Hosokawa Alpine is a member of the Hosokawa Micron Group, responding to global needs through emphasis on materials science and engineering. The Group is an international provider of equipment and technology for powder and particle processing, plastics processing and confectionery products. The Group maintains facilities for research, engineering, manufacturing and service in each of the world’s major industrial markets.

© Hosokawa Alpine 2007. Printed in Germany.
The HOSOKAWA MICRON GROUP is an international provider of equipment and systems serving a broad range of industries which includes chemical, minerals, pharmaceutical, polymer, food, blown film processing, confectionery and bakery, and specialised food.

POWDER PROCESSING TECHNOLOGY EXPERTISE IN PHARMACEUTICALS

Hosokawa is a global operation with sales, manufacturing and test centers throughout the world. The pharmaceutical industry is an important business sector for the Hosokawa Group and significant investment has been made over the years, to enhance and streamline our operations in this area, enabling us to offer increasing levels of expertise, technological development and service.

The Hosokawa Group is a recognised world leader in powder processing technology and is highly innovative with developments coming out of its research centres based in Europe, USA and Japan. All products are designed, engineered and manufactured in house by the individual Hosokawa units which gives our customers a single source supply for guaranteed plants with validation documentation.

We can offer the pharmaceutical industry complete systems in the following areas:

- Mixing, Powder Blending
- Vacuum Drying
- Size Reduction / Size Enlargement
- Micronisation / Jet Milling
- Classification
- Compaction / Agglomeration / Low Pressure Extrusion
- Process Containment
- Hygienic Filling and Weighing

The HOSOKAWA MICRON GROUP’s broad range of powder and particle processing capabilities includes equipment and technologies for a variety of applications including:

- Drying / Vacuum Drying
- Size Reduction / Micronisation
- Screening / Air Classification
- Mixing / Powder Blending
- Product Collection
- Containment
- Agglomeration / Granulation
- Compaction / Low-Pressure Extrusion
- Hygienic Filling and Weighing
- Toll Processing

It is the strategic objective of the Hosokawa Micron Group to extend its leadership into future markets with high-technology products, to provide economic technical solutions and to ensure customer satisfaction.

HOSOKAWA MICRON places a strong emphasis on research and development. Major technical centres are located around the world. They are equipped and operated for the dual purpose of conducting original research work and demonstrating various processing systems. For our customers, the technical centres are used to develop and test formulations to meet their specific needs for powder and particle processing applications.

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HOW SYSTEMS ARE DESIGNED
Many design standards are used, for example:
- cGMP directives
- GAMP directives
- FDA requirements
- ISPE Bulk Guide
- 3-A Sanitary standards
- US. Dairy standards (USDA)
- A.S.M.E. or BS 5500
- DIN/ISO
- Alpine Pharma factory standards
- EHDEG directives

SYSTEM DESIGN FOR CIP/SIP
An increasing requirement for powder processing systems in the pharmaceutical industry is the need for them to meet CIP and SIP as this has several advantages:
- Reliable calibration, qualification and validation.
- Reproducibility of the cleaning parameters.
- Cleaning agents do not endanger personnel.
- Savings through shorter down times and reduced equipment dismantling times.
Special equipment designs, which facilitate CIP/SIP are offered, such as special seal bearings, one piece construction of equipment machined from a single piece of stainless steel and electropolished or finished surfaces down to Ra = 0.4 microns.

TAILOR-MADE SOLUTIONS
Our philosophy is not to just offer a standard machine but to work alongside our customers and provide tailor-made solutions to process problems using our maxim “customer and market orientation”.
With our in-house expertise, supported by major test centres throughout the world, we are able to supply solutions to even the most challenging processing problems.

