



## PAT Conference 2008

# Exercising Real Control Over API & Excipient Isolation

## ***The Power of Sonocrystallization!***

30 October 2008, Heidelberg, Germany

*Christian Jones, Business Development Manager, Prosonix Ltd.*

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## Agenda

- Company Overview
- The Critical Importance of Controlled Crystallization in Manufacture
- Sonocrystallization and Ultrasonic Particle Engineering
  - The Key to Controlled Crystallization of Bulk API and Excipient
  - #1 Theory and Examples
  - #2 Commercial scale solutions
- Advanced Ultrasonic Particle Engineering of Difficult to Manufacture products, such as those for Inhalation

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# Prosonix Ltd



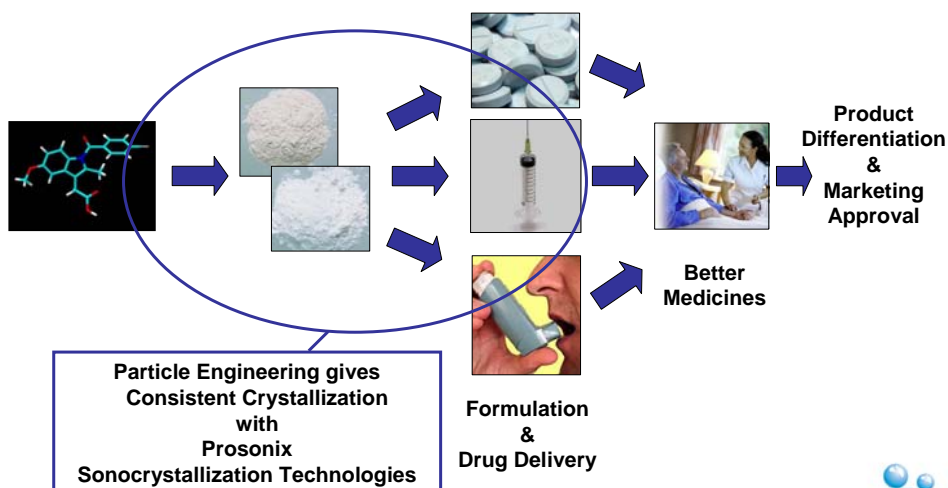
- Based in Oxford, UK
- Focused on patented ultrasonic particle engineering technology using proprietary sonocrystallization techniques to make better medicines
- Income stream from partner funded collaborations, licensing, and product supply
- Development collaborations with 8 of top 10 pharmaceutical companies
- *NEW* recent Milestone success with Pfizer

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# Prosonix Vision

*"Making Better Medicines More Efficiently"*



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## *The Critical Importance of Controlled Crystallization in Manufacture*

## Pharmaceutical Manufacturing & QbD



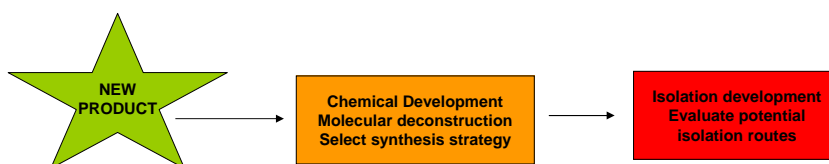
- **Selection Criteria for NCE's are:**
  - Clinical Efficacy
  - Bioavailability
  - Stability
  - Processability
- **Manufacturing and ultimate product success is dictated by:**
  - Product physical form
    - *polymorphism, crystal habit etc.*
  - Process scale-up and manufacturing problems
    - *raw material variations*
    - *synthetic complexity*
- Improved understanding of manufacture and design space could also lead to better asset utilisation, quality and lower failure rates
- Sonocrystallization approaches can transform productivity at the same time as improving flexibility and manufacturing compliance

## Importance of Controlled Crystallization

- Crystallization is a ubiquitous and critical manufacturing unit operation
- Almost every chemical process that produces solid form involves at least one crystallization step, either for intermediate separation, final product purification, or for the removal of key impurities
- Crystallization processes are poorly understood and are difficult to control
- Control of the nucleation difficult but is the key to process control
- Process robustness governs process productivity and economics
- Physical form dictates drug product quality and effectiveness

## Importance of Materials Science

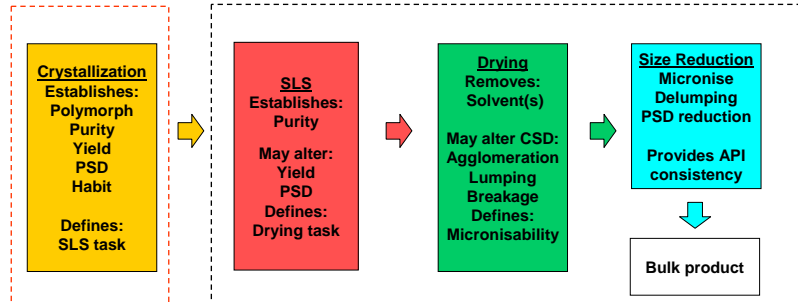
A lack of understanding in early development stores up future problems



