Material Processing Technologies

MATERIAL PROCESSING

Pharmaceutical Technologies International, Inc.
Princeton, New Jersey, USA

# Particle Size Reduction
# MILLING TECHNOLOGY

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QUADRO Leading Process Equipment Innovation

FITZPATRICK®

Microfluidics

# Agenda

1. INTRODUCTION TO QUADRO, MPT, & IDEX
2. SIZE REDUCTION OVERVIEW
3. EVOLUTION OF MILLING TECHNOLOGY
4. OVERVIEW OF COMMON MILLING TECHNOLOGIES
5. CONICAL MILLING TECHNOLOGY
6. MILL SELECTION CRITERIA

# About Quadro

- **History: Since 1976**
- **Manufacturing: 45,000 $ft^2$ (4180 $m^2$)**
- **Employees: 93**
- **In-house Engineering**
- **Machining, Welding, Polishing, Electrical, Assembly**
- **ISO Registered, cGMP**
- **R&D Center**

# About Quadro

- **Part of IDEX Corporation since 2007**
- **Member of Material Processing Technologies (MPT) platform along with**
  - **The Fitzpatrick Company, Illinois**
  - **Microfluidics, Mass.**
  - **Matcon, UK**



# Size Reduction Overview

## Advantages of Compressed Tablets (Oral Solid Dosage)

- Accurate dosage of medicament
- Easy to transport - bulk and by patient
- Uniform final product - weight and appearance
- Usually more stable than liquid medicines
- Release rate of drug can be varied
- Mass production - simple and quick & low cost

# Size Reduction Overview

***Size reduction is an essential process requirement in the practice of Solid Dosage Preparation***

***The capability to produce a tight particle distribution suitable for compaction and dissolution is directly dependent on the mechanism selected for size reduction***

# Size Reduction Overview

## Tablet Manufacturing

- **Objectives**
  - Uniformity
  - Potency
  - Batch to batch reproducibility
  - Damage resistance
  - Lack of defects

- **How**
  - ✓ Powders must flow
  - ✓ Powders must compress
  - ✓ Particles must lock together
  - ✓ PSD control → Weight control

# Size Reduction Overview

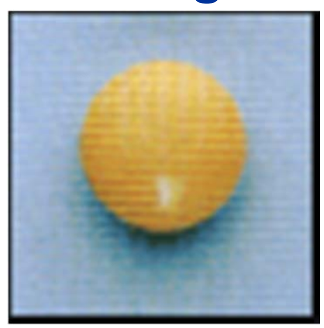
## Common Tableting Problems


Capping

Sticking

Chipping

Breaking



Discoloring

Porosity

Tablet weight is the key to controlling hardness and friability.

Controlling tablet weights within a tight range will contribute to better tablet hardness and friability.

**Key weight control factors are product uniformity in particle size & density**

## Size Reduction Overview

### *Why Size Reduce*

- Increase Surface Area
- Create Homogeneity
- Control Bulk Density
- Prepare Products for Post Processes

- Specifically for Tablets:
  - Increase bioavailability
  - Improve Flow
  - Reduce Segregation
  - Enhance Drying
  - Control Particle size
  - Repeatability – Batch to Batch

## What Affects Size Reduction?

- Mechanical – Sizing Method (Type of Equipment)
- Fracture Mechanics of Particles – Types of Granules
- Properties of OSD ingredients:
  - **Active Pharmaceutical Ingredient (API)**
  - **Excipients - Inactive "helpers":**
    - Anti-adherents/Lubricants: e.g. Magnesium Stearate
    - Binders
      - Wet: Gelatin, Starch, Sucrose, Glycol (dissolved in water or alcohol)
      - Dry: MCC, Polyethylene Glycol
    - Fillers: Lactose, Sorbitol, Calcium Carbonate
    - Flavouring/Colouring
    - Preservatives: Benzoic Acid, Cresol, Parabens, etc.
- Other physical properties – friability, toughness, abrasiveness, corrosiveness, etc.

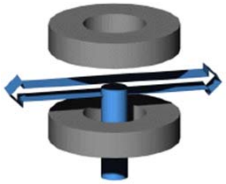
## Common Size Reduction Mechanisms

**Size reduction equipment is available in many different designs, however, they all stem from four basic principles:**

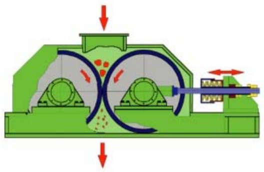
- **IMPACT:** particle concussion by a single force
- **COMPRESSION:** particle disintegration by two rigid forces
- **SHEAR:** produced by particle to particle interaction
- **ATTRITION:** arising from particles scraping against one another or against a rigid surface



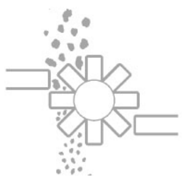
# EVOLUTION OF MILLING TECHNOLOGY



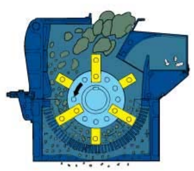
***Stone Grinder***



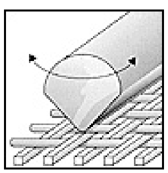
***Roll Crusher***



***Lump Breaker***



***Hammer Mill***



***Oscillator***

***Tornado Mill***

**Approx.
50 Years**

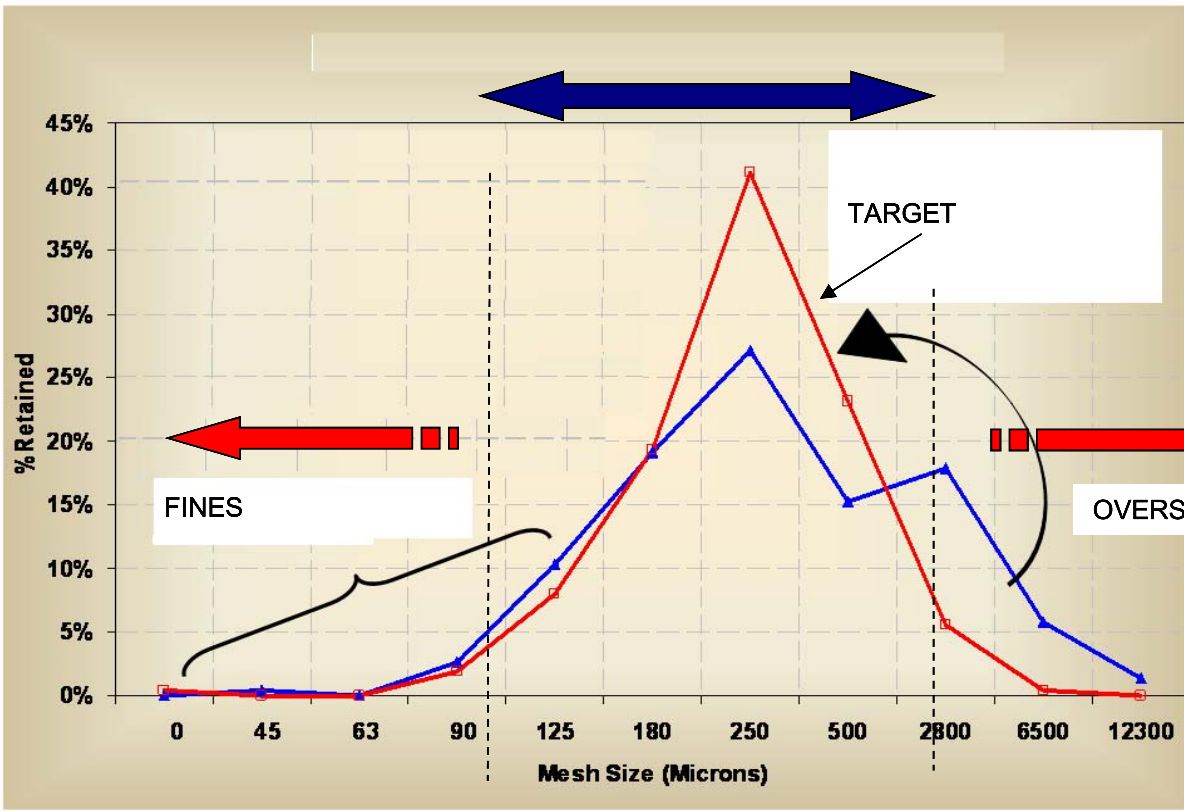
**Approx. 80 Years of recorded history**

**Conical Screen Mill**

**The most common method over the last 30 years**

# Milling

One of the most essential process requirements in the practice of Solid Dosage Manufacturing



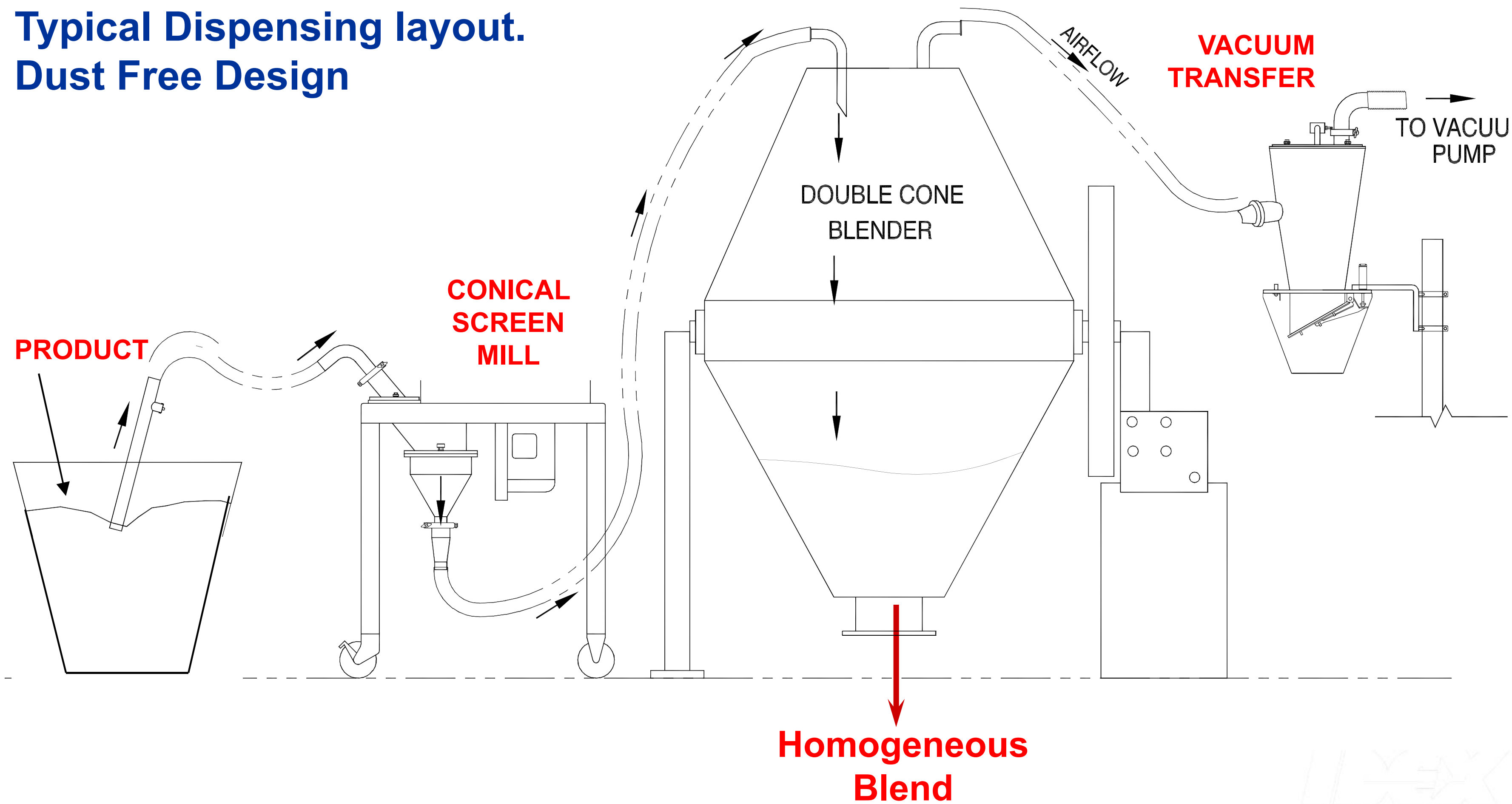

PARTICLE SIZE DISTRIBUTION BELL CURVE

## Common Milling Applications in the Manufacturing Process

- Dispensing – **De-agglomeration and security screen**
- Pre-Milling – **Particle Size Distribution**
- Post Granulating – **De-agglomeration/Dispersion**
- Dry Milling – **Sizing Dried Blend**
- Final Milling – **Size/De-lump/Calibrate**
- Reclaim - **Off-Spec Tablets/Compacts**