CONSULTATION AND TRIALS
- Size reduction and micronisation
- Collection
- Mixing
- Compacting
- Granulation
- Low-pressure extrusion
- Spheronisation
- Filling, weighing and containment
- Analysis

BASIC ENGINEERING
- Conceptual studies
- Flowcharts - System layouts
- Safety concepts (risk analysis, Atex)
- Project documentation

PROCESS AUTOMATION
- Design, programming and networking of visualisation systems

SYSTEM ENGINEERING
- Project co-ordination / management
- Turnkey projects
- Construction site management
- Assembly - Commissioning
- CE certification

RENTAL MACHINES

TECHNICAL SERVICES
- System optimisation
- System upgrades
- Mechanical start-up and commissioning
- On site repairs
- Maintenance Contracts
- Servicing
- Spare parts

ANALYSIS
- Particle size analysis
- Air jet sieving
- Powder characterisation
- Sympatec (Helos/Rodos)
- Insitec particle size analysis
- Malvern Master Sizer
- Coulter Counter - Sedigraph
- Fischer Sieve Sizer analyses
- Scanning electron microscopy
- BET
- Vibrating screen - Wet screening
- Thermal Analysis TG/DTA and DSC

DOCUMENTATION
- Preparation of documentation (operating manuals, as-built documentation, qualification documentation, DQ, IQ, OQ)
- Implementation of IQ and OQ measures

QUALITY CONTROL (machines/systems)
- Surface roughness measurements
- Welding seam inspection
(X-radiology + ultrasound)
- Fluorescent penetration processes
**GLOBAL FACILITIES**

Hosokawa is a truly global operation with many operating units offering not only single machines but complete systems. Research, development, process optimisation, system design/engineering, project execution, project management, installation and commissioning - all can be provided for complete customer satisfaction.

Full manufacturing programme for each Hosokawa unit on request.

**TESTING FACILITIES**

Process guarantees are offered when materials are sent to our Test Centres for machine/process evaluation. Many units offer this facility and one of the largest and most comprehensive is with Alpine AG in Augsburg, Germany. The multi million dollar Test Centre completed in 1987 is one of the largest of its kind in the world.

Many of today’s drugs and pharmaceutical chemicals are toxic and cannot be handled safely away from their manufacturing base. Frequently placebos or similar low risk compounds are used to evaluate machines in supplier test centres. However as a Group we offer a rental machine service where specific equipment can be hired and tested on the customer’s own site using Hosokawa supplied installation/instruction teams. This rental route is a very useful one and provides customers with temporary production or pilot plant facilities. A further example of Hosokawa’s total commitment in satisfying customer needs.

**RENTAL MACHINES**

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In the pharmaceutical industry, especially when it comes to vacuum drying, we see a tendency towards multipurpose plants in which it is relatively easy to switch from product to product.

Thanks to flexibility in design (the product decides what technology is used), we are able to offer a wide range of technologies, which are all ideally suited to process the different active ingredients and excipients used in secondary pharmaceuticals. Our Vrieco-Nauta conical screw dryer is well known for drying temperature-sensitive products. Given the fact that it can work under vacuum condition, it enables drying even at ambient temperatures. Its well proven conical design makes it a very flexible dryer. Powder, filter cakes, paste, viscous slurries, no matter how free flowing or how sticky, can be handled. The conical shape makes the Vrieco-Nauta dryer self cleaning, leaving minimal product residue after discharge. To facilitate cleaning, we have developed the Cyberjet, our unique robotised CIP-system. Using gas, it is ideal for dry-cleaning optimising product recovery. Using wet cleaning, it is ideal for minimising liquid consumption whilst the reproducibility of the cleaning cycle ensures the validation of your cleaning process.

For drying under vacuum conditions, our vertical ribbon dryer (CT dryer) could be of interest, especially for free flowing powders and filter cakes. Furthermore it is excellent for sterilizing in place (SIP) and ensures optimal heat transfer for free flowing products.

A big step forward in the field of freeze drying as well as in powder-technology: In just one step and in one single unit, the Hosokawa Stirred Freeze Dryer (patent pending) creates the possibility to produce a non-lumpy and therefore easy to process uniform powder under low temperatures and low pressure. Suitable for temperature sensitive substances, living organisms and nano-materials.