- Classic series based approach to isolation and development brings problems

## Importance of Controlled Crystallization

But by fixing things early by design enhances productivity and control



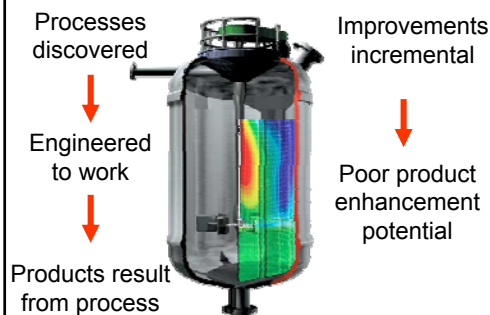
- Controlled crystallisation eliminates downstream problems
- Sonocrystallization potentially “best available technology” for API manufacture

## QbD Manufacture: A Cultural Change

Acknowledgement to Prof. Kevin Roberts, University of Leeds

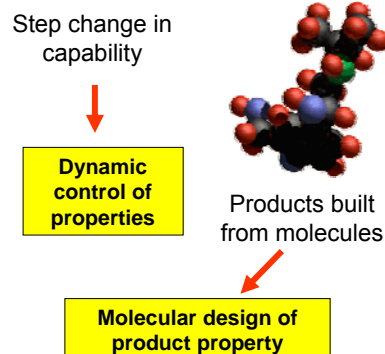
### Historic Approach


“Process Down”



### Future QbD

“Molecule Up”





# *Sonocrystallization*

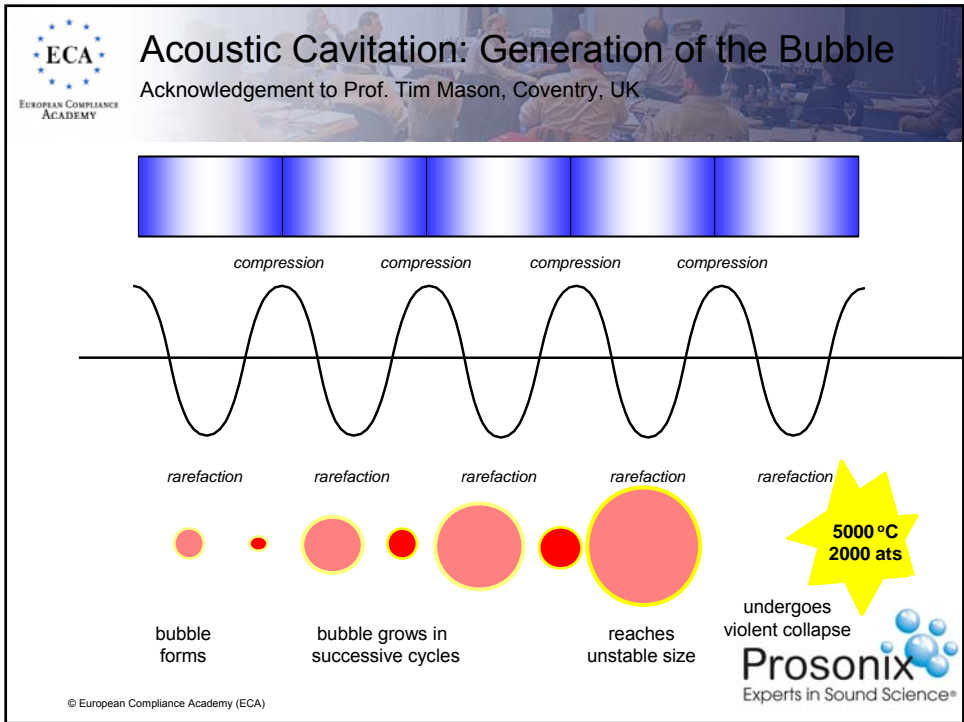
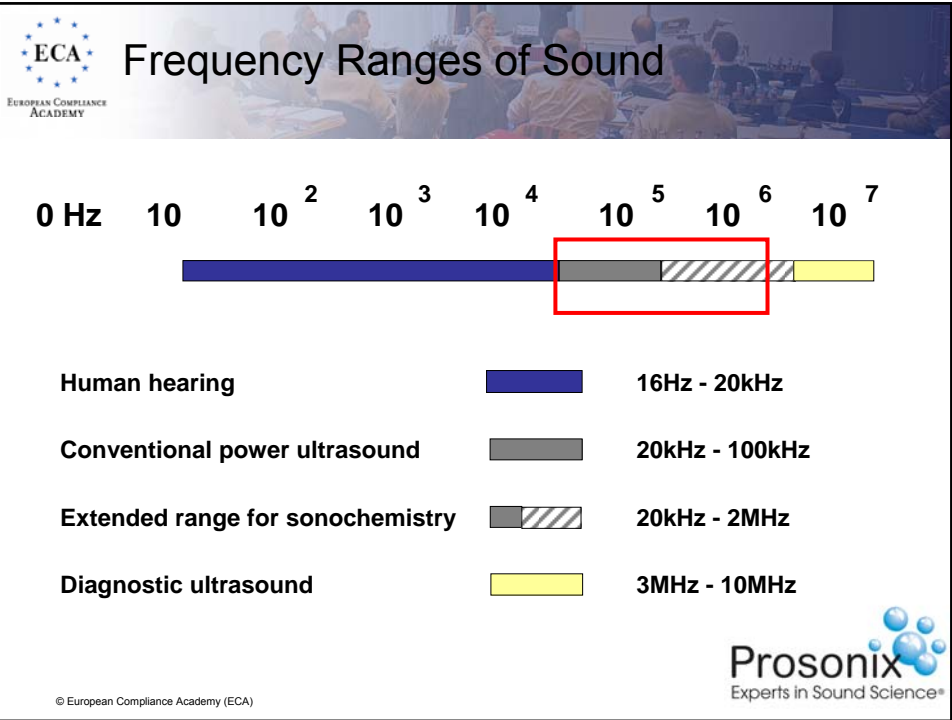
## *The Key to Controlled Crystallization of Bulk API's and Excipients*

