INNOVATIVE MILLING & MICRONIZATION TECHNIQUES FOR THE PHARMACEUTICAL INDUSTRY

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1. INTRODUCTION

The demand for improved milling techniques within the pharmaceutical industry is growing. Increased surface areas, improved bioavailability, and reproducible steep particle size distributions can all be achieved by choosing the precise milling technology for the proper application. This paper will investigate several mechanical milling and micronization techniques and outline their distinct process advantages within the pharmaceutical industry. Conventional dry size reduction of pharmaceutical powders is accomplished by impact size reduction. Equipment commonly used falls into in the categories of either mechanical impact mills or fluid energy impact mills. Examples of mechanical impact mills are hammer and screen mills, pin mills, and air classifying mills. Spiral jet mills and fluidized bed jet mills are examples of fluid energy impact mills.

2. MATERIAL CHARACTERISTICS

The selection of the proper size reduction equipment depends on the characteristics of the product to be processed, the particle size distribution required, and the special requirements of the industry being served.

Material characteristics influence the selection of size reduction equipment. Hard and brittle material can be processed very easily with impact size reduction methods. Fibrous materials such as animal and vegetable products and plastics are more easily handled by cutting mills. Compression mills are generally used for low energy applications/granulation of pharmaceutical powders prior to tabletting. Material hardness and potential abrasion will also dictate the type of mill selected. Materials with Moh's hardness exceeding 3 or with a significant quantity of abrasive impurity require special handling. In the Moh's scale of material hardness, a material of a given hardness will scratch the surface of any material with a lower Moh's hardness value, and itself be scratched by any material with a higher hardness value. The following table gives examples of the Moh's table of material hardness.

THE MOH'S SCALE OF MATERIAL HARDNESS

Degree of Hardness	Moh's Scale Value	Material Example
Soft	1	Talcum
Soft	2	Gypsum
Soft	3	Calcite
Medium-Hard	4	Fluorite
Medium-Hard	5	Apatite
Medium-Hard	6	Feldspar
Hard	7	Quartz

Degree of Hardness	Moh's Scale Value	Material Example
Hard	8	Topaz
Hard	9	Corundum
Hard	10	Diamond

***It should be noted that most pharmaceutical products are no more than value 3 on the Moh's hardness scale.

The degree of size reduction or end product fineness also determines the energy input for grinding and therefore the method of size reduction. For example, easy to grind materials requiring medium fineness can be processed with mechanical impact grinding mills. Those products requiring high fineness are usually processed with fluid energy jet mills. Finally, the shape of the particle size distribution is considered in the selection of a grinding system. If a steep particle size distribution is required, a mill with internal or external classification is considered. It is important to select a mill that does not impart unnecessary energy into the process, yet still includes the power to reduce the product.

3. PARTICLE SIZE DEFINITION

One of the most important criteria used when defining the required mill for the application is particle size distribution. It is imperative that the proper requirements be stated. For example, in a typical specification, a D50 size refers to the equivalent diameter greater than 50% of the particles by mass. In other words, a required particle size of 10 microns should be further defined in reference to a D50 or D97 of 10 microns. Since a resultant distribution with a D50 of 10 micron actually requires a top end of 15-20 micron, less energy is required to produce a D97 of 10 micron.

4. PROCESS CONSIDERATIONS

Among the considerations for selection of a size reduction system are product purity, reproducible particle size control, cleanability, and process validation. In addition, the issues of product and explosion containment must be addressed, particularly with respect to the deflagration values and design exposure limits required for the specific product.

5. COMPRESSIVE FORCE SIZE REDUCTION MILLS

In the pharmaceutical industry, compressive force mills are defined as those mills in which particles are compressed against a screen wall by means of a rotating bar or rotor. Examples of such mills include conical screen mills, oscillating granulators, and rotating sieve mills. Size reduction is caused by forcing material through a screen or perforated plate, and some slight interparticle collisions. This gentle action is ideal for applications requiring minimal energy, with low heat generation.

In the conical screen mill, material enters the milling chamber via gravity and exits through the screen holes. Variables in particle size reduction include size and shape of the holes, rotor speed. This type of mill is also ideal for the milling of wet granulations prior to fluid bed drying. Its gentle action allows the product to be deagglomerated, thus increasing surface area and reducing overall

drying times.