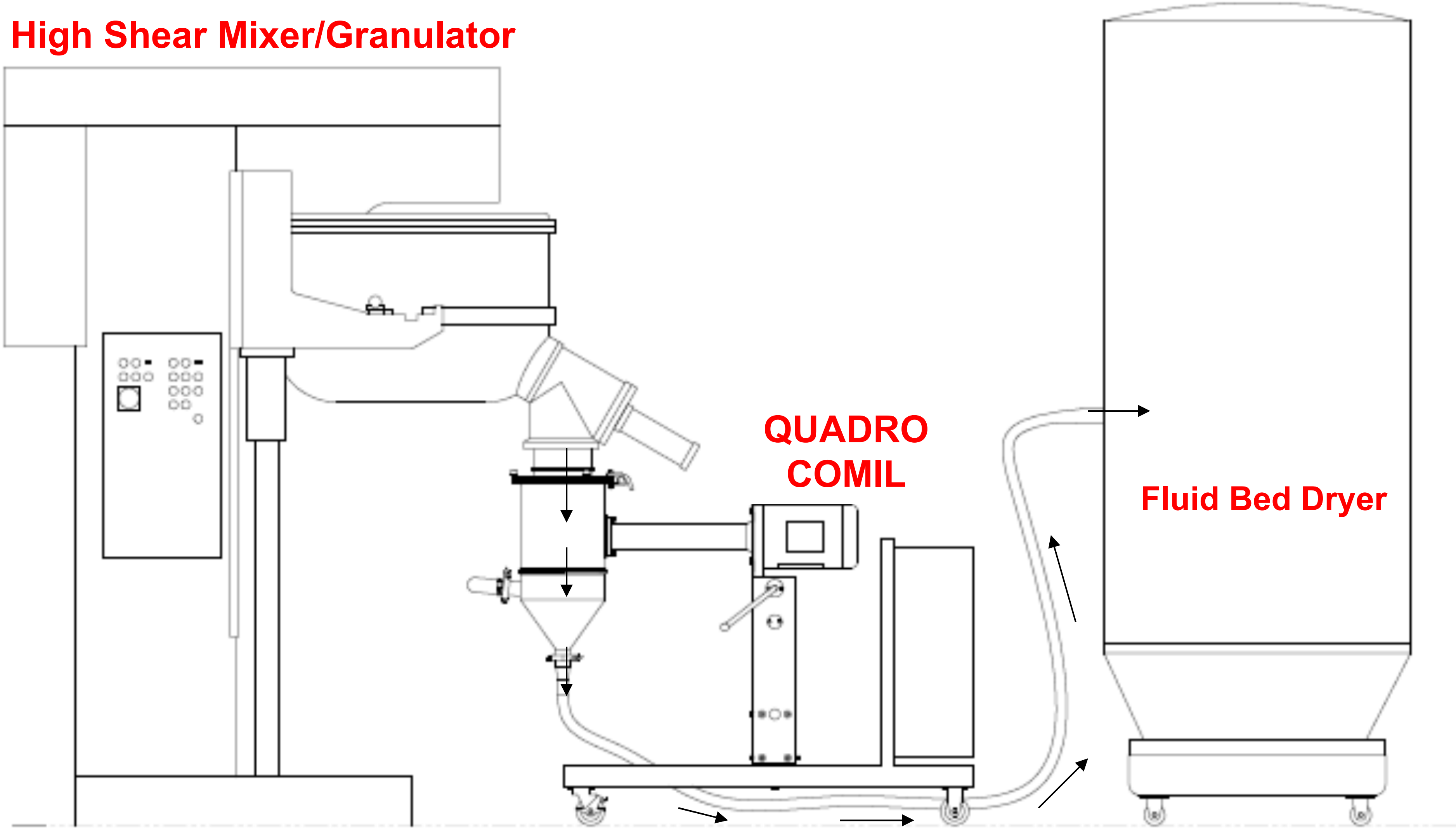
# Milling

## Typical Dispensing layout.
## Dust Free Design



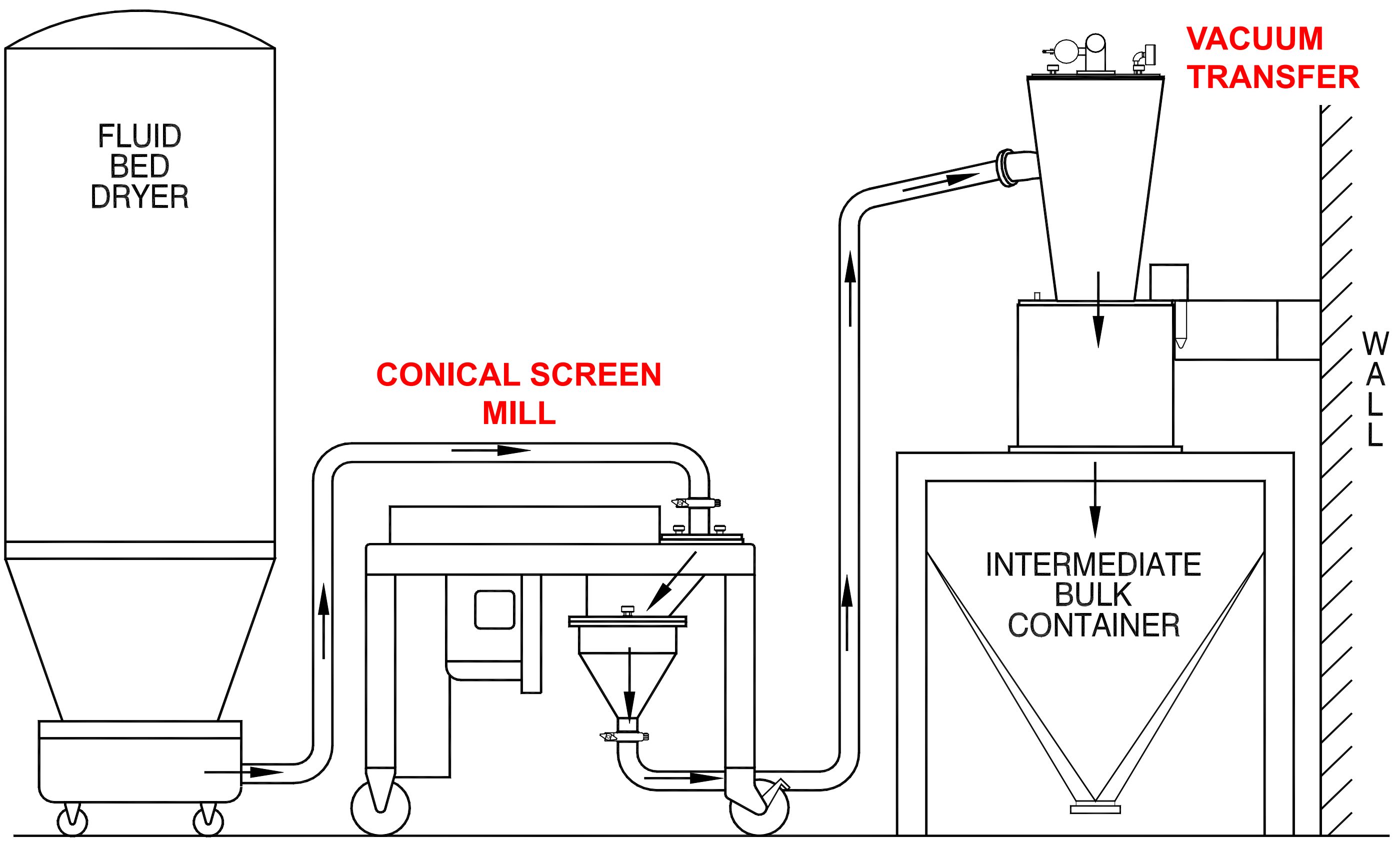
# Milling

## Wet Dispersion Prior To Drying - Typical Integrated Design



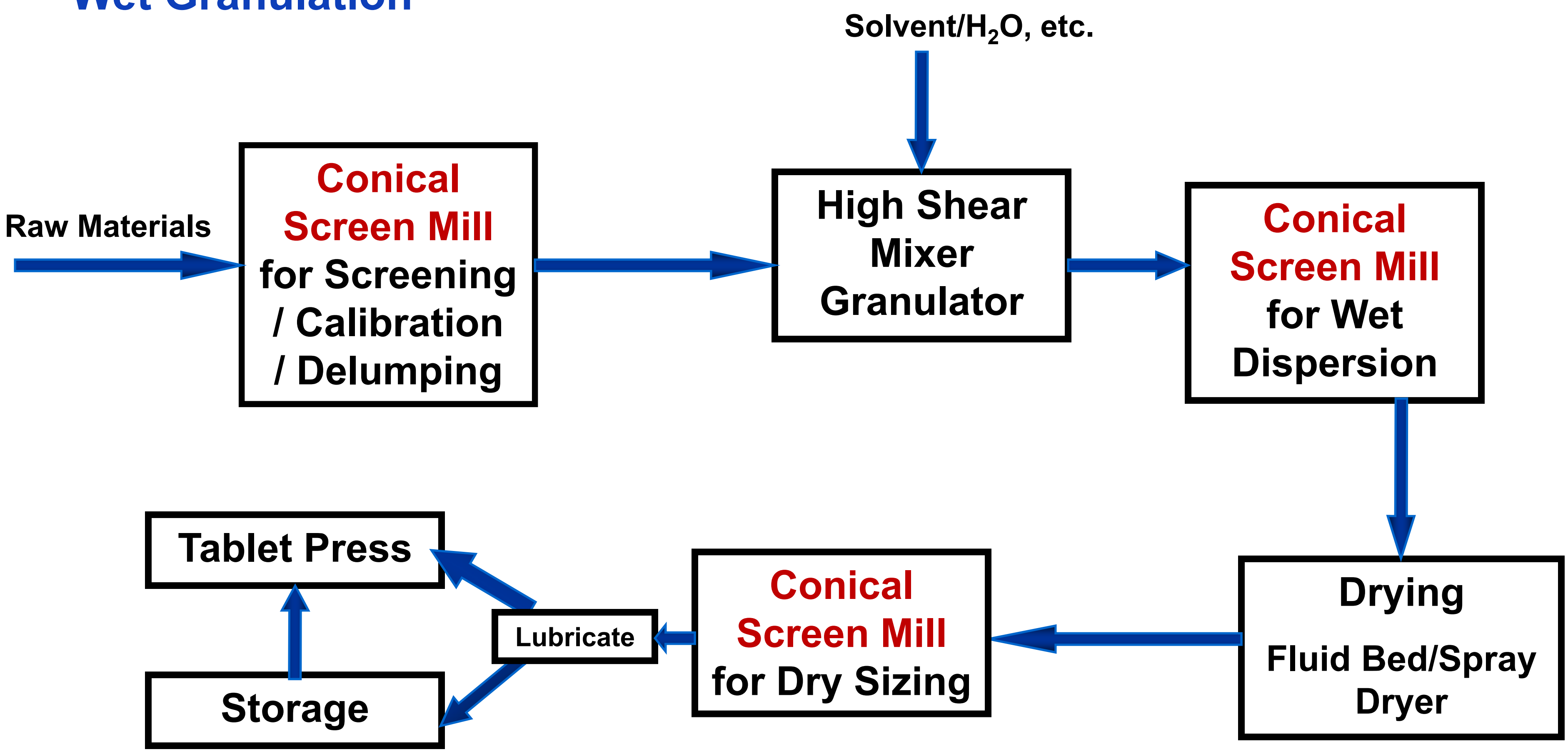
# Milling

## Dry Milling After Fluid Bed Dryer
## Typical Integrated Design c/w Vacuum Transfer



# Tablet Manufacturing

## Wet Granulation



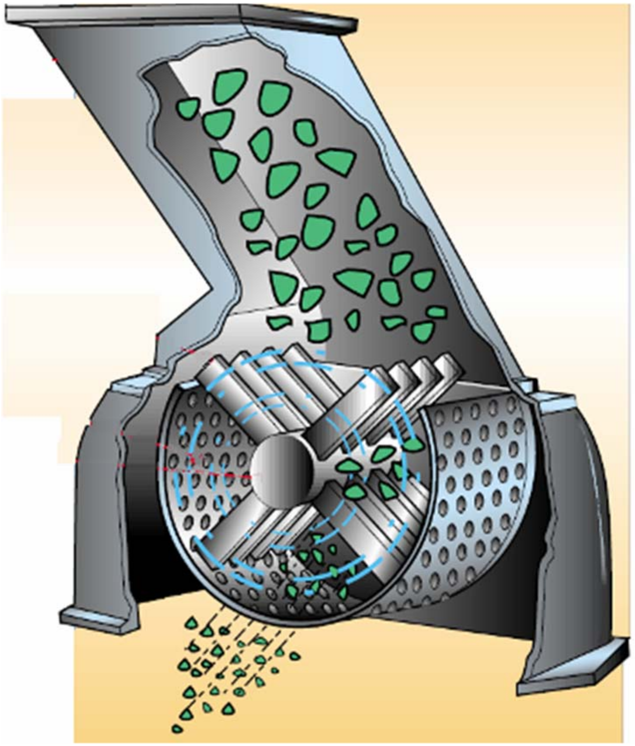

GEA
Niro Pharma Systems
Aeromatic-Fielder AG
Comil U20
Wet Milling - Direct Discharge