### *#1 Theory and Examples*

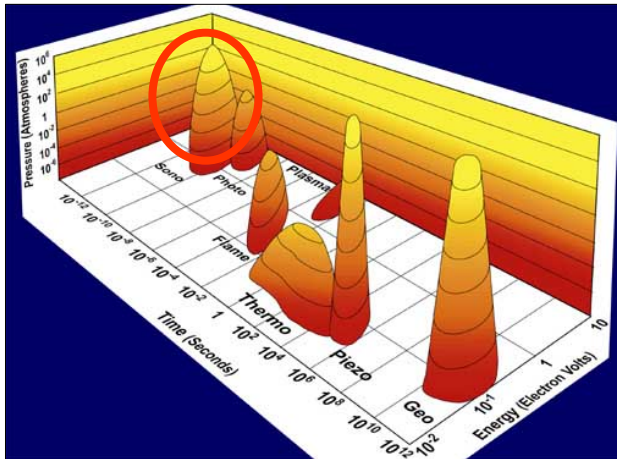


## Key Benefits of Sonocrystallization

- Control particle size, shape, crystallinity, polymorphism
- Improve batch consistency, filtration, isolation and drying
- Improve formulation consistency, stability and performance
- Enhance dissolution of poorly soluble drugs
- Replace problem physical seeding
- Increase cGMP compliance



## Comparison of Acoustical Energy to Other Sources



- Utilisation of ultrasound is a process intensification method in comparison to other energy applications

- Enables delivery of large quantities of energy in short timeframes on microscales, but for controlled macro process effect

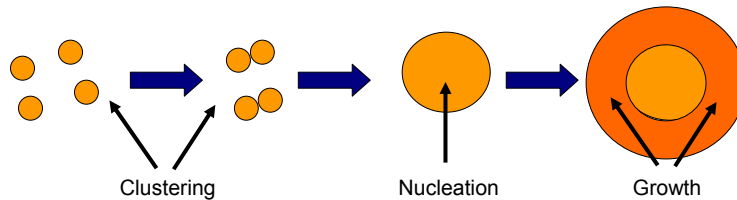
Suslick, K. S.; Didenko, Y.; Fang, M. M.; Hyeon, T.; Kolbeck, K. J.; McNamara, W. B. III; Mdeleeni, M. M.; Wong, M. "Acoustic Cavitation and Its Chemical Consequences" Phil. Trans. Roy. Soc. London A, 1999, 357, 335-353.

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## Sonocrystallization

Consistent crystallization for API and Excipients

- Classically **Nucleation** is random, and resultant crystallization processes are uncontrolled, leading to poorly performing API, and drug formulations
- Molecules of product assemble in clusters. The clusters will progressively increase in size to become viable crystals



- Controlled** nucleation is fundamental to crystallization control
- Power **ultrasound** via cavitation allows controlled nucleation, i.e. *Sonocrystallization*
- Increasingly recognised and used for manufacturing improvement by *Merck* (Aaron Moment, Jan 2008, Leeds RSC SonoChemistry Conference), *AZ* (Literature), *Pfizer* (Material Science Presentation, Ivan Marziano APS meeting 2007)

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**ECA** **Control of Crystal Size**  
 EUROPEAN COMPLIANCE ACADEMY General Rules on the Effects of Cavitation on a Saturated Solution