One of the advantages of working with Hosokawa Micron is the fact that we offer complete integration of Hosokawa equipment, for instance drying and containment technologies. That combination ensures an absolute minimum of risk of contamination or pollution while charging or discharging, maintenance or taking samples.
The classic exponent of this type of mill is the spiral jet mill which is characterised by its ease of operation, excellent cleaning possibilities and the lack of rotating parts.

The new product line developed by Hosokawa Alpine retains all the time-proven elements but integrates a whole battery of new features to meet the requirements of the pharmaceutical industry, i.e. ease of dismantling, cleaning and sterilising, right up to CIP and SIP capability.

Various types of jet mills are employed for micronising active ingredients. This type of impact comminution in a gas jet generates end fineness of between 1 and 30 µm. With the fluidised bed opposed jet mills, even micronisation of extremely "difficult" products down to the µm range is possible. The integration of a dynamic air classifier in this jet mill guarantees reproducible ultra-steep particle size distributions with exact top size limitation. The carefully selected machine sizes range from laboratory and pilot applications up to production scale applications with throughputs of several hundred kg/h.

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**SIZE ENLARGEMENT / COMPACTION**

**DRY COMPACTION**

These unfavourable characteristics of finely powdered solid materials can be decisively improved through agglomeration. Press agglomeration is the most economic way to enlarge the particle size. Finely dispersed bulk materials are compacted and pressed into flakes, without using a fluid binding agent. Either smooth or profiled rolls are used. These flakes are crushed and screened to dust-free, easy-flowing granules.

The criteria for the machine design is easy cleaning and quick roll and predensifier screw replacement. A variety of screw and roll configurations are available to optimise the process.

**HOSOKAWA BEPEX PHARMAPAKTOR MODEL K 200/50**

with Flake Crusher in isolator. All drives and control components are in the separated non-hazardous area.

**HOSOKAWA BEPEX BEXROLLER**

AGGLOMERATION

The Schugi process for production of free flowing, closely sized granules with very good dispersing properties is well known and the FLEXOMIX continuous process can also be used for bulk pharmaceutical manufacture. A liquid binder(s) is sprayed into the flexing mixing chamber where adjustable blades or knives create a highly turbulent powder flow regime. Evenly sized granules mainly ranging between 0.2 to 1.5 mm are produced.

**HOSOKAWA BEPEX BEXTRUDER**

For the production of cylindrical pellets with diameters between 0.7 and 3 mm the BEXTRUDER will be used. The basis of these systems is the low pressure extrusion of products with sufficient gliding characteristics. For the production of spherical granules the BEXROLLER should be used. The batch sizes of this equipment are in the range from 0.2 ltr. to 50 ltr.

**SCHUGI FLEXOMIX MODEL FX 100 SHOWING BLADE KNIVES**

**SIZE ENLARGEMENT / AGGLOMERATION**

**BATCH FLUIDBED PROCESSING**

The Agglomaster’s unique fluid bed bottom design, with rotating slit disk and agitation blades together with its opposed pulse jet mechanism and the facility for liquid injection in different positions, creates a wide range of controls of not only the particle size, but also for instance the shape and density of particles. The Agglomerator design meets the requirements regarding easy access, dismantling and cleaning.

The Hosokawa Agglomaster, type AGM-2PJ&SD batch fluidbed processor, is a multi-purpose twin-unit of which one provided with “Opposed Pulse Jet” Technology and the other with “Spray Drying” Technology.

This multipurpose lab-unit is especially designed for research and development work.

**EXTRUD-O-MIX**

Designed to continuously mix, agglomerate and extrude, the Hosokawa Rietz Extrud-O-Mix operates with a kneading action making it suitable for use with materials ranging from light pastes to heavy doughs. Dry materials may be mixed and extruded with small quantities of liquid for agglomeration with additional liquids introduced through injection points along the Extrud-O-Mix barrel.