**Fully Integrated Solid Dosage Preparation Plant**
**(Class 100,000 Room)**


Comil U20
Wet Milling - Direct Discharge

# Hammer Mill

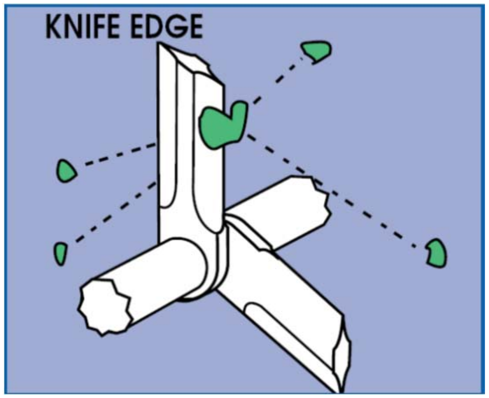
- High shear mechanism
- Various In-feed designs
- Variable speed, blade & hammer assembly
- 120° discharge area
- Common output range
  (6” – 12” – 30” wide screens)

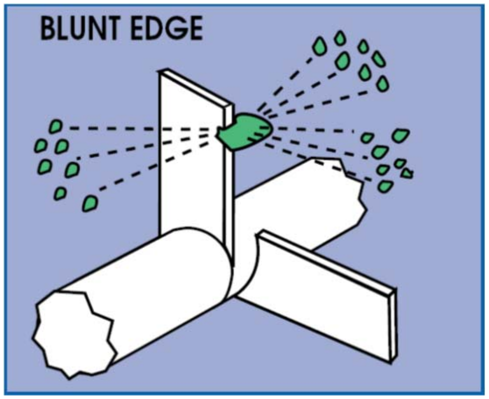


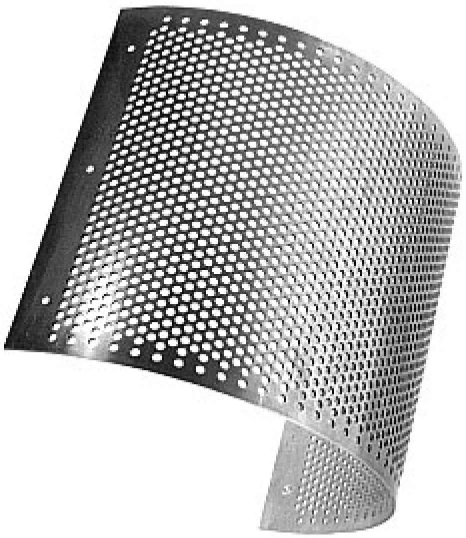
## Hammer Mill Cont…

### Blade & Screen Types

- The blade assembly is reversible.
- The most common blade arrangement is one blunt edge and one knife edge.
- Product can be hammered or cut.
- Hardened Blades available for abrasive applications



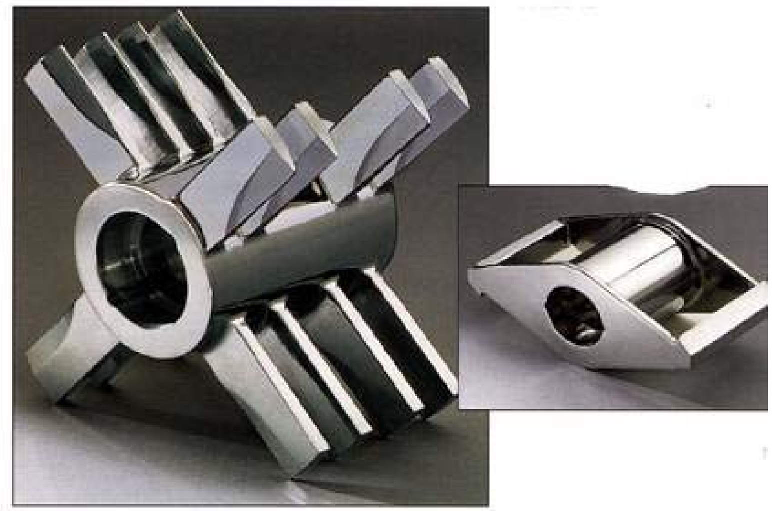



# Milling Technologies

## Hammer Mill Cont…

- Hammer Mills require control feed.
- Changes in feed rates may change product retention time.
  - **will effect products that can easily dense**
  - **increased fines & friction**
  - **will effect products with low melting temperature**



# Milling Technologies

## Hammer Mill Cont…

### Advantages

- Wide range in Size
- Medium  to High Shear
- Vertical/Horizontal Designs
- Blades/Screens Interchangeable
- Suitable for Milling Hard Materials

### Disadvantages

- High Noise Levels
- % Fines High
- Must be control-fed
- Belt Slip Common
- High Dusting
- Ventilation Requirement
- Screen change complex
- Difficult to Scale-Up

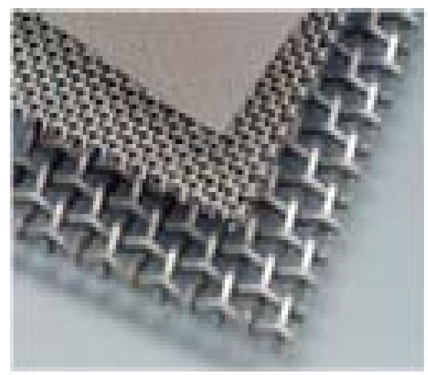
# Oscillator

- This machine was commonly used in the past for low shear applications.
- Some similar designs are continuous and do not oscillate.
- Suitable for low volume manufacturing.

# Oscillator Cont…

- Uses mesh screens, not perforated plates.
- Cast Body
- Discharge - tray or drum
- High Wear rate.






# Oscillator Cont…

## Advantages

- Gentle
- Easy to operate
- Fixed speed
- Low cost equipment
- Low Tech Functions
- Portable

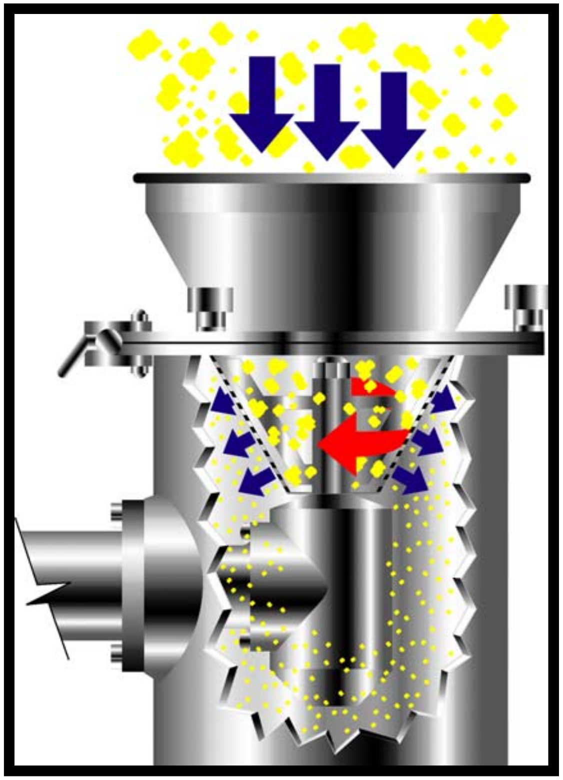
## Disadvantages

- Low Capacity
- Metal to Metal contact
- Non GMP design
- Not suitable for integrated processes
- Cleaning - complex
- Loss of Active material

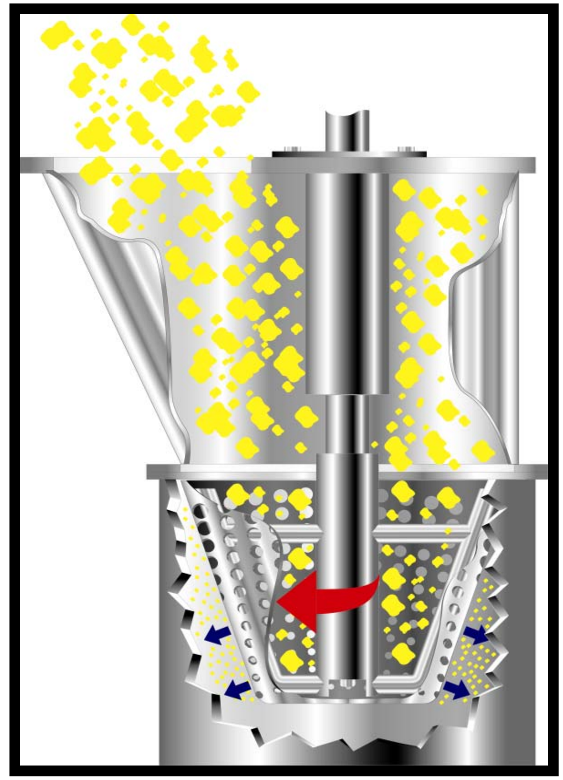
# Conical Milling

- Infeed falls into conical screen chamber
- Rotating impeller imparts vortex flow pattern to infeed material
- Centrifugal acceleration forces particulates to screen surface
- Particles are continuously delivered to “action zone” between screen and impeller
- Particles are size reduced (as fine as 150 micron) and instantly discharged through screen openings

# Conical Milling



Underdriven Comil
(Invented 1990)