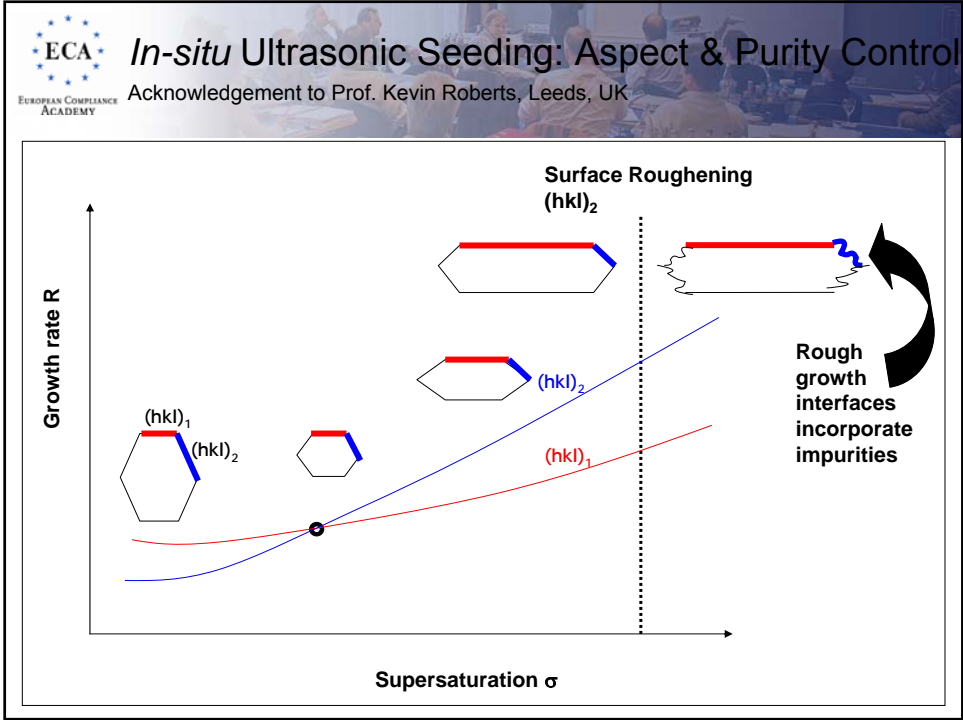
**ULTRASONIC TREATMENT OF SUPERSATURATED SOLUTION**

1. Continuous insonation produces many nuclei resulting in small crystals
2. Initial insonation produces finite nuclei which can be grown into large crystals
3. Pulsed insonation gives tailored crystal size

**ULTRASONIC TREATMENT BEFORE & AFTER CRYSTALLIZATION**

4. Continuous insonation throughout supersaturation produces many nuclei resulting in small crystals. Application of ultrasound thereafter can condition the crystals produced

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**ECA** **Polymorph Control with Ultrasound #1**  
 EUROPEAN COMPLIANCE ACADEMY L-Glutamic Acid

- L-glutamic acid has two polymorphic forms:  $\alpha$  &  $\beta$
- Metastable  $\alpha$ -form: produced under kinetic control
- The transformation of form  $\alpha$  to  $\beta$  is solution mediated
- The metastable form is difficult to obtain
- Use power ultrasound to reproducibly prepare the  $\alpha$  or  $\beta$  form
- Sononucleation at different supersaturation
- **PAT Tool: Online Raman**

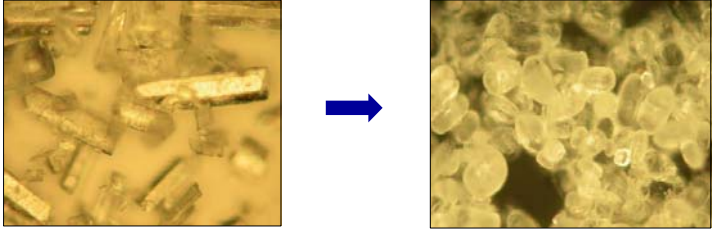
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**ECA** **Polymorph Control with Ultrasound #2**  
 EUROPEAN COMPLIANCE ACADEMY Advanced small molecule API

**Key results: reduced median crystal size, tighter CSD, polymorph control**  
**PAT Tools: Online Raman and Lasentec**

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**ECA** APIs - PRT Improves flowability  
 EUROPEAN COMPLIANCE ACADEMY Diltiazem Hypertension Product

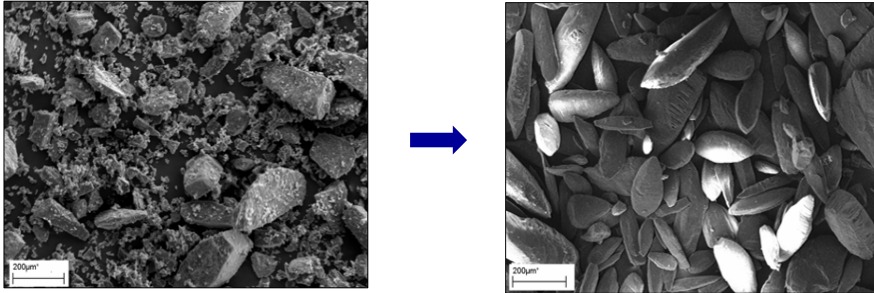


**Raw powder** **Rounded powder**

- Improved uniform packing density of powders
- Enhanced flow of powders
- Reduced electro-static charges
- Manufacturing by direct compression without granulation
- Higher filler loading in composite pastes
- Bypass patents on particle size/shape
- Significantly enhanced flowability
- Improved stability on storage (no agglomeration)

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**ECA** Excipients – PRT applied to Lactose  
 EUROPEAN COMPLIANCE ACADEMY