- Split barrel for easy cleaning and plate changes
- Negative pressure dust elimination for clean environments
- Exchangeable intervals design for process optimisation

**HOSOKAWA BEPEX PHARMAPAKTOR C 250**

**HOSOKAWA BEPEX BEXTRUDER**

**AGGLOMASTER AGM-2PJ&SD**

**PROCESS TECHNOLOGIES FOR TOMORROW™**

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CONTAINMENT TECHNOLOGY

Incorporating a wide range of inflatable and extraction type sealing heads the filling and weighing systems when combined with a Vitalair downflow booth maintain the highest levels of dust control, hygiene and product integrity. Accurate, integrated weighing platforms ensure critical and repeatable packing specifications can be met. These facilities are suitable for use with a range of bags, sacks, drums and boxes with or without liners, both the Stott filling systems and Vitalair booths are available for manual or automated operation.

DUST FREE TIPPING BOOTHS
Containment Level 500 - 1000 µg/m³

Safe, hygienic discharge of drums or bags can be achieved within a purpose designed, manual action or automated Stott drum tipping booth. Container disposal and cleaning can be incorporated into this system for increased product containment and operator safety.

STOTT FILLING AND WEIGHING SYSTEM WITHIN A VITALAIR DOWNFLOW RECIRCULATION BOOTH

QUAD CELL, SOLIDS DISCHARGE DRUM TIPPING BOOTH

DISPENSING SUITE INCORPORATING VITALAIR DOWNFLOW BOOTH

LAMINAR FLOW BOOTHS
Containment Level 100 - 500 µg/m³

For increased levels of environmental protection, operator safety and product integrity the range of Stott laminar flow booths with their single pass, non turbulent air flow and entrance protecting air curtain can be utilised in conjunction with the Stott filling and weighing systems. They are also suitable for inspection, product transfer or liquid pumping applications. As the requirement for greater levels of containment increases, Hosokawa specialist barrier/isolation technology is more widely used to safe guard the environment, personnel and maintain product integrity.

Hosokawa’s extensive experience of clean air environments and associated technology means we are able to work closely with our customers from initial specification to commissioning to ensure individual requirements.

STOTT FILLING AND WEIGHING SYSTEM WITHIN A VITALAIR DOWNFLOW RECIRCULATION BOOTH

DOWFLOW BOOTHS
Containment Level: < 25 - 100 µg/m³

Fully self contained areas for the handling of hazardous powders and liquids, downflow booths use the vertical passage of clean air from the booths ceiling plenum to push dust or vapours away from the operators breathing zone. Achieving a minimum 99.99% filtration performance the high levels of operator protection and product integrity offered makes them ideal for all dispensing, transfer, sampling, mixing and weighing applications.

GLOVEBOXES AND ISOLATORS
Containment Level: < 50 ng/m³ - < 5 µg/m³

Where pharmaceutical companies wish to retain a shirt sleeve environment without the need for operators to wear protective suits, isolators offer an ergonomic option. We can incorporate process equipment inside isolators to provide the ultimate clean environment for processing, cleaning and maintenance.

Although world leaders in containment of dry particulate powders, the Wet Chemistry isolator has been designed primarily for working with liquid forms of potent active ingredients to give easy but contained operator access with OEL’s < 1 µg/m³.

ISOLATOR (OEL < 1 µg/m³)
WITH 50 AS AND PHARMA MICRO METERING SCREW PMD

INTEGRATION OF ALPINE 315 UPZ INTO STOTT ISOLATOR

WET CHEMISTRY ISOLATOR

Innovative design has seen the development of the Flexible Compact Isolator FC whose modular design and canopy flexibility meets demands for a cost effective, flexible barrier containment solution, offering high product and personnel protection.

STOTT KEG FILLING ISOLATOR INTEGRATED WITH VITALAIR DOWNFLOW BOOTH

INTEGRATION OF ALPINE 315 UPZ INTO STOTT ISOLATOR

FELXIBLE ISOLATOR (OEL < 10 µg/m³) WITH 50 AS IN PVDF

Powder and Particle Processing

Hosokawa Containment are setting the standard for innovative, high quality process containment for the pharmaceutical industry.

Process Technologies for Tomorrow™
The Hosokawa Micron Group offers a large range of ancillaries of own manufacture and superior quality. These components are tailor-made to our customers’ requirements.