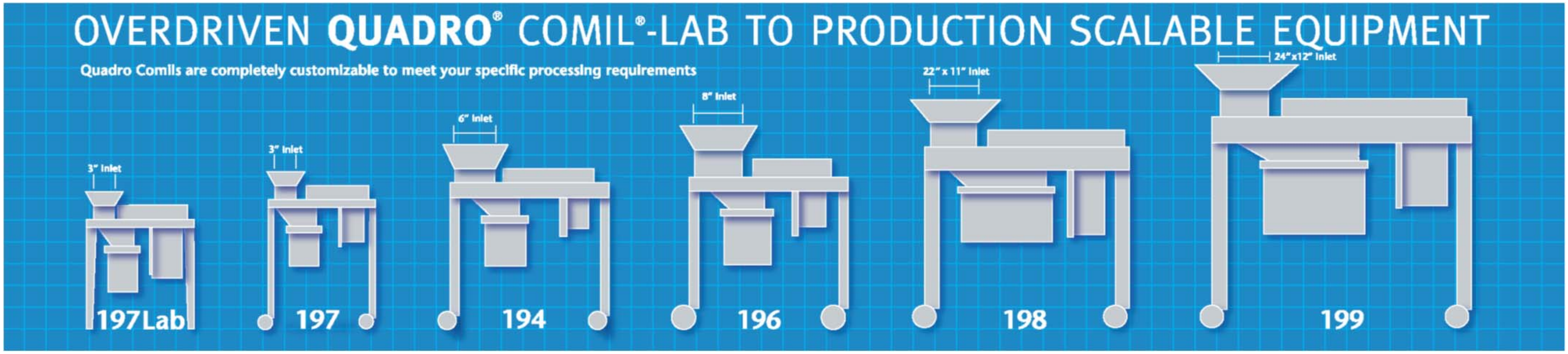


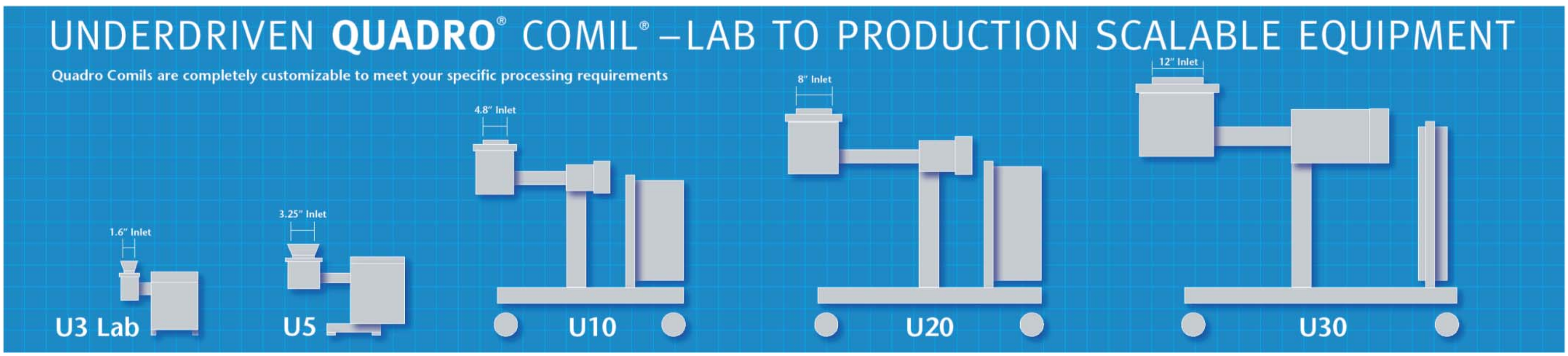
Overdriven Comil
(Invented 1976)

# Conical Milling – Quadro COMIL

| Scale | Quadro Comil Model | | Power | Standard Impeller speed | Scale-Up Factor | Tip Speed M/sec (Ft/min) | Screen Diameter | Capacity Lb/hr (kg/hr) |
|---|---|---|---|---|---|---|---|---|
| | OVERDRIVEN | UNDERDRIVEN | | | | | | |
| Lab | | U3 | 0.246 KW (0.33 hp) | 4500 RPM | 0.25X | 14.2 (2800) | 2.55” (65mm) | From 3oz/100g to 220lb (100kg) |
| | | U5 | 0.375 KW (0.5 hp) | 3450 RPM | 0.5X | 14.2 (2800) | 3.25” (83mm) | 425 (195) |
| Pilot | 197 | U10 | 1.5 KW (2.0 hp) | 2400 RPM | 1 X | 14.2 (2800) | 4.84” (123mm) | 800-850 (360-390) |
| Production | 194 | U20 | 4.0 KW (5.4 hp) | 1400 RPM | 5 X | 14.2 (2800) | 8.2” (208mm) | 3900-4250 (1750-1950) |
| | 196 | U30 | 7.5 KW (10 hp) | 900 RPM | 10 X | 14.2 (2800) | 12.17” (309mm) | 7800-8500 (3500-3900) |
| Large Production | 198 | | 15 KW (20 hp) | 450 RPM | 20 X | 14.2 (2800) | 24” (609mm) | 15,600 (7000) |
| | 199 | | 22 KW (30 hp) | 360 RPM | 40 X | 14.2 (2800) | 30” (761mm) | 20,000 (9000) |