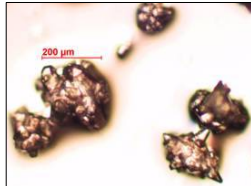
**Raw powder** **Rounded powder**

**PAT Tool: Online Lasentec**

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# Sonocrystallization, Sonomilling, Particle rounding

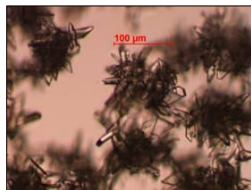
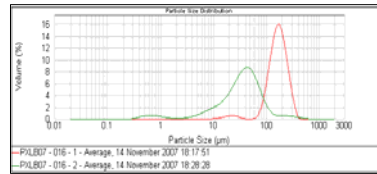
Specific angiotensin II type 1 antagonist - Hypertension



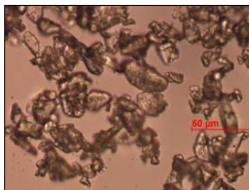
Cooling crystallisation



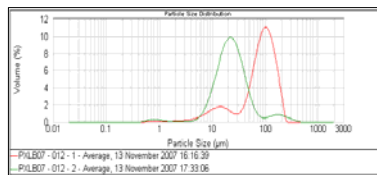
Sonomilling and rounding



Sonocrystallisation



Sonocrystallization,  
Sonomilling and rounding



- Agglomeration and solvent inclusion is avoided
- Circumvent micronisation

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## Sonocrystallization The Key to Controlled Crystallization of Bulk API's and Excipients #2 Commercial Scale Solutions

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## Probe Problems:

Cavitation surface erosion hitherto prohibited commercial use

**Liquid jet penetrates bubble during asymmetric collapse**

**Damage to a solid caused by jet impact and emission of shock waves as a result of repetitive bubble implosions**

Vessel wall  
Probe tip  
Solid surface

Bubble collapse

Jet impact

Bubble implosion  
Liquid in-flow

**Probes can not be used for commercial scale production**

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## Prosonitron™ processing

Surface erosion compared with other ultrasonic devices

Intensity Region	Surface Intensity (W/cm²)	Process Intensity (W/litre)	Characteristics
Low Intensity	0.1 - 1	10 - 100	No Surface Erosion
Medium Intensity	1 - 10	100 - 1000	Possible Surface Erosion
High Intensity	10 - 100	1000 - 100000	Decoupling of Liquid, Cavitation at Surface, Likely Surface Erosion

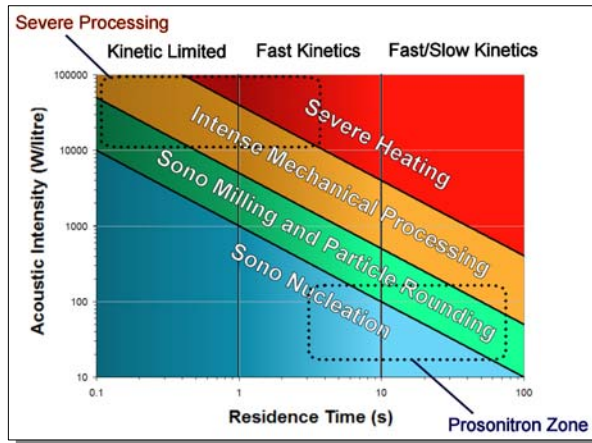
- Spreading of ultrasonic input over the whole surface of the cell allows significant specific power input to the fluid without demanding high surface intensity

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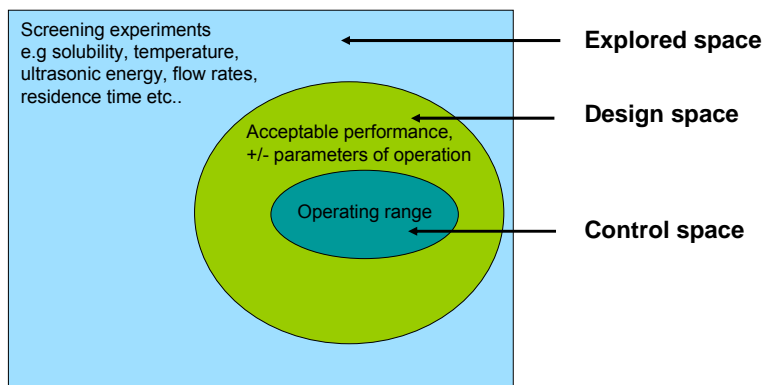
## Consideration of Ultrasonic Design Space

Understand zones of operation to match desired process duty



- Based on Prosonix field experience
- Residence time of several seconds required to allow time for process kinetics, heat transfer and mixing to keep pace
- Particular important consideration in crystallization

## Sonocrystallization Design Space for QbD



Process understanding via:  
**Critical Quality Attributes and Critical Process Parameters**