Benefits of the conical mill include low heat and gentle action. However, its limitations lie in the inability to mill to a fine particle size (usually no finer than 150 micron (100 mesh)). It should be noted that there have been cases where finer resultant distributions have been obtained, but only if the application is a deagglomeration of already sized fine material.

6. HAMMERMILLS

Particles within the hammermill are mostly reduced by impact against rigid surfaces, for example, impact against the mill housing and a screen. The grinding process is affected by three basic variables: screen hole size and shape, hammer type, and peripheral speed of the hammers, which can range from 20-60 m/s.

Hammermills are ideal for a wide variety of particle size ranges, due to the ability to quickly change the screen size and resultant particle size distribution. These machines are used to process medium to medium fine particle sizes, and handle mostly soft to medium hard materials. Sample applications include pigments (chrome yellow, iron blue), spice grinding, and various food ingredients (oat fibers, sugar, lactose, pasta regrind). Resultant particle size distributions can vary from 850 micron to as fine as 90 microns, with production rates as high as 30,000 lbs/hr.

Special design features in the hammermill configuration permit cryogenic grinding, which employs liquid nitrogen to reduce material temperatures. This embrittles the material prior to size reduction and makes grinding tough (such as fibrous materials or thermoplastics) or heat sensitive (such as certain spice blends) materials much easier.

Key disadvantages with hammermills are the high energy consumption and resultant heat generation, thus making processing of heat sensitive materials particularly difficult.

7. UNIVERSAL AND PIN MILLS

Universal mills are often also referred to as fine grinding impact mills. The ability to utilize a variety of grinding media within the same milling chamber allows for complete flexibility in resulting particle size distributions. The possibilities in grinding media run from equipping the unit with pin discs, or hammers/beaters with and without screens, as well as various grinding tracks .

In all of the options, particle size reduction occurs by impact against the grinding media, and through inter-particle attrition. For example, a universal mill equipped with pin discs consists of one stationary set of pins, and one rotating set of pins. Material enters the grinding chamber via gravity, and is accelerated by centrifugal force against the meshing pins. The strength of this force is set by the speed of the discs, which can be as high as 200 m/s. The feed rate and the peripheral speed of the pin discs determine particle size.

The ability to quickly change the grinding media of the universal mill makes it a good size reduction choice for several different materials at a variety of size ranges. For instance, by changing the pin disc components to a peripherally mounted sieve insert or peripherally mounted grinding track, the ability to process both medium fine to very fine particles can be achieved. The overall result is a host of practical equipment combinations to cope with many size reduction tasks.

Due to their versatility and accessibility, universal mills are often used a fine grinders for a wide variety of applications, inclusive of the milling of pharmaceuticals, cryogenic herb and spice milling (ie ginger, paprika, cinnamon), food and confectioneries, animal feeds, mineral powders (such as limestone and gypsum) and various chemicals, (including fertilizers, pesticides, paints and pigments.). Typical resultant particle size distributions can range anywhere from D_{97} of 200μ, to as fine as D_{97} of 10μ or less. This type of size reduction is ideal when the desired particle size distribution is narrow.

The pin mill configuration can also be equipped with a wider milling chamber, in order to dissipate and minimize the heat generated within the grinding zone. For example, pin mills with wider chambers are often used for such heat sensitive products as cocoa powder.

Universal mechanical milling is perfect for fine grinding applications that do not require the higher energy input of jet milling or the strict top size control of an air classifying mill. In all mechanical impact mills, material hardness is limited to 3 Mohs or less.