# Conical Milling – Quadro COMIL



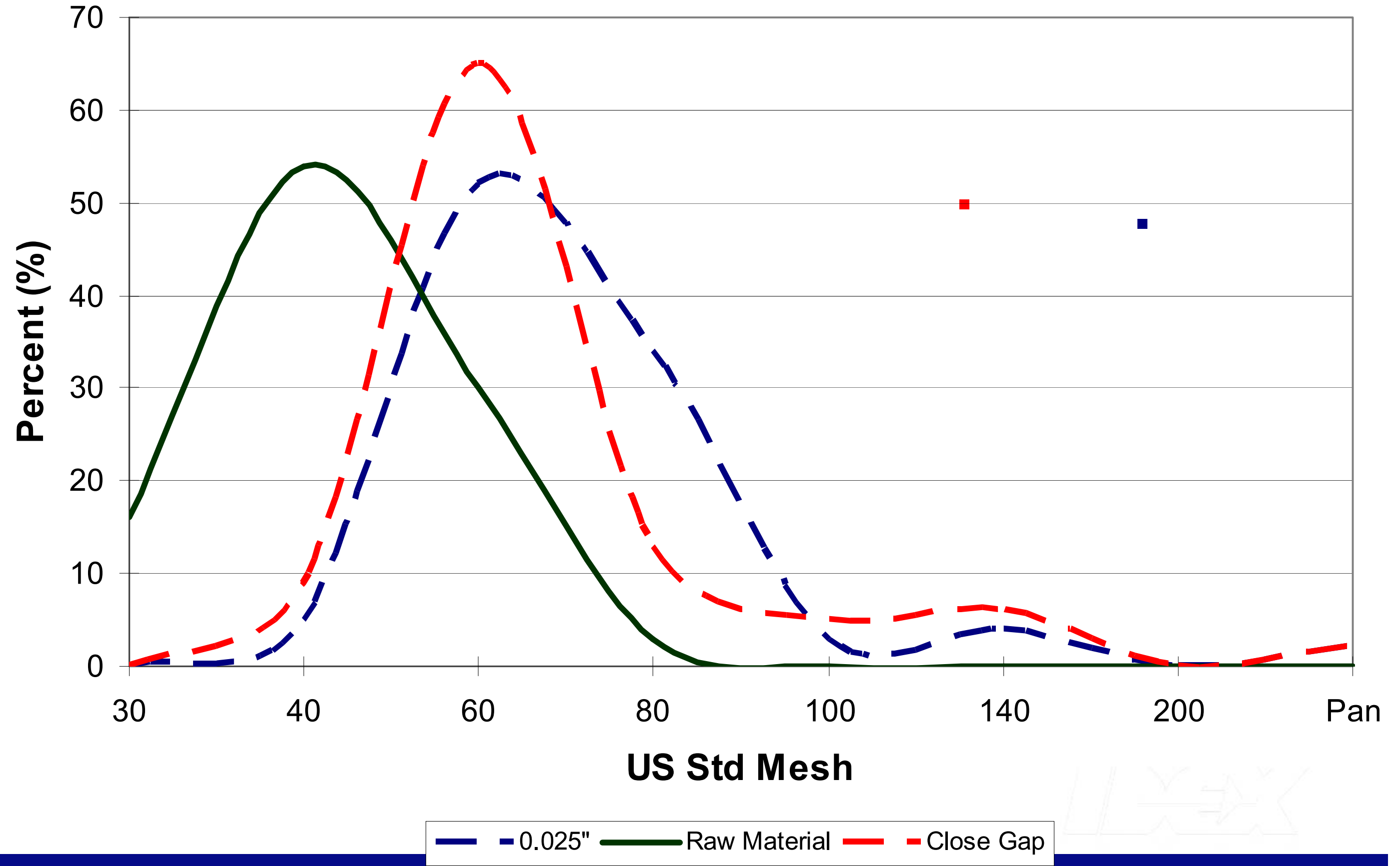



# Conical Milling

## Critical Factors for Optimum Conical Milling Characteristics

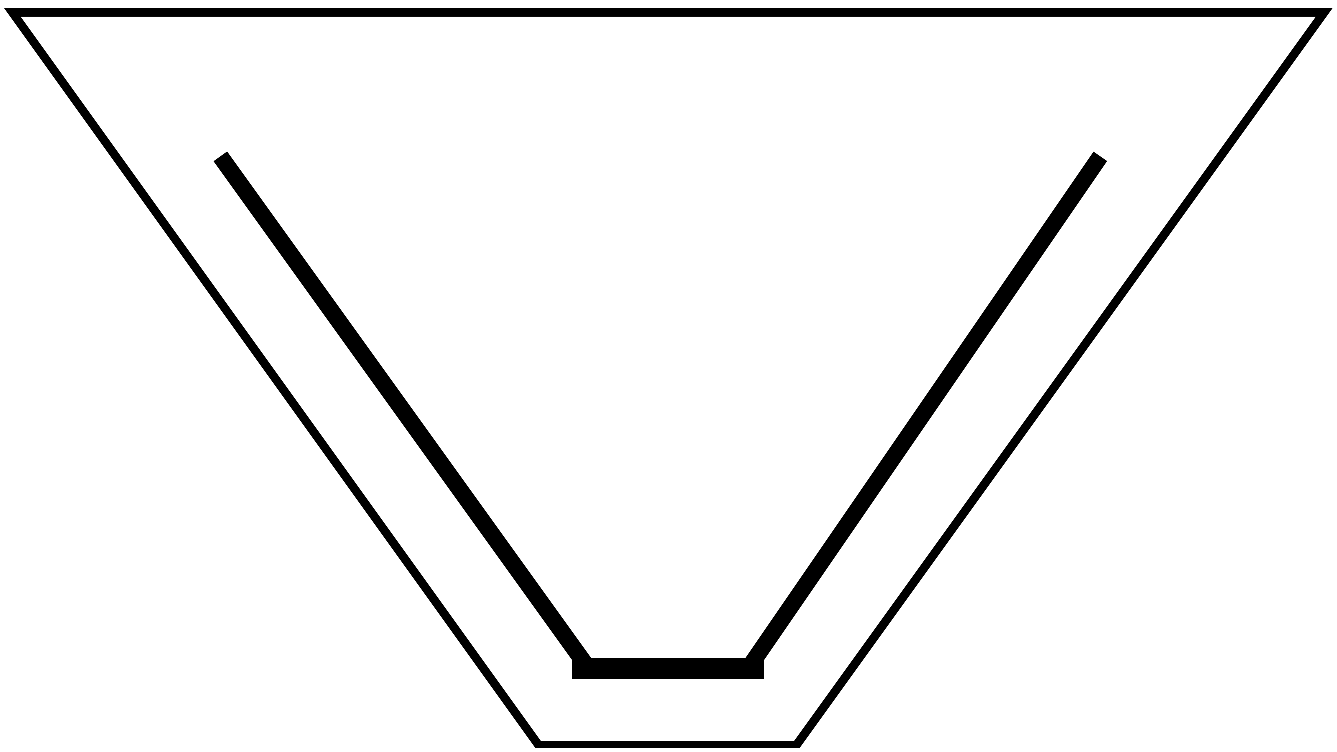
### Close impeller / Screen Gap

- Less fines
- High Yield

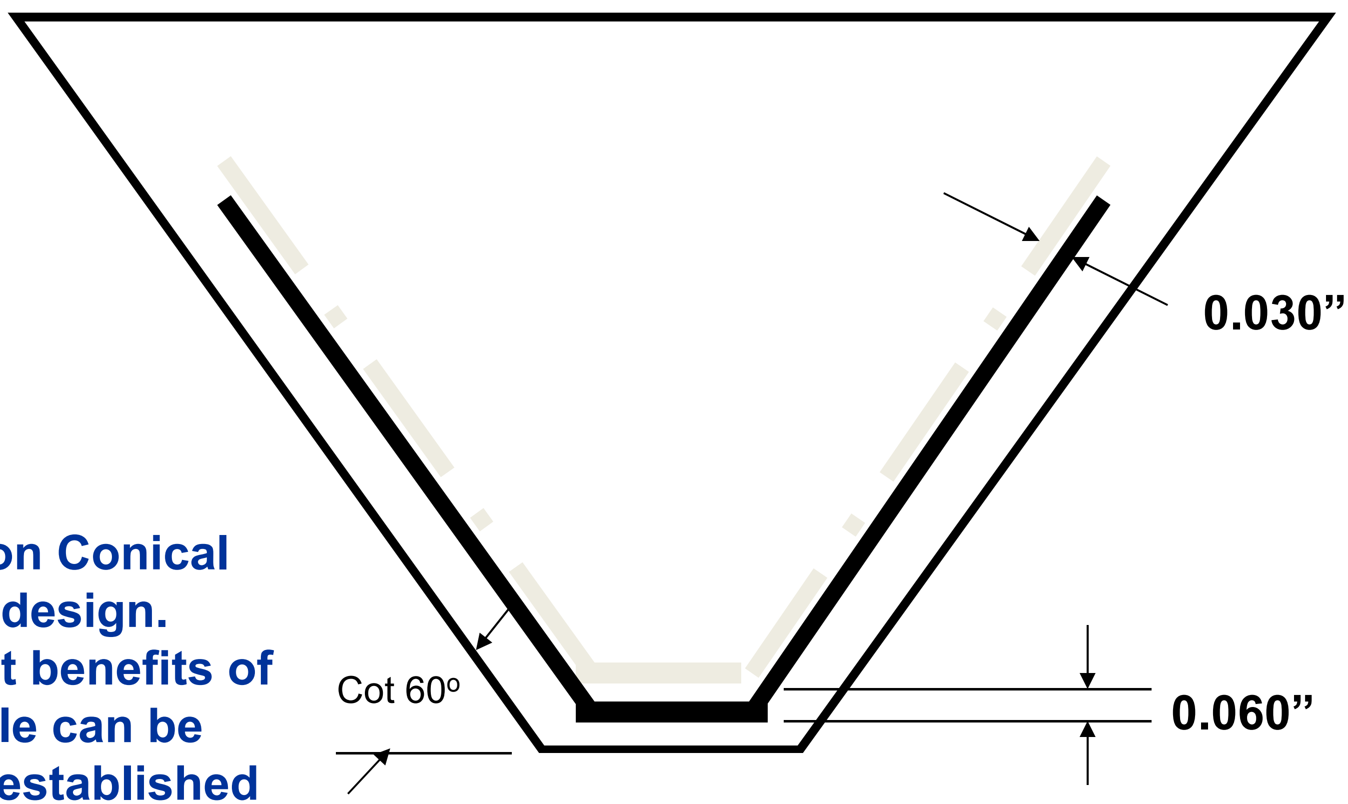


# Conical Milling

## Critical Milling Factors:
## Close Gap



## Critical Milling Factors:
## Close Gap



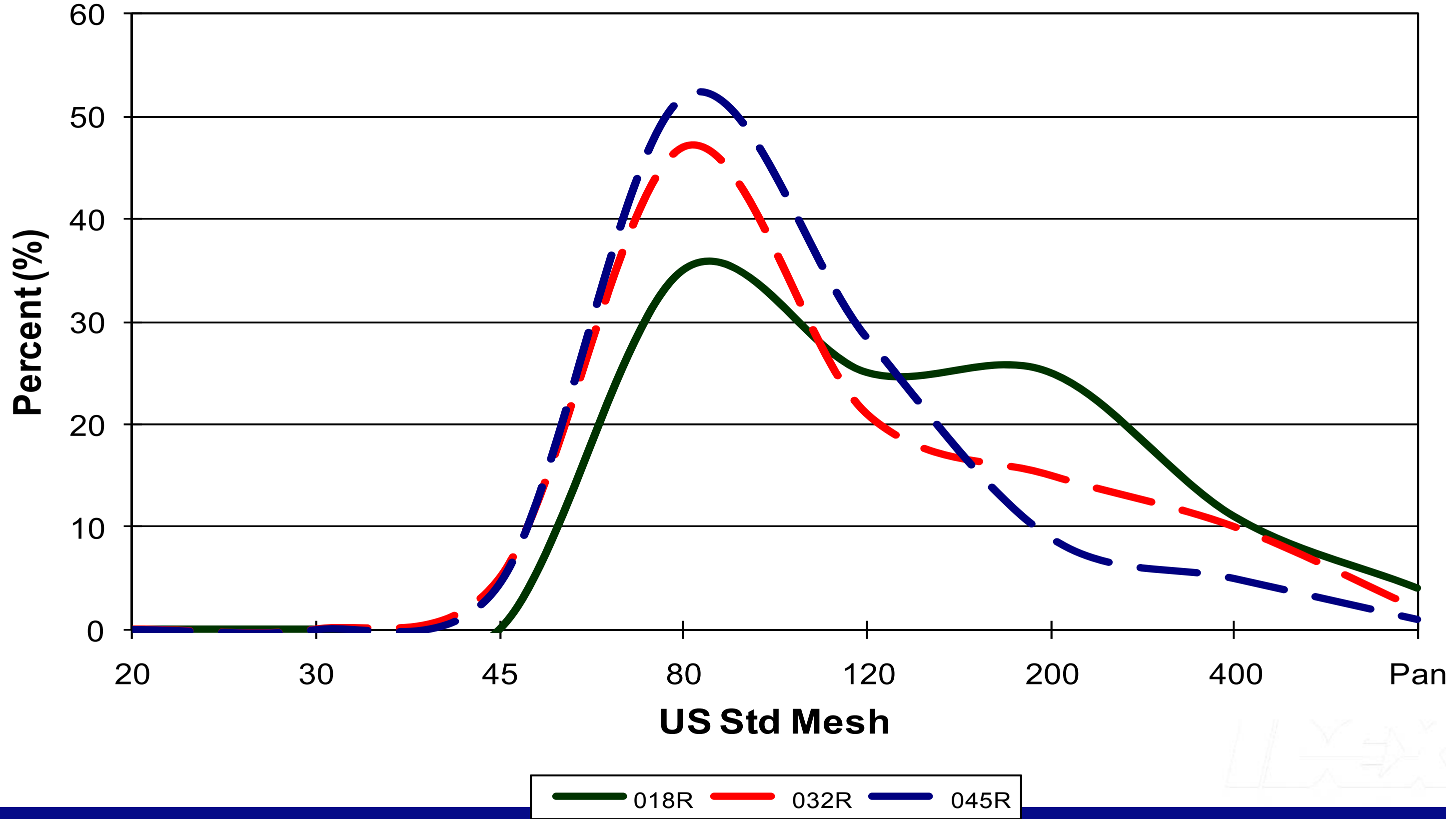

**Based on Conical Screen design. Inherent benefits of the angle can be readily established as a 2:1 ratio.**

# Conical Milling

## Critical Factors for Optimum Conical Milling Characteristics

### Proper Tooling Selection – Screens

**Effect of screen hole size on particle size distribution: generally a finer screen produces more fines and less overs.**



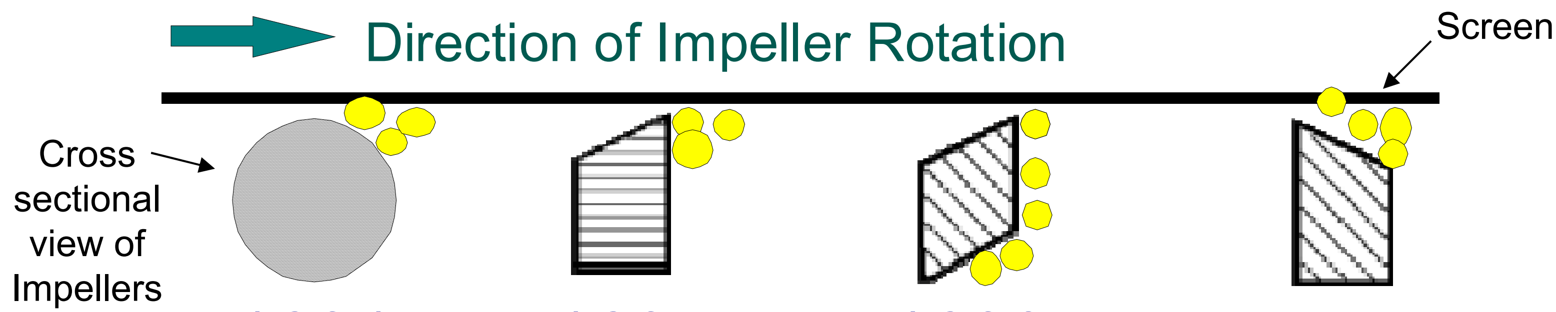
# Conical Milling

**Critical Milling Factors:**
**Proper Tooling Selection - Screens**

| R | Q | S | G |
| --- | --- | --- | --- |
| R – Round holes (Dry Material) | Q - Square holes (Wet Material) | S – Slotted (Pseudo Plastic) | G - Grater holes (Hard & Dry) |

# Conical Milling

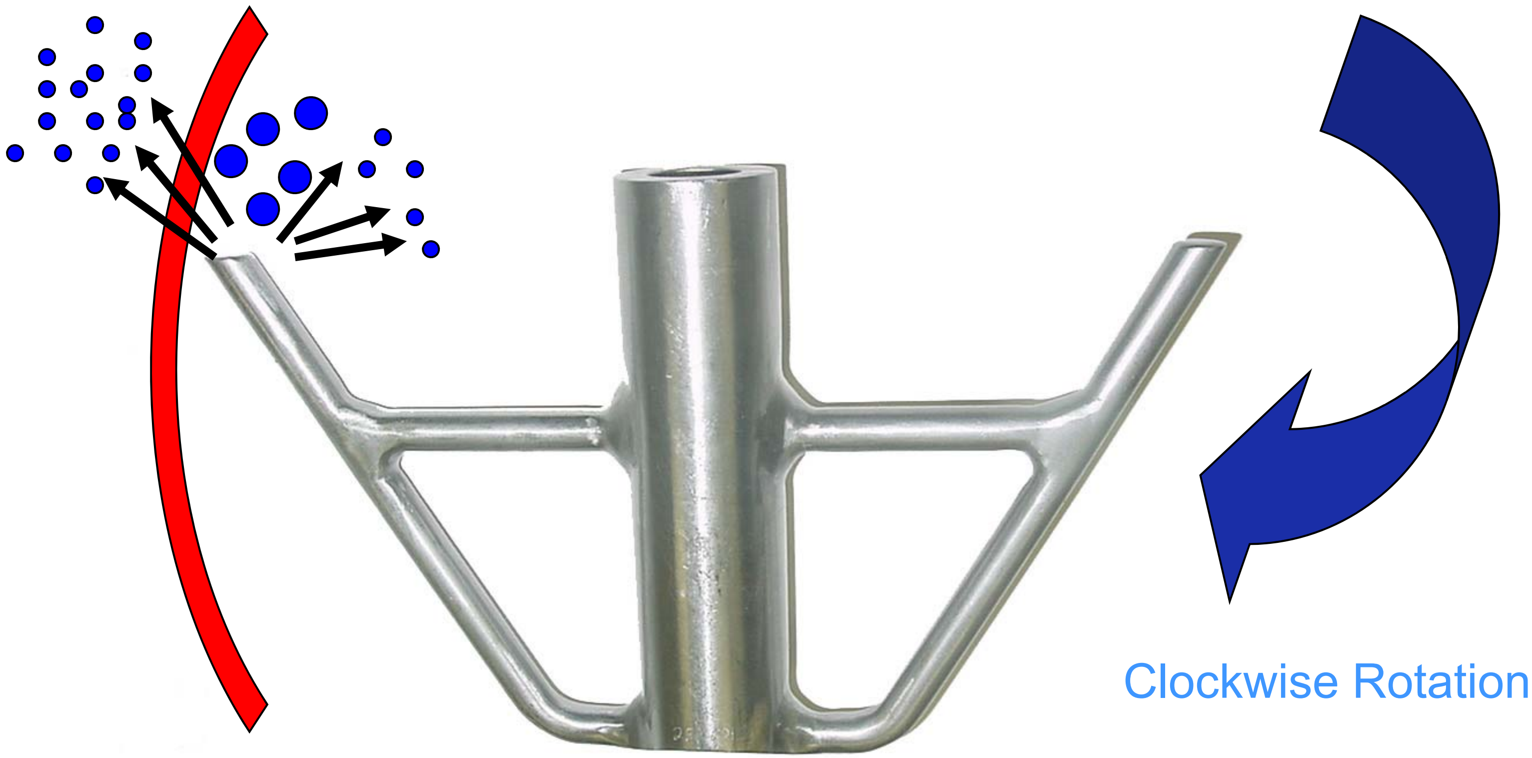
## Critical Milling Factors:
## Proper Tooling Selection - Impellers




| | 1601 (Compression) | 1607 (Low Shear) | 1609 (High Shear) | 1612 (Special) |
|---|---|---|---|---|
| **Capacity** | 2 | 3 | 4 | 1 |
| **Fines** | 2 | 1 | 3 | 4 |
| **Screen Pressure** | 2 | 3 | 4 | 1 |
| **Amperage** | 2 | 3 | 4 | 1 |