## Prosonix Ultrasonic Particle Engineering 'Prosonitron™' Technology for Commercial Scale

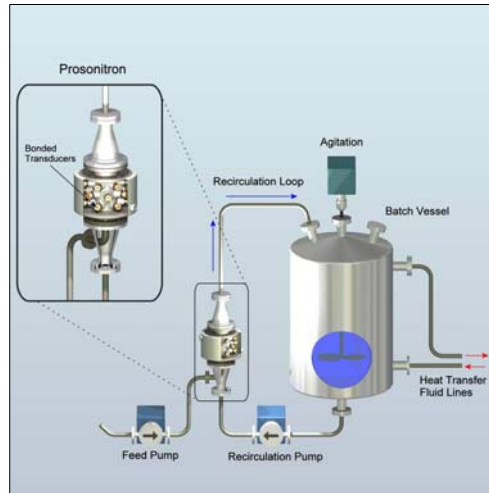


SonoLab™ SL-250



5L Prosonitron™

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## Scale-Up Factors

### Engineering Parameters to Maintain

- **Specific Power Input** – Intensity of acoustic power going into the process liquid (W / litre)
- **Specific Energy Input** – Intensity of acoustic energy used to achieve the process effect (J / litre)
- **Surface Intensity** – Acoustic power per unit area used to supply (W / cm<sup>2</sup>)
- **Residence Time** – Required duration inside field to achieve process effect (s)
- **Reynolds Number** – Internal mixing and flow pattern within acoustic field (-)

### Prosonitron™ Design Benefits

- Ease of maintaining specific power input to the process liquid and surface intensity at all scales.
- Ability to reproduce flow regime and residence time by configuration choice.
- Result is a system that can deliver consistent processing throughout scale-up from pilot to production.

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## PAT & Complete Crystallization Control™

- Use CQA's and CPP's to understand and control manufacturing
- Use ultrasonic technology at scale to provide real time process control
- Need online measurement and feedback to achieve:
  - Control of ultrasonic energy
  - Control of temperature profiles
  - Turbidity / Lasentech for onset of nucleation
  - Particle size distribution
  - Polymorphic forms in solution
  - Supersaturation ?

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## Prosonitron™ – Proven at commercial scale

*"Best available crystallization technology"* potential in pharma production

- Prosonitron™ at Pfizer, UCB & others...
- Pfizer Ireland acquire Prosonitron™ technology for Primary API Manufacture
- 4 year co-development relationship with UCB
- Many new & current trials at major and specialty pharma worldwide
- Primary for oral, but exciting developments in inhalation, nanosuspensions, parenteral, sub Q, and dermatological delivery



Prosonitron™ linked to Lasentec



- Prosonitron™ system in operation in alumina
- Over 3 years continuous service to date
- Follow on global deal with Alcoa

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## Advanced Particle Engineering of Difficult to Manufacture products

e.g. Delivery by Inhalation

## Product properties of particulate systems

Its much more than just size control....

**Product property =  $f$ (Dispersity, Chemical Composition)**

- Dispersity characterised by:
  - Particle Size
    - Aerodynamic  $\varnothing$  0.5 - 5 $\mu$ m
  - Particle Shape
    - Conferred spherical geometry
  - Particle Surface Morphology
    - Minimise surface free energy - crystals
  - Particle Surface properties
    - Reduce contact area - spherical, rugged surface
- Control of interfacial interactions (adhesion/cohesion) is governed by surface forces
- Geometry, not surface chemistry, is the central design principle in controlling interfaces and their interactions.

***Design of particles for end use properties!***

## Solution to Particle Technologies

Dr Ivan Marziano, Pfizer Material Science, APS Inhalation meeting 28 March 2007

### Micronisation is often not feasible for inhaled medicines!

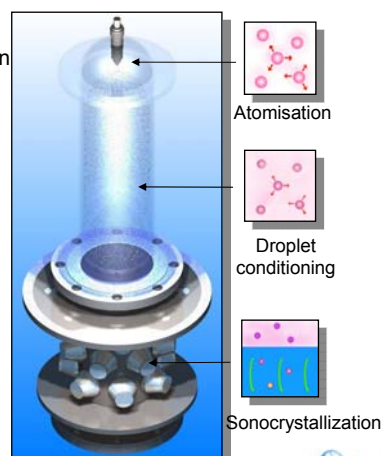
*Solution to Particle technologies are based on the formation of highly supersaturated droplets either through spraying or dispersion in non-miscible media; Particle growth occurs within confined space (= droplet)*

- Aerosol flow reactor (VTT)
- SAX™: solution atomisation and crystallization by sonication (**Prosonix**)
- Emulsion crystallization
- Quasi emulsion/spherical crystallization
- Cryogenic spray freezing/liquid extraction
- Spray freezing into liquids/spray freeze drying
- Spray drying
- EPAS: evaporative precipitation into aqueous solution (Dow)
- Segregated flow tubular reactor ("Bubbletube")

## SAX™ – New "Solution to Particle" Technology

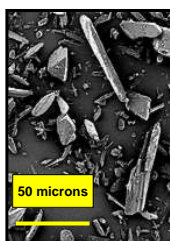
The future solution to ultimate particle control ?