8. MECHANICAL MILLS WITH INTERNAL AIR CLASSIFIERS

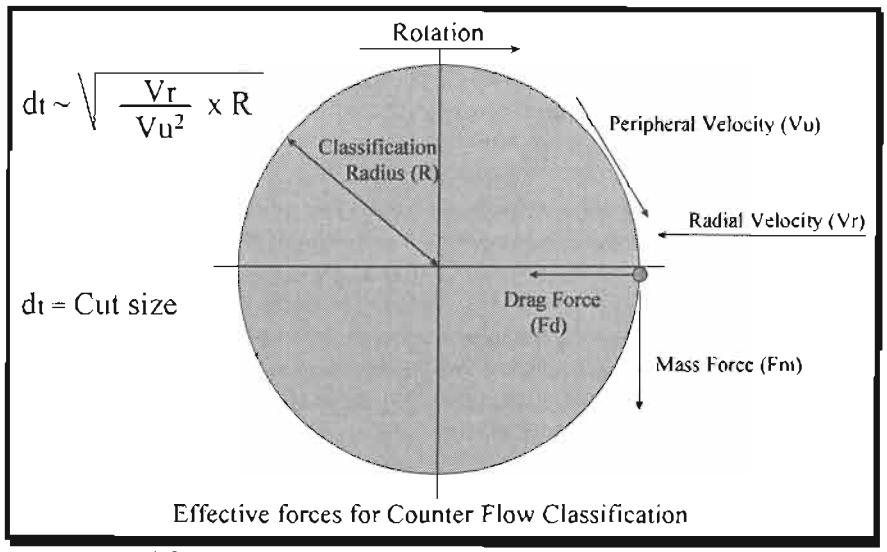
When the required particle size distribution is narrow, a hammermill design with an integral air classifying wheel can be utilized. This classifier, an integral component of the mill, allows only particles below a certain size to pass. Material to be ground is conveyed into the mill chamber to a rotor equipped with pins or hammers. As particles decrease in size, they are entrained by an airstream, and eventually pass through the classifier wheel to the product collector. Those particles rejected by the classifier are continuously recycled back to the hammers for further size reduction.

Due to the constant flow of air passing through this *air classifying mill*, the system maintains a relatively low temperature, making it an ideal grinder for handling materials with a low melting or softening point. Such low operating temperatures makes it an ideal mill for processing sugar, at a variety of particle size distributions, (e.g. 10x (D_{97} of 200 mesh), and 12x (D_{97} of 400 mesh)). Particle size is controlled by rotor speed, classifier wheel speed and airflow. Airflow is a critical factor in determining classifier mill capacities.

The air classifying mill is also ideal for processing various heat sensitive materials such as dextrose and many pharmaceutical compounds. Its ability to maintain a tight distribution, combined with the added features of an easy clean design make it an ideal mill for processing pharmaceutical products. Particle sizes as fine as 30 microns are possible, dependent upon the material and application.

The basic principle of operation of an air classifier can be defined as follows:

AIR VOLUME	CLASSIFIER SPEED	PARTICLE SIZE
Constant	Constant	No change
Constant	Higher	Finer
Constant	Lower	Coarser
Higher	Constant	Coarser
Lower	Constant	Finer



OPERATING PRINCIPLE OF A CLASSIFIER

9. WHAT IS POWDER MICRONIZATION?

Micronization is a term used to describe size reduction where the resulting particle size distribution is less than 10 microns. Micronization size reduction involves acceleration of particles so that grinding occurs by particle to particle impact or impact against a solid surface. Fluid energy mills are used for micronization because of the high impact velocities possible as a result of particle acceleration in a fast gas stream. Particle velocities in a jet mill are in the range of 300 to 500 meters per second, compared with 50 to 150 meters per second in a mechanical impact mill. In fact, the generic term has been used to describe various types of 'spiral jet mills' or 'pancake mills'. This mill type has been used effectively for many years for size reduction in the 'micronization' range.

Reproducible steep particle size distributions, those with a minimum of fine particles and strict control of oversized particles; combined with improved methods to measure particle size distributions has led to a change in micronizing techniques. The spiral jet mill is gradually yielding to the next generation of higher technology fluidized bed jet mills. The fluidized bed jet mill combines high-energy micronization with an integral forced vortex air classifier. This combination allows greater control of the maximum product particle size and usually a reduction in generated fines.

10. SPIRAL JET MILL MICRONIZATION

The spiral jet mill is suitable for the fine and ultra-fine size reduction of materials up to a Moh's' hardness of 3 that display brittle crystalline grinding characteristics. They are typically used in applications where a high ultra-fine portion is required.

The spiral jet mill is simple in design, consisting of a flat cylindrical grinding chamber with several nozzles arranged tangentially in the peripheral wall, a pneumatic feed injector and a feed funnel. Operation is just as simple. The feed is accelerated into the grinding chamber through the feed injector. The material inside the grinding chamber is subjected to two opposing forces. They are the free vortex created by centrifugal force (mass force) imparted on the particles by the nozzles, and the drag force created by the airflow as it spirals toward the center of the mill. The larger particles are affected to a greater degree by the mass force, circulating around the periphery of the mill undergoing collisions with other particles. As the particles become finer, the drag force exerts a greater effect drawing the particles with the airstream to the central outlet of the mill.

