS75

Critech's Anhydro MS75

Nominal Process Nitrogen Flow	75 kg/hr.
Water Evaporation Capacity	3 L/hr.
Approximate Production Scale	10-200 g/hour
Aqueous Processing	✓
Volatile Solvent Compatible	✓
Multiple Nozzle Configurations	✓

 **Anhydro[®]**



cGMP SD Manufacturing – Anhydro MS150

Critech's Anhydro MS75

Nominal Process Nitrogen Flow	150 kg/hr.
Water Evaporation Capacity	14 L/hr.
Approximate Production Scale	50-2,000 g/hour
Aqueous Processing	✓
Volatile Solvent Compatible	✓
Multiple Nozzle Configurations	✓

 **Anhydro[®]**



Formulation and Manufacturing Services



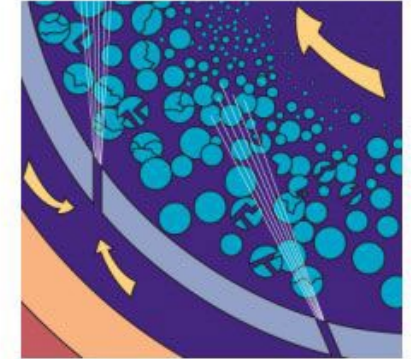
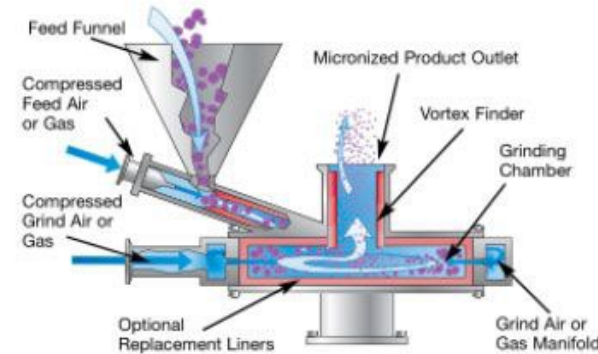
Spray Drying

Jet Milling

Critech formulates and produces materials for pre-clinical and clinical studies using the technology that best suits our clients' needs

Jet Milling Capabilities

Coarse powder entering the air jet mill is suspended in a high-volume air flow. Smaller particles of the desired particle size exit the mill and are collected while the larger, heavier particles remain in the mill. Particle size reduction is achieved by particle-to-particle collisions.



- Capacity of 0.45-7.0 kg/hr.
- Minimal increase in temperature
- Narrow particle size distribution
- Particularly useful when particles of 1 micron or larger are desired
- Powders produced with an air jet mill can be useful for delivery via a dry powder inhaler

Jet Pulverizer Micron Master® 2" Jet Mill



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Pre-Formulation
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**Fill-Finish
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Analytical
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Capsule and Vial Filling Services

Profiller[®] Manual
Capsule Filler



Up to 2,000 Capsules Per Hour

PerFil[®] By Weight
Vial Powder Filler



Up to 180 Vials Per Hour

Dott-Bonapace
Capsule Filler



Up to 3,000 Capsules Per Hour

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Material Characterization and Analytical Services

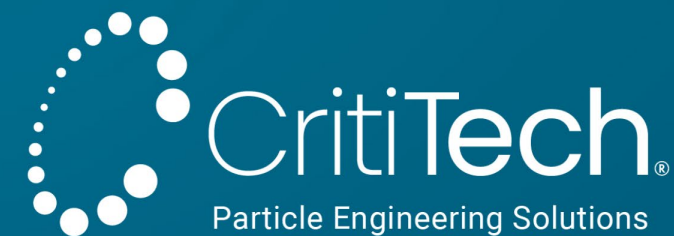
Critech provides a broad range analytical services to support our clients drug development projects from proof-of-concept through cGMP production. Our testing data and documentation is reviewed by experienced technical and quality staff to ensure it can be used to support regulatory filings.

- 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

Why Choose CritiTech as your Drug Development Partner?

- Experts in solubility and bioavailability enhancement of poorly soluble drugs
- Deep particle engineering and pre-formulation expertise
- Unique formulations enabled with Purcison™ Technology
- Inhaled drug development expertise
- Proven track record – developed and manufactured multiple drugs for numerous clinical trials
- Clients include three “Top 15” pharmaceutical companies
- Technical leadership team with >150 years of industry experience
- Highly-skilled, professional, and collaborative technical staff
- Rapid project turnaround times
- Best-in-class customer service and high-quality deliverables





Let's connect

For inquiries please contact:

Matthew McClorey

President

785-330-7816

mmcclorey@crititech.com