- SAX™ builds on the Prosonitron™ IP
- Designed to produce 1 to 5 µm crystalline combination particles tailored uniquely for inhalation
- 20 customer studies completed to date
- Combination of proven unit operations:
  - Solution of API / mixtures of API + excipients
  - Atomization creates spherical droplets
  - Controlled evaporation
  - Controlled crystallization by Sonocrystallization
  - Simple and proven isolation procedure
- Tested on a range of APIs and NCEs
  - Stable crystalline particles
  - Combinations of 2 or 3 drugs possible
  - Improved *in-vitro* performance



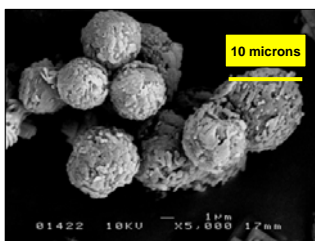
**ECA** **Unprecedented Process & Product Control**  
 EUROPEAN COMPLIANCE ACADEMY Optimal SAX™ drug particles should give better inhalation clinical performance

- Current destructive (i.e. micronisation) production techniques are severely limited
- API particles can be fully engineered from the the “ground up” via controlled SAX crystallization
- Improved SAX™ drug particles gives optimum formulation performance and patient benefit across all inhalation delivery platforms



**Micronisation**

Size



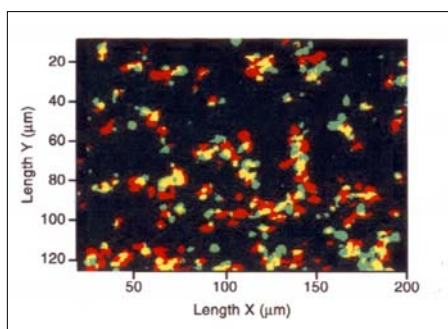
**SAX™**

- Size
- Shape
- Surface Morphology
- Surface properties
- Crystallinity
- Stability

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**ECA** **Seretide Combination: Single vs separate inhalers?**  
 EUROPEAN COMPLIANCE ACADEMY Nelson et al J. Allergy Clin. Immunol. Vol 112 (1), 2003, 30



Raman laser analysis of Seretide metered-dose inhaler formulation on stage 4 ACI

*Key:*  
 Fluticasone (green),  
 Salmeterol (red)  
 Co-association (yellow)

- 4 Separate clinical studies showed equivalence viz primary efficacy
- Consistent trend in favour of combination therapy
- Increased efficacy over concurrent use of same doses of same 2 drugs
- Co-deposition offers increased opportunity for synergistic interaction

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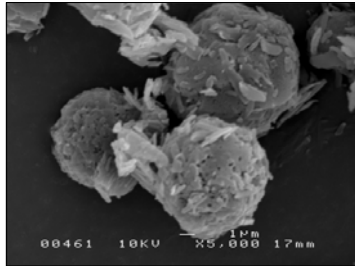
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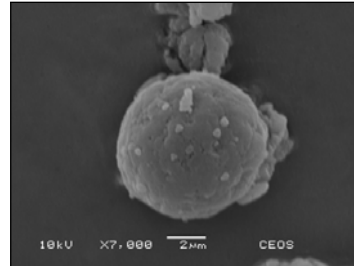
## SAX™ - Designed Combination Particles

A new way to treat Asthma/COPD and other disease states?

- Eliminate variability associated with blending of 2 or more micronised powders
- Multiple API's in the correct dose ratio can be symbiotically crystallized in a single perfect particle
- Controlled Combination Therapy Delivery



Fluticasone and Salmeterol (1:3.448)



Budesonide and Formoterol (1:17.71)

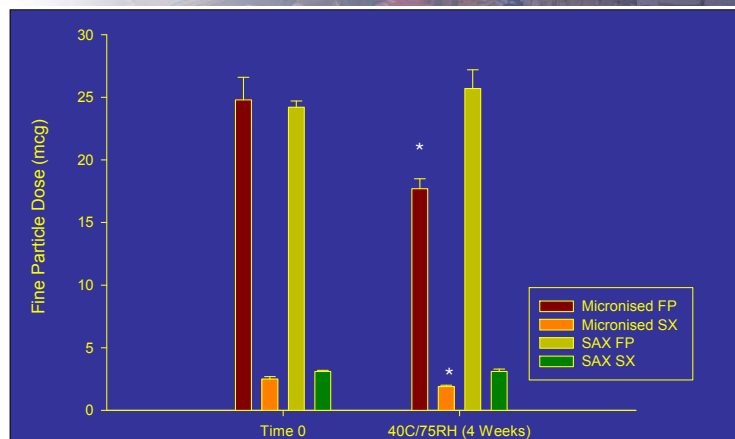
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## Improved Product Stability with SAX™