Feed particle size is critical, restricted by the size of the feed injector. For mills of 200 - 300 mm., the feed size can be a maximum of 1.5 mm. For smaller size mills, the feed size is correspondingly finer.

There are several factors, both operational and physical which affect the fineness of the end product.

These are:	Feed rate	Airflow rate
	Nozzle size	Feed particle size
	Nozzle pressure	Chamber diameter and width
	Nozzle angle	Product outlet diameter

All of these variables can be adjusted during operation, but it is more likely that once in operation, only feed rate will be varied to meet the required particle size distribution.

Spiral jet mills are effective tools for micronization, especially in the pharmaceutical industry, but they have several limitations. First, as mentioned above, is the limitation in feed size due to the method of product injection. Oversized feed particles can cause blockage in the feed hopper, and result in variations in particle size distribution caused by fluctuating feed rates. Presizing the feed, proper design of the feed system and applying vibration to dislodge build-up in the feed chute can control this. There is also the possibility of buildup and scaling in the mill due to the impact that occurs on the mill walls. This is especially a problem with sticky substances such as steroids. But perhaps the most serious drawback is the lack of control of particle size distribution, especially top size limitation. These process limitations led to the development of the fluidized bed jet mill.

11. FLUIDIZED BED JET MILL MICRONIZATION

The fluidized bed jet mill is suitable for the fine and ultra-fine size reduction of any material up to a Moh's' hardness of 10 that can be fluidized by the expanded compressed gas in the grinding chamber. They are typically used in applications where a fine to ultra-fine micronization is required, and are not limited by feed size, heat sensitivity of the material, or abrasive characteristics. They are characterized by decreased energy consumption, reduced wear and build-up in the grinding chamber, steeper particle size distribution and low noise emission.

The fluidized bed jet mill actually consists of two distinct segments and thus processes. The lower grinding section comprises the actual grinding chamber with several nozzles arranged radially in the chamber wall and gravity feed inlet. The upper classifier section is

a centrifugal forced vortex air classifier, which is responsible for particle size control. The two processes work together to give the fluidized bed jet mill its characteristic steep particle size distribution and sharp top size control.

Operation of the fluidized bed jet mill is quite simple. Feed material is introduced to the grinding chamber through a large gravity feed inlet. During normal operation, there is a fluidized bed of material inside the grinding chamber. The high velocity gas streams created by the nozzles entrain material, and size reduction occurs as a result of particle to particle collision in the gas stream and at the focal point of the nozzles. The expanded gas conveys ground particles upward toward the centrifugal air classifier. The classifier allows material of a given fineness to exit the mill while rejecting oversized particles back into the grinding chamber for additional size reduction. Equilibrium is established with an internal recirculation, the introduction of fresh feed material and a constant discharge of ground material from the mill.

The key to maintaining a consistent particle size distribution is the integral air classifier. Air classification is defined as the separation of bulk material according to their settling velocity in a gas. As in the spiral jet mill the same two opposing forces are acting on the particles: mass force and drag force. Mass force is the force exerted on the particle by acceleration due to gravity, inertia, or centrifugal force. Drag force is the force exerted on a particle by the surrounding medium as affected by its aerodynamic properties. In a centrifugal air classifier the mass force is exerted on the particle by the peripheral velocity of the classifier wheel.

The drag force is exerted on the particle by the carrying fluid, which in the case of a jet mill is the expanded grinding gas. The particle size at which the mass force and drag force act equally on the particle is defined as the cut point. As in the spiral jet mill, the mass force exerts a greater influence on the particles that are coarser than the cut size, and they are returned to the grinding zone of the jet mill. The drag force acts upon the particles that are finer than the cut size, and they are carried through the classifier wheel and recovered as product.

Most of the limitations inherent in the spiral jet mill do not exist in a fluidized bed jet mill. There is no real limitation on feed size as the gravity feed inlet varies in size from two to six inches. The problem of material build-up and scaling in the mill is also virtually non-existent. Material does not circulate or impact against the mill walls, in fact the vertical velocity of air and product in the chamber is only about 1.5 meters per second. The most important improvement in the fluidized bed jet mill process is the ability to control the particle size distribution of the product. The upper particle size of the product is strictly controlled by adjustment of the integral air classifier. By increasing the rotational velocity of the classifier wheel, a greater mass force is exerted on the particles; smaller particles will be rejected and returned to the grinding zone. The end result is a finer particle size distribution. Conversely, decreasing the classifier speed will allow larger particles to pass through the classifier wheel, the end result a coarser particle size distribution. Airflow also has an effect. A higher airflow through the classifier wheel results in an increased drag force, and a coarser particle size distribution. With this degree of control, a fluidized bed jet mill is able to produce an infinitely adjustable particle size distribution.