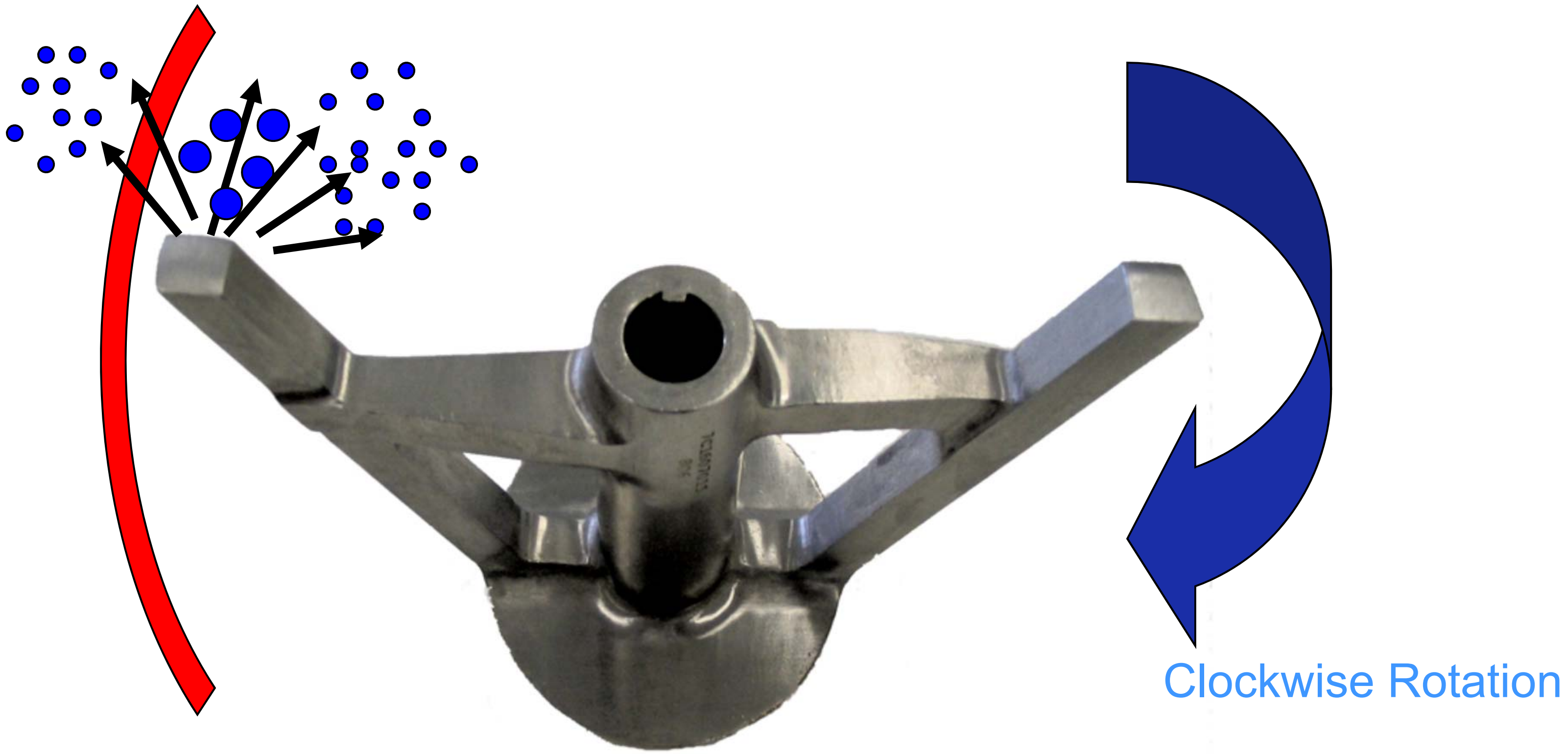
**1=Highest 4=Lowest**

## Comil Impellers – Round Arms #1601



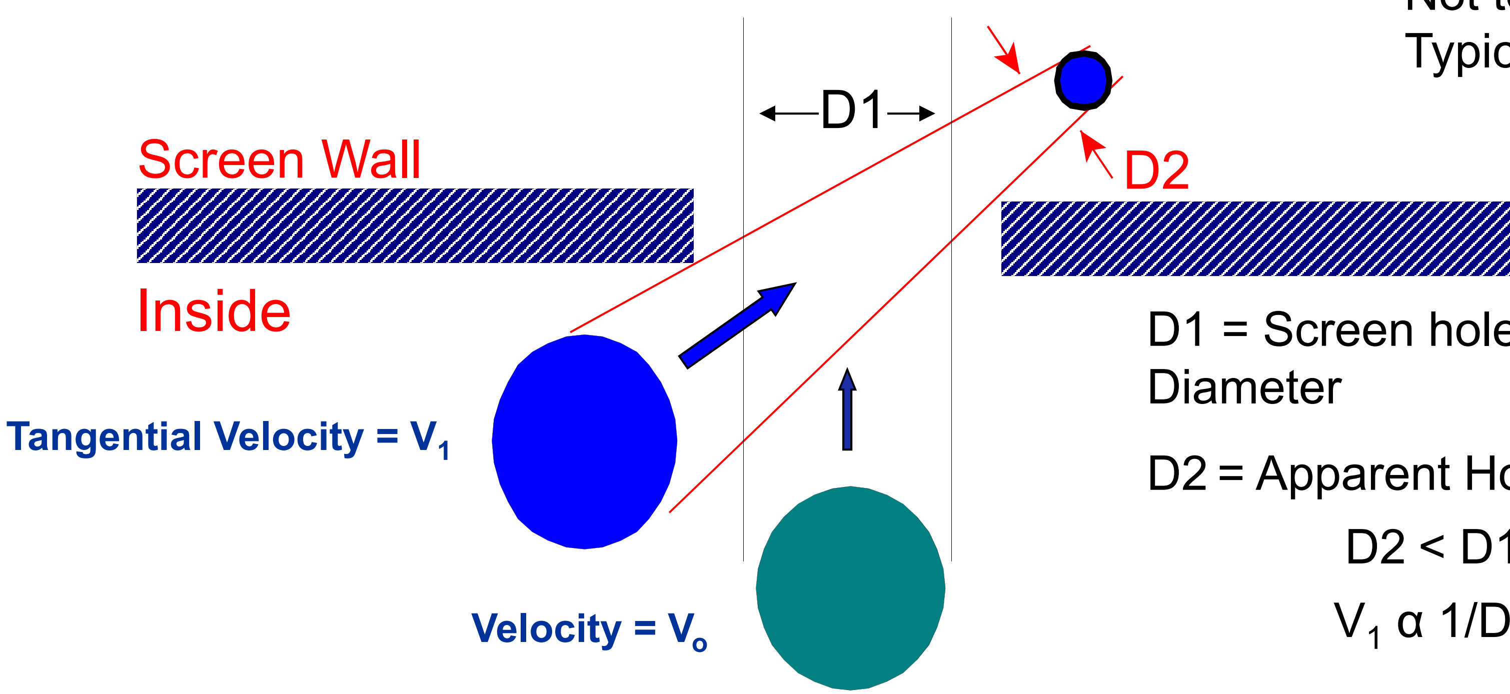

Round arms - primarily for dry sizing, some wet milling

# Comil Impellers – Rectangular Arms Positive Leading Edge #1607




Square Arms – “Universal” for wet milling and dry sizing

# Critical Milling Factors:
# Screens - Apparent Hole Size




D1 = Screen hole Diameter

D2 = Apparent Hole Size

$D2 < D1$

$V_1 \propto 1/D2$

# Fine Milling

- Accepted definition of Fine Milling is **psd** between 5 - 100 Microns and for Micronization **psd** between 1 - 30 micron in diameter.

- It is possible to use some of the previously discussed equipment to reduce the particle size distribution of a product down to this range (Hammer Mill) however, distribution curve can be fairly wide spread and possibly even bimodal whereas a tight **psd** and unimodal curve is the goal of most processes.

- Equipment commonly used for fine milling are: Pin Mills, Hammer Mills, Fine Grind, & Jet Mills

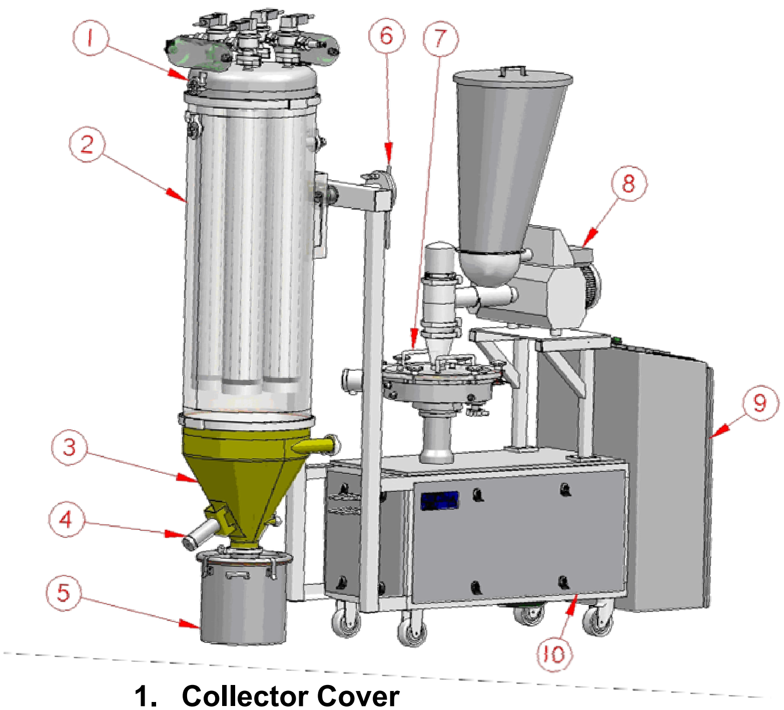
# Fine Milling

**SIZE REDUCTION CAPABILITY COMPARISON**

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Comil** | | | | | | | | | | | | | | | | | |
| **F10 Fine Grind** | | | | | | | | | | | | | | | | | |
| **Hammermill** | | | | | | | | | | | | | | | | | |
| **Pin Mill** | | | | | | | | | | | | | | | | | |
| **Jet Mill** | | | | | | | | | | | | | | | | | |
| **Micron** | **-5** | **-2.5** | **1** | **5** | **10** | **25** | **38** | **45** | **75** | **125** | **150** | **180** | **250** | **300** | **425** | **600** | **1000** |
| **US Mesh** | **-** | **-** | **-** | **-** | **-** | **-** | **400** | **325** | **200** | **120** | **100** | **80** | **60** | **50** | **40** | **30** | **18** |

# Fine Milling

## Quadro Fine Grind F10

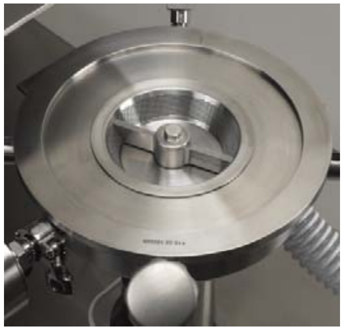



1. Collector Cover
2. Product Collector Body
3. Product Hopper
4. Pneumatic Vibrator
5. Outlet container
6. Rotation Hinge
7. Milling Head
8. Screw Feeder
9. Control Panel
10. Access Panel