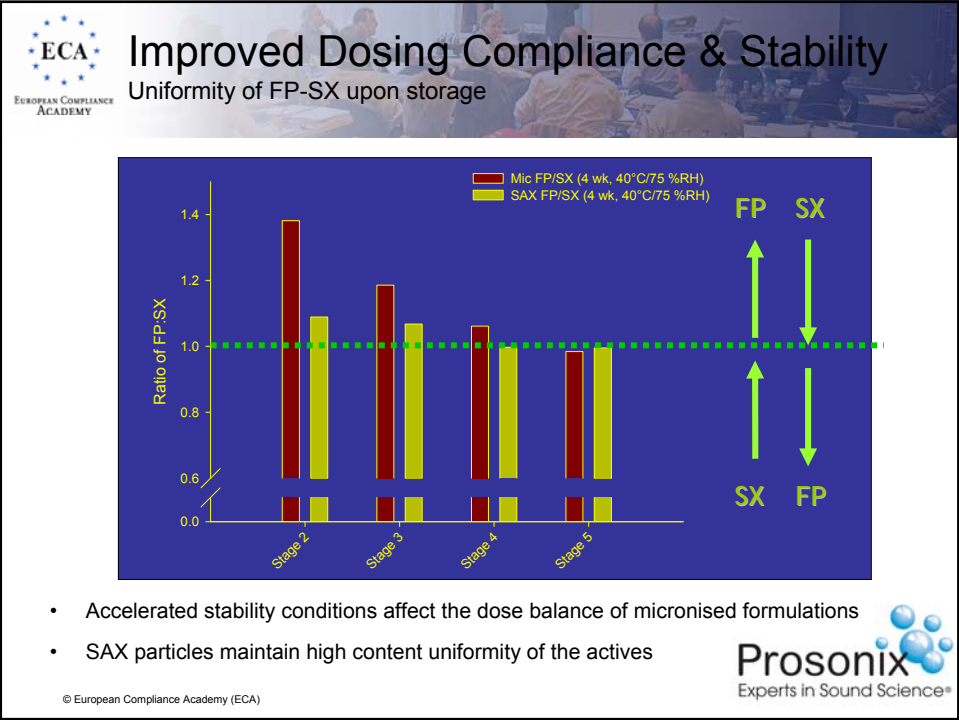
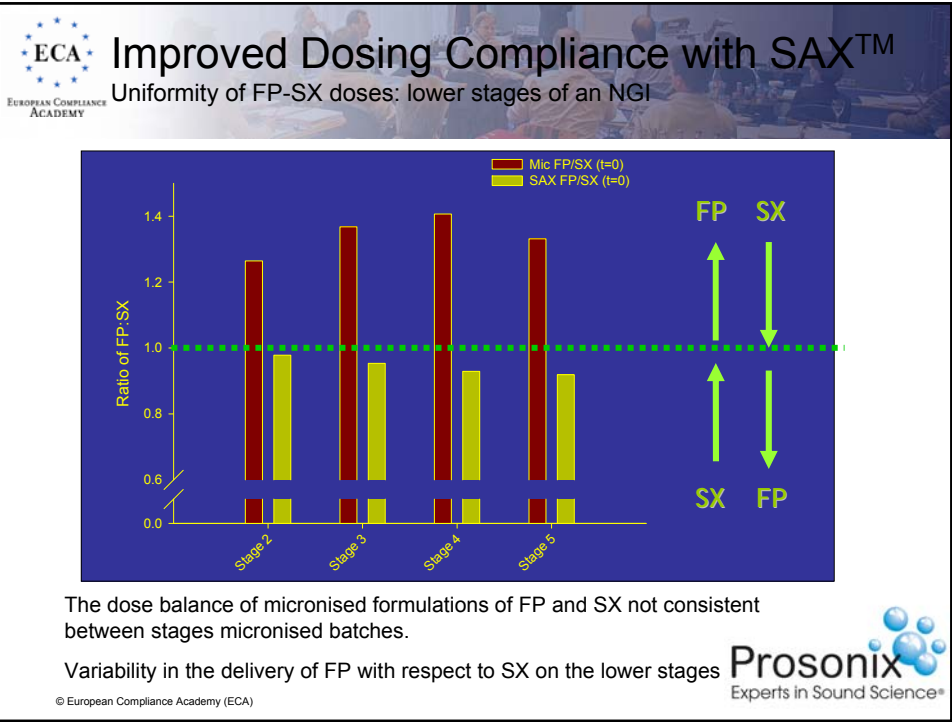
Carrier based DPI formulation



- Carrier based DPI formulations (FP: SX 1:5)
- In vitro apparatus: NGI @ 60 L/min; Monohaler DPI device
- Seamless transition and increased stability

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## Summary

- Now possible to engineer and produce “Designed for Purpose” Particles
- QbD provides process understanding
- PAT provides repeatable and robust processes
- Key benefits include
  - Control particle size, shape, crystallinity, polymorphism
  - Improved batch consistency, filtration, isolation and drying
  - Replacement of problem physical seeding
  - Increased cGMP compliance
  - Improved formulation consistency, stability and performance
  - Increased return on investment
  - Reduced time to market
- Ultrasonic Particle Engineering and Sonocrystallization gives levels of control over isolation that current manufacture cannot deliver

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