Because of the integrated classifier, spatter grain particles are virtually eliminated from the finished product. Control of the upper particle size also reduces the possibility of

overgrinding the product in order to ensure a top size. The first graph comparing the resulting particle size distribution from a fluidized bed jet mill to that from a spiral jet mill clearly shows a more precise cut point and a reduction in the ultrafine fraction.

If there is a limitation at all to a fluidized bed jet mill, it is the ability to process very small samples. During normal operation, there is a certain quantity of product in internal recirculation, and a small amount of residual material left in the mill at the conclusion of the process. This can be an inconvenience if only small sample quantities are available, and these applications would be better served in a spiral jet mill.

12. REFERENCE GUIDELINES

As listed above, each of the size reduction techniques outlined

TYPE	HOSOKAWA MODEL	INTERNAL CLASSIFIER	COARSE (1-5 MM)	MEDIUM FINE (500–1000 MICRON)	FINE (150-500 MICRON)	FINE (50 – 150 MICRON)	SUPER FINE (10-50 MICRON)	ULTRAFINE (2–10 MICRON)
CONICAL SCREEN MILLL	BEXMILL	NO	XXXXXXX XXXXXXX XXXXXXX	XXXXXXX XXXXXXX XXXXXXX	XXXXXXXX XXXXXXXX XXXXXXXXX			
HAMMER/ SCREEN MILL	MIKRO – PULVERIZER MIKRO-BANTAM	NO		XXXXXXX XXXXXXX XXXXXXX XXXXXXX	XXXXXXXX XXXXXXXX XXXXXXXXX XXXXXXXXX	XXXXXXX XXXXXXX XXXXXXX XXXXXXX		
AIR SWEPT MILL	MIKRO-ACM ALPINE-ZPS	YES		XXXXXXX XXXXXXX XXXXXXX	XXXXXXXX XXXXXXXX XXXXXXXXX	XXXXXXX XXXXXXX XXXXXXX		
UNIVERSAL MILL	ALPINE UPZ	NO		XXXXXXX XXXXXXX XXXXXXX	XXXXXXXX XXXXXXXX XXXXXXXX	XXXXXXX XXXXXXX XXXXXXX	XXXXXXX XXXXXXX XXXXXXX	
FLUIDIZED BED JET MILL	ALPINE AFG	YES			XXXXXXX XXXXXXX XXXXXXX	XXXXXXX XXXXXXX XXXXXXX	XXXXXX XXXXXX XXXXXX	XXXXXXXX XXXXXXXX XXXXXXXX
SPIRAL JET MILL	ALPINE AS	NO			XXXXXXX XXXXXXX XXXXXXX	XXXXXXX XXXXXXX XXXXXXX	XXXXXXX XXXXXXX XXXXXXX	XXXXXXX XXXXXXX XXXXXXX

13. PROCESSING PHARMACEUTICAL POWDERS

In the past several years, the requirements of the pharmaceutical industry have changed. There are many new demands on the processor to manufacture powders with finer and tighter particle size distributions, less spatter grains, and reduced contamination. In addition, processes are required with increased efficiency, better process control, and provision of documentation validating the complete system. Further, regulatory agencies such as FDA and OSHA demand greater operator safety and product protection. The options that reflect these requirements are:

Clean in place
Sterilize in place
Explosion protection or containment
Product protection
Operator protection
Higher surface finish

14. EXPLOSION CONTAINMENT

As pharmaceutical powders are potentially explosive, the issue of explosion safety also has to be addressed. There are several methods to protect against explosion of powder: inerting with nitrogen or other gas, containment of the explosion gases within the confines of the grinding system, explosion suppression, and venting. Most pharmaceutical process systems use either inert gas processing or pressure containment up to 10 BAR.

An inert system uses nitrogen or another inert gas as the grinding medium. The system can be rather complex with closed loop gas piping, and an elaborate control system to monitor and control the oxygen level in the system. A closed loop system designed to recycle the grinding gas is more economical to operate than a single pass system.