# Fine Milling

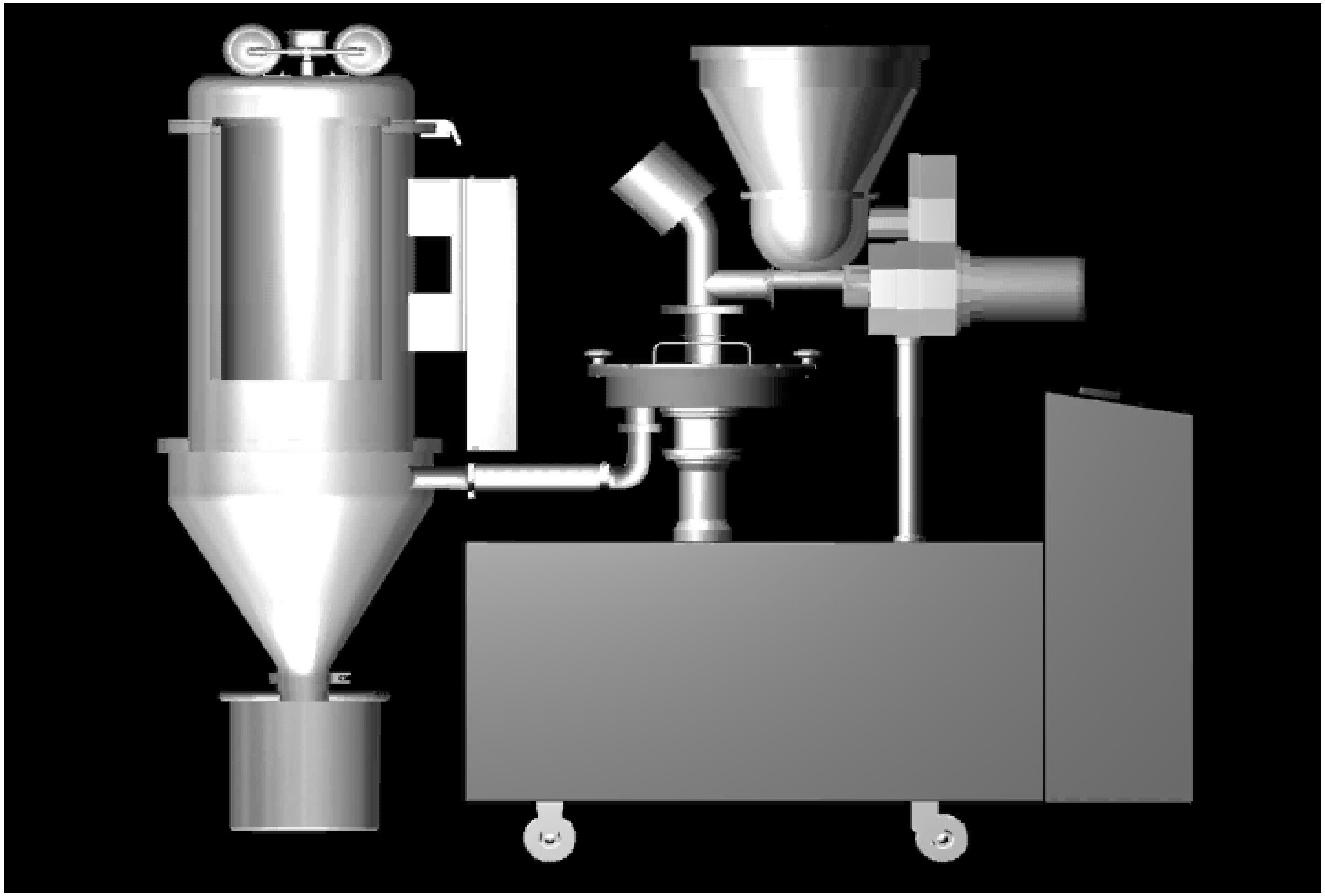
- Fine Grind F10 was developed to produce tailored **PSD** between 15 and 100 microns.
- Mobile, stand alone system (a complete plant) operates at low noise, dust heat and energy consumption.
- **The operating principle;**
  - control feed product into upper conical screen chamber.
  - a rotating impeller calibrates incoming material.
  - calibrated product then passes through to the lower chamber
  - a second intensifying impeller accelerates the particles.

**Upper Chamber**



**Lower Chamber**

# Fine Milling



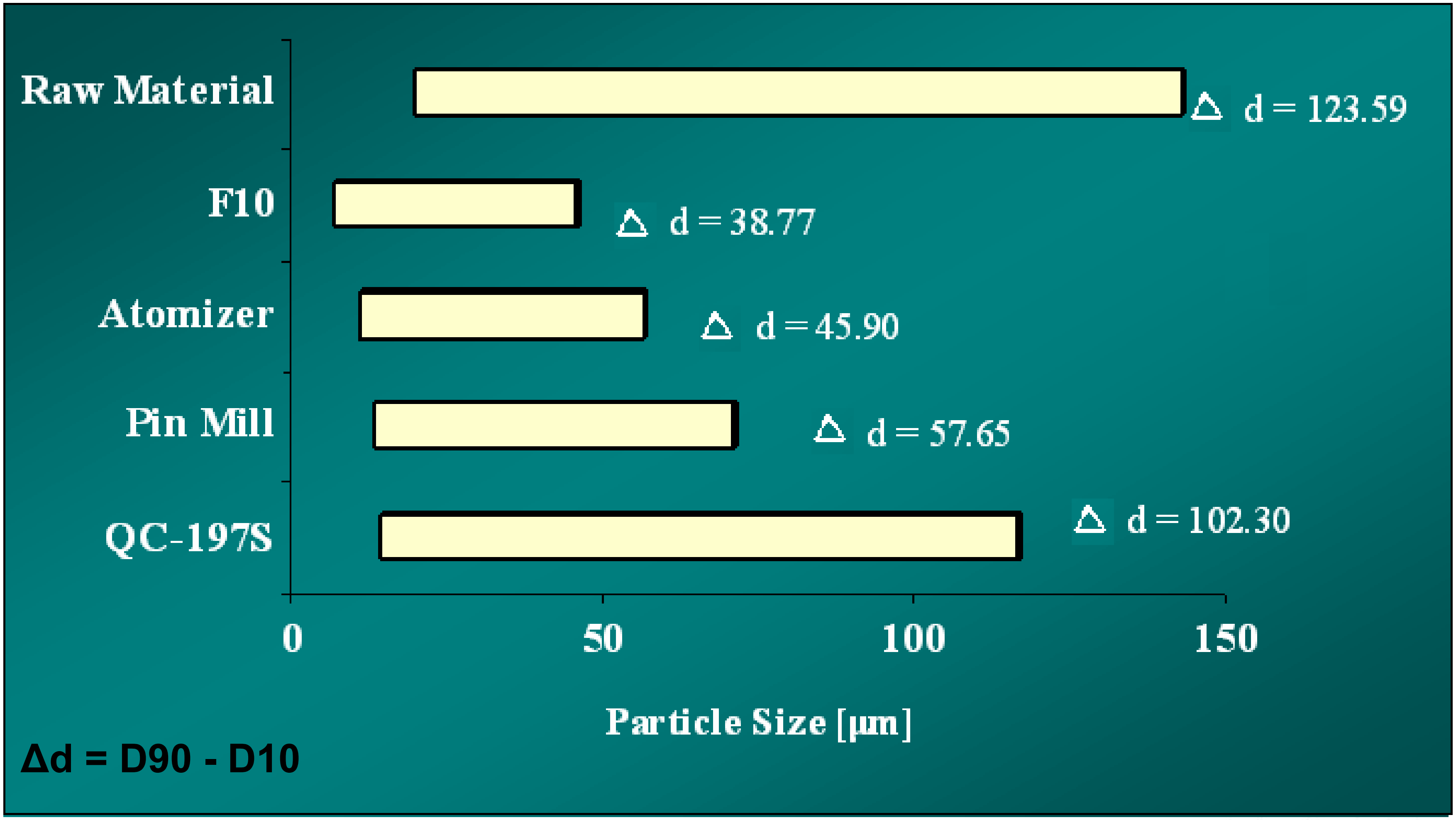
# Fine Milling

F10 Breakthroughs

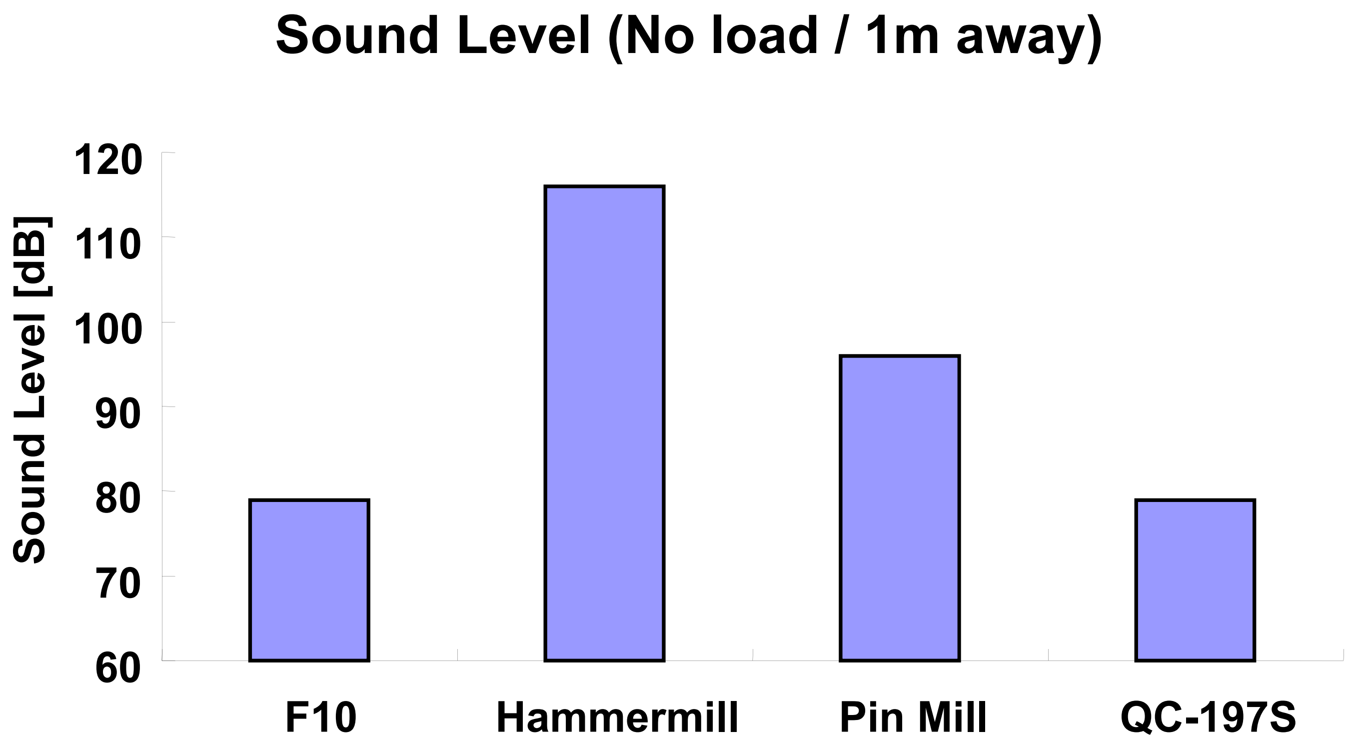
- Very tight Particle Size Distribution
- Very high Product Recovery rate (>99%)
- Dust-tight
- Mobile, All-In-One unit, no ancillaries required
- Operator-friendly: Easy to clean & Low-Noise Operation
- Sanitary, GMP design; Developed specifically for Pharmaceutical API Industry

# Fine Milling

## Technology Comparison – Lactose 200M



## Technology Comparison – Noise



# Case Study – Teva, Israel

## MILLING EXPERIMENTS WITH PROTOTYPES OF THE QUADRO FINE-GRIND F-10 MILL


### ABSTRACT

Quadro Fine grind (F-10) is a versatile mill which is effective in the range of 20-60 µm. Three Prototypes were received for experiments in Teva's API division. Different active pharmaceutical ingredients were tested to explore the mill's performance. Based on the conclusions, the final model was built. Improvements included enlargement of the milling chamber, Control over speed and vacuum, and introduction of water cooling. It was found that the milling range covers the particle size reduction range obtained today by either single or multiple milling in hammer-mills, and can provide comparable results to those of a pin-mill.

# Case Study – Teva, Israel

## INTRODUCTION

Teva's API division manufacturers over 200 molecules for various pharmaceutical clients. The physical properties of the products are tailor-made in order to meet various customer requests and optimize the formulation [1]. Because of the large number of products and different physical grades, it is required that mills will be versatile, i.e. capable to produce a wide spectrum of P.S.D by changing only the operating parameter.

The P.S.D range of ~20-40 microns is considered to be difficult to obtain. Larger particles can be controlled by Hammer-mills, Comils or other mechanical mills. Particles under 20 microns can be obtained by fluid-jet mills. However, only few mills can obtain narrow P.S.D in this range without having too many fines or oversized particles. One of these mills is the Pinmill [2]. Few main drawbacks of this mill are the heat generation and the very narrow gap that make it prone to blockages. Therefore, a great interest was found in the Quadro Fine grind (F-10). Two prototypes were tested, and based on Teva's findings, the final version was constructed and successfully applied in routine production.