**FOR EXAMPLE:**

- **THE PHARMA DOUBLE FEED METERING SCREW PDD**
  - Alpines metering screw was developed especially for cGMP pharma applications. Characteristic for the twin metering screw is its modular design (drive unit, bearing unit, product bin) and ease of dismantling. A clear division between product-contact zone and drive as well as the ability of autoclaving the subassemblies are also advantages.

- **BALL SEGMENT VALVES**
  - An integrated horizontal agitator prevents the formation of arches above the feed screws, even if the bulk material has poor flow properties. The pharma feed screw is also certified for operation in potentially explosive atmospheres (ATEX zones 1 and 21). The metering screw is available in volumetric or gravimetric – i.e. as a differential weighbelt feeder – design. The feed rate ranges from approx. 2 to 130 l/h, dependent on the product line. Hosokawa Alpine also offers a micro feed screw for small throughputs, whereby the feed rate here is between 0.15 and 2.8 l/h. Because of the pharma-qualified design of both feed metering units, product residues are reduced to a minimum.

- **HEPA FILTERS**
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- **INLINE HEPA FILTER**
  - A range of pre-filtration high efficiency easy clean cyclones are also available for collection of pharmaceutical products and they are sometimes used prior to the final product filtration unit to collect the majority of product.

- **HEPA FILTERS**
  - Responding to customer needs we offer a safe change push-push technology HEPA/Ultrafilter unit, designed for all toxic or sterile systems. Elements specially designed for fitting to the units can be supplied up to grade EU14. Filter housings manufactured in a variety of materials, from stainless steel to special chemically inert polymers, tailored to suit individual customer processes. Special design for inline filtration up to 10 bar g PSR with CIP options.

**PROCESS TECHNOLOGIES FOR TOMORROW**

- **ANCILLARIES**
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Hosokawa offer a total engineered solution from initial process conception to final validated plant.

We are your single source supply for integrated powder and particulate processing systems and component machinery. We offer a range of services to ensure your pharmaceutical processing needs are met:
- Laboratory testing
- Full scale trials or site trials
- Process design
- Procurement
- Engineering and project management
- Installation
- Commissioning
- OEL testing

We provide a complete service and give documentation and assistance with the four basic stages of our customer’s validation namely DQ, IQ, OQ, and PQ.

**PROCESS TECHNOLOGIES FOR TOMORROW**

**TURNKEY PROCESS SYSTEMS**

**MATERIALS OF CONSTRUCTION**

High quality stainless steel such as AISI 304, 304L, 316, 316L, or even Hastelloy or Titanium are used. One piece construction of individual machines using CNC machining to create Hosokawa’s unique “mono-block” designs is used wherever appropriate.

**OPERATIONAL TRIAL EQUIPMENT**

Hosokawa are able to offer a range of equipment on loan/rental to pharmaceutical companies to enable operational trials to take place. This ensures that process parameters can be finalised and production flows monitored prior to equipment and process layout finalisation. At this stage the highly experienced Hosokawa engineers will work very closely with your in-house engineering team to advise and develop the best solution to your processing requirements.

**SERVICE**

Hosokawa is committed to providing continual customer support, long after the plant has been installed and commissioned. We have highly skilled Service engineers to cover machinery breakdowns, routine inspections and servicing on site. Whilst our experienced technical engineers can provide both process and maintenance advice.

**MILLING SYSTEM WITH MIKRO ACM 10 CLASSIFIER MILL**

Process Guarantees can be given after testwork in our Group Test Centres, hence a one-source totally engineered package is offered. CAD systems are used to create flow-sheets, P & ID drawings, layouts, detailed designs to whatever code is being employed and units operate to the Quality System ISO 9001. The design of a safe system is of paramount importance and dust explosions with organic pharmaceutical powders are nearly always a real risk. This risk can be minimised by avoiding a source of ignition but this is frequently not possible in high-speed rotating equipment, and then the system has to be designed to contain any explosion. Normal explosion relief by venting is not usual in the pharmaceutical field, but if this is acceptable then this method too can be designed in. A pressure-shock-resistant (PSR) design is more usual, and here the system is designed to withstand the maximum explosion pressure, usually under 10 bars, without rupture. A typical design code is the German VDI 2263, and this calls for all vessels to be specially strengthened, and in some cases full pressure vessel design codes may be specified. Running systems under an inert gas such as nitrogen is also frequently used to stop any explosion from occurring, and Hosokawa has supplied many such systems for size reduction, blending and drying.