A containment designed system requires a mill that is more robustly built to withstand an internal pressure of up to 10 BAR G. There are other considerations as well, to protect the operator and contain the product. These are the location and type of all seals, the mill clamping arrangement, and the mill inlet and outlet have to be totally contained. Because there is only a slight additional cost to manufacture a pressure resistant mill, most of the pharmaceutical mills manufactured by Hosokawa Alpine are standard 10 BAR PSR construction. The same mill can then be used for either an inert or containment system.

In addition to the mill, all other system components must be protected against the pressure wave and flame front resulting from an explosion. In most cases the feeder and dust collector are designed for containment, and an explosion barrier valve protects the downstream HEPA filter and exhaust fan.

15. PROCESS STERILIZATION

Designing for sterilization in place (SIP) requires a number of design considerations.

These include: Surface finishes to Ra = 0.4 microns
Seals must withstand sterilization pressures of up to 3 BAR G and temperatures of 130-140 C.
High points must be vented and low points drained
Equipment must be capable of being dried, either by hot sterile air or vacuum
Pressure and temperature measurements

The same considerations must be taken for the complete system as well as the appropriate mill. Most times, the sterilization process is applied only to selected system components. The barrier valves already in the system isolate the sterile components from the non-sterile

components during the sterilization process. During sterilization, the barrier valves remain closed, and then are open for the grinding process.

16. CLEAN IN PLACE

The terminology 'Clean in place' (CIP) is very loosely defined and can result in confusion between the processor and equipment manufacturer. There are several methods for cleaning equipment in place.

Manually disassemble and clean at a remote washing station.

Rinse the equipment of loose dust, then disassemble and clean at a remote station.

Manually remove the difficult to clean items from the machine, then clean the housing in place.

Automatically wash the entire system in place, without opening, using a validated cleaning process.

Only the last method is a true 'clean in place' operation. Most plants however, will use a combination of the above methods to accomplish the task.

Like with sterilize in place systems, clean in place systems have some design considerations that have to be addressed.

These include:
Surface finish
Location and selection of seals
All low points must drain
All surfaces must be accessible to cleaning fluid
The system has to be easily dried

Before the decision is made to design a clean in place system or to offer an existing CIP machine for an application, the product itself must be tested for solubility in a particular cleaning agent. If the material is not soluble or only moderately soluble, a manual cleaning program will have to be instituted.

17. PRODUCT CONTAINMENT

With the onset of an increased number of highly potent compounds, the issue of operator exposure limits (OEL'S) within a process is critical. In order to ensure complete operator safety, several design features ca n be incorporated into a system for total product containment including:

- Glove Box Isolators at all Feed and Discharge Points (OEL's of less than 10 micrograms/cu meter
- Purged Seal Rotary Airlocks
- HEPA Filtration at inlet and outlet process gas points

In addition, process systems requiring product collection by means of reverse pulse baghouses can incorporate a wide variety of design features including:

- Bag In/Bag Out Filter removal – also included in HEPA cartridge designs
- CIP design additions – spray balls dynamic and static
- Static dissipating filter media
- Options in filter configurations – ie pleated elements, sintered metal elements for overall smaller collector sizes, more efficient filtration.

18. SURFACE FINISH

The internal surfaces within Process equipment are usually all polished to at least an Ra of 0.8 micron. Subsequent electropolishing is often included to help reduce the surface tension on the cleaning fluid and therefore improve the performance of the clean in place procedures.

19. VALIDATION

The driving force behind the development of the advances in powder micronization technology discussed in this paper have come from statements made by regulatory agencies such as the Food and Drug Administration (FDA).

> "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

A high quality system that will produce a consistent high quality product batch to batch is only one of the requirements. Documentation to back up the process design as well as the process capabilities of the machine must be in place.

There are four main validation stages relating to the mechanical process design.

Design Qualification	(DQ)
Installation Qualification	(IQ)
Operation Qualification	(OQ)
Performance Qualification	(PQ)

As an equipment manufacturer, we are involved in the first three of these stages, even at times producing all of the required DQ, IQ, and OQ documentation, and implementing the protocols.

As the buyer of equipment it is imperative that coordination on the required documentation from the equipment vendor be addressed in the early stages of the project, thus accelerating the validation process.

Additional information on any of the topics listed above can be obtained from Hosokawa Micron Systems, Sharon Yaeger (908-277-9280.)

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