# Fine Milling

## Case Study – Teva, Israel

Teva Paper at CHoPS Conference Italy, Aug 2006
"Development of the F10 in Teva, API"

Paper Synopsis

Goal: PSD 20 to 40 µm range

Previous: Pin Mill. Heat changed product characteristics.
Narrow gap between pins prone to blockage
(9 hrs to clean vs. F10 at 1 hour)

Validation: 6+ API's validated with F10

# Fine Milling

## Case Study – Teva, Israel

| Customer Requirement | Observations & Discussion: | | | |
|---|---|---|---|---|
| F10 comparison versus Pin Mill and Hammermill | Material "A": F10 vs. Pin Mill / Hammermill | | | |
| | Material A | $D_{10}$ (µm) | $D_{50}$ (µm) | $D_{90}$ (µm) |
| | Unmilled | 60 | 180 | 410 |
| | Pin Mill | 2 | 15 | 45 |
| | Hammermill Double Pass | 4 | 20 | 50 |
| | **F10 Single Pass** | **1.6** | **11.9** | **49.4** |

1. PSD Comparison between F10 versus Pin Mill and/or Hammermill results provided equal or better PSD distribution.
2. Material "A" is a proprietary pharmaceutical API

# Fine Milling

## Case Study – Teva, Israel

| **Customer Requirement** | **Observations & Discussion:** | | | |
|---|---|---|---|---|
| | Material "B": F10 vs. Hammermill | | | |
| | Material B | $D_{10}$ µm | $D_{50}$ µm | $D_{90}$ µm |
| F10 comparison versus Hammermill | Unmilled | 12.73 | 66.33 | 211.83 |
| | Hammermill | 8 | 50 | 150 |
| | **F10** | **3.44** | **18.69** | **63.33** |

1. PSD Comparison between F10 versus Hammermill results provided better PSD distribution.
2. Comil was also tested: D90 180 µm, D50 70 µm, D10 10 µm
3. Material "B" is a proprietary pharmaceutical API

# Fine Milling

## Case Study – Teva, Israel

| Customer Requirement | Observations & Discussion: | | | |
|---|---|---|---|---|
| | Material "C": F10 vs. Hammermill | | | |
| | Material C | $D_{10}$ µm | $D_{50}$ µm | $D_{90}$ µm |
| F10 comparison versus Hammermill | Unmilled | 24.33 | 118.91 | 339.14 |
| | Hammermill | 7.96 | 57.34 | 157.62 |
| | **F10** | **7.59** | **30.84** | **85.04** |

1. PSD Comparison between F10 versus Hammermill results provided equal or better PSD distribution.
2. Material "C" is a proprietary pharmaceutical API

# Fine Milling

## Case Study – Apotex, Canada

Customer using Hammermill: 4-5 passes for $d_{90}$ = 70 µm

F10: $d_{90}$ = 53.6µm (single pass) 7200RPM and 20.4µm 8400RPM

| Alendronate Sodium Trihydrate | | Impeller Speed = 7200 rpm | | Impeller Speed=8400 rpm | |
|---|---|---|---|---|---|
| | | Run 1 | Run 1.1 | Run 2 | Run 2.1 |
| PSD | Starting Material | PSD Run 1 | PSD Run1.1 | PSD Run 2 | PSD Run 2.1 |
| D(v,0.1) | 8.847 µm | 3.503 µm | 2.523 µm | 2.694 µm | 2.876 µm |
| D(v,0.5) | 49.214 µm | 18.03 µm | 7.408 µm | 7.585 µm | 7.05 µm |
| D(v,0.9) | 262.787 µm | 53.601 µm | 19.442 µm | 20.451 µm | 14.805 µm |

First Pass

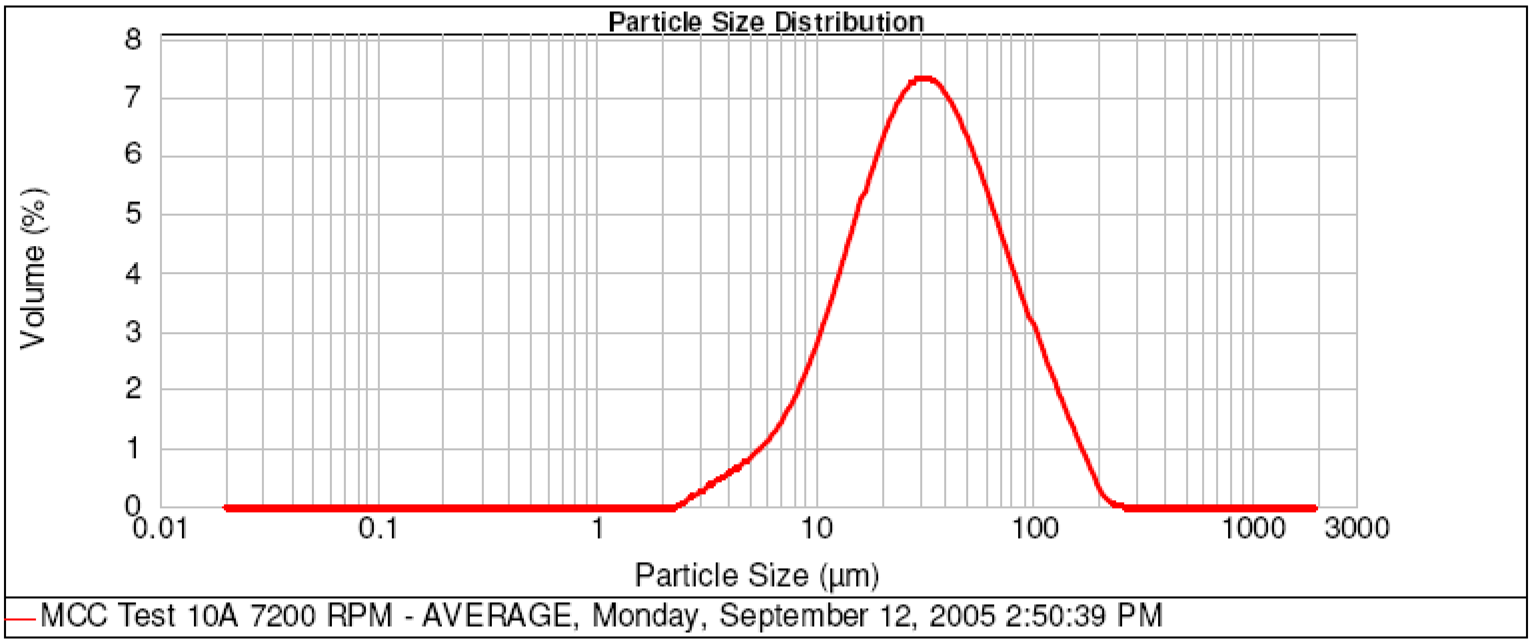
Second Pass

# Fine Milling

## Typical F10 PSD Graph – MCC

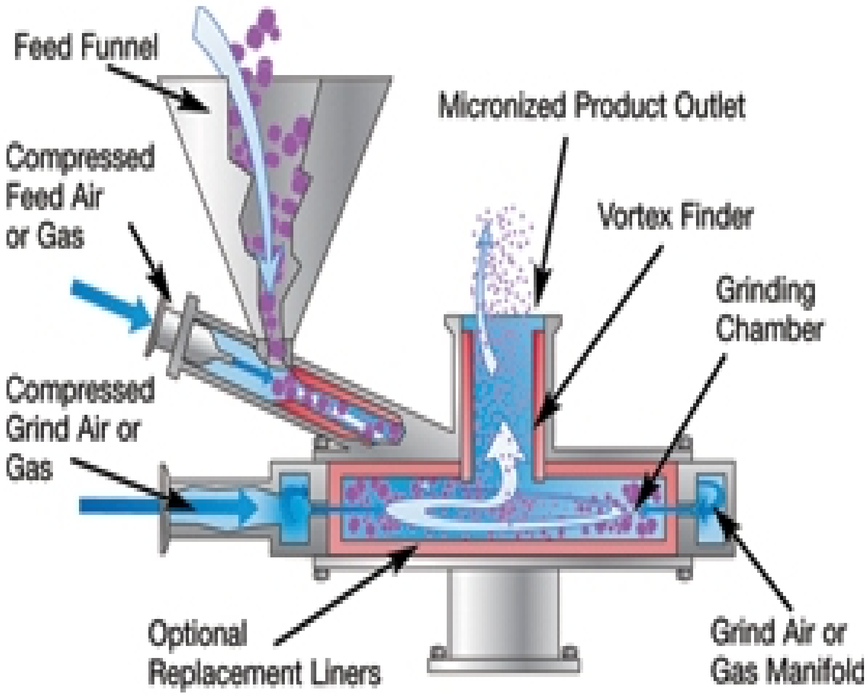
Specific Surface Area: 0.275 m²/g
Surface Weighted Mean D[3,2]: 21.805 um
Vol. Weighted Mean D[4,3]: 42.411 um

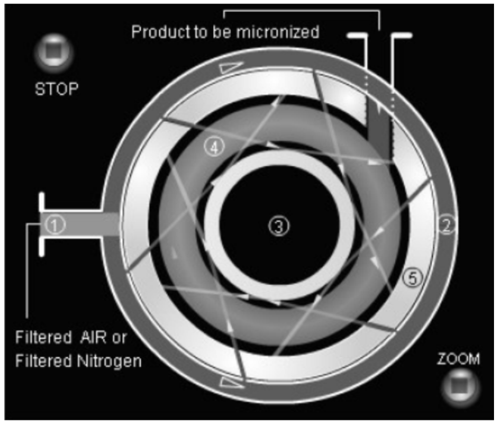
d(0.1): 10.560 um
d(0.5): 31.714 um
d(0.9): 89.907 um

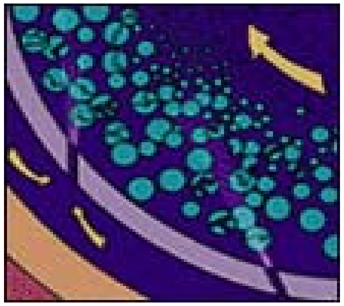



**F10 was run at standard speed (7200RPM), 045R screen;**
**Malvern Mastersizer 2000 Results**

# Jet Mills & Micronizers



# Jet Mills & Micronizers

- **The principle of micronizing fluid energy mills (also known as jet mills or spiral mills) is the size reduction of particles through inter-particulate collisions combined with surface collisions due to acceleration of product.**
- **These mills use accelerated fluid streams (normally compressed air, super heated steam or inert gas) to generate a high speed vortex which the particles are introduced into.**
- **The vacuum created by a venturi-nozzle propels the product throughout the milling chamber, forcing particles to collide with themselves as well as the chamber walls.**

# Jet Mills & Micronizers

Key Components and attributes that affect micronization:

- **Nozzle design and direction of air jets**
- **Efficiency of air compressors**
- **Efficiency of filters and separators**

# Mill Selection Criteria

Properties of Feed Material:
- Size
- Shape
- Moisture content
- Physical and chemical properties
- Temperature sensitivity
- Grindability

Final Product Specification:
- Size
- Particle size distribution
- Shape

Versatility of Operation:
- Change of speed and screens
- Safety features

# Mill Selection Criteria

Scale-Up:
- Capacity of the mill
- Production rate requirements

Dust Control:
- Loss of costly drugs
- Health hazards
- Contamination of plant
- Safety

Sanitation:
- Ease of cleaning and sterilization
- Design and material finish

Auxiliary Equipment:
- Cooling system
- Dust collectors
- Forced feeding

# Mill Selection Criteria

Economical Factors:

- Equipment cost
- Power consumption
- Space occupied
- Labor cost

# Ability to handle dust explosions

General guidelines for inert milling:
Minimum Ignition Energy: (ref. BS5958 Part 1; 1991)

**< 500 mJ** Low sensitivity to ignition. Solution: **Earth plant**.
**< 100 mJ** Recommended at this point that customer seek expert advice. Common solution: **Earth personnel**.
**< 25 mJ** Majority of incidents occur when MIE is at or below this level. Solution: **Inert with nitrogen**.
**< 10 mJ** High sensitivity to ignition. Solution: **Inert with nitrogen and monitor allowable oxygen levels**.

# Thank you