The process components delivered by Hosokawa and the associated control panels and cabinets all fully meet the requirements laid down in the prevailing national and international directives, especially 94/9/EC (ATEX) and 21 CFR part 11.

**MULTI-PROCESSING MILLING SYSTEM INCORPORATING ALPINE 70 ZPS AND 140 AFG**

**SYSTEM DESIGN EXPLOSION PROTECTION**

The integration of several powder processing operations into one turnkey system calls for carefully managed and executed engineering and it is in this field that Hosokawa units have extensive experience.

* = available

<table>
<thead>
<tr>
<th>GAS-EX</th>
<th>DUST-EX</th>
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<tbody>
<tr>
<td>Zone 0</td>
<td>Zone 1</td>
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<tr>
<td>Control panel</td>
<td>●</td>
</tr>
<tr>
<td>Drive technology</td>
<td>●</td>
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<tr>
<td>Actuators (valves)</td>
<td>●</td>
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<tr>
<td>Sensors</td>
<td>●</td>
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<tr>
<td>Measuring technology</td>
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</tbody>
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**= available**

Feed metering screw with feed bin and shut-off valve
Fluidised bed opposed jet mill AFG
Automatic reverse jet filter with bin and fluidisation unit
Filter head
Rotary valve
Explosion-protection valve
Safety filter
Fan
Packing machine
Sampler
Control cabinet
The connection of field measurement technology to the control unit is being realised increasingly via communication systems such as Profibus DP, FMS, and PA or via the industrial Ethernet. Intelligent network components which can also be used in potentially explosive areas minimise the amount of wiring necessary, thus contributing to a reliable and moreover visually aesthetic solution. The lifecycle approach as described in the GAMP directives is our model in fulfilling this solution. The scope of activities ranges from preparing the hardware and software specifications to writing programs based on PLC systems or also highly integrated visualisation systems. Great store is set by data integrity and data archiving as well as error message protocols and batch records. The integration of electronic signatures is being realised according to the requirements stipulated in 21 CFR Part 11.

Because state-of-the-art GMP-compatible process solutions demand sophisticated and integrated automation, Hosokawa has extended its range of products and services beyond the supply of mere hardware.

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PROCESS TECHNOLOGIES FOR TOMORROW

1. POWDER AND PARTICLE PROCESSING

HOSOKAWA is the world's largest provider of processing systems for the field of powder and particle processing. Renowned names such as ALPINE, Hosokawa Bepex, Stott, Vitalair, Hosokawa Rietz, Mikro, Micron, and Vrieco-Nauta are all included in the Group's range. Regardless of the size, i.e. production-scale systems, pilot systems or laboratory equipment, HOSOKAWA's products and technologies are used in numerous process stages, for example during comminution, mixing, drying, agglomeration, classification, weighing and metering.

2. BLOWN FILM PROCESSING

HOSOKAWA ALPINE is one of the world's foremost suppliers of film blowing systems. As a one-stop shopping partner, Alpine supplies complete systems for the manufacture of blown film, from granule feeding systems to film winders, from single-layer die heads to 7-layer lines, and from simple speed regulators to state-of-the-art process control systems. And with ALPINE's own film orientation lines, complete systems are now available which facilitate film upgrading and enhancement processes.

3. CONFECTIONERY & BAKERY TECHNOLOGY

The vast fund of know-how built up by the Bepex, Kreuter and Ter Braak companies over many long years makes the HOSOKAWA Confectionery and Bakery Group the ideal partner for the confectionary industry. A complete range of machines and production systems is available or can be custom-designed for each process step, from preparation of the raw materials and confectionery pastes to the end product.

The group maintains facilities for research, engineering, manufacturing and service in each of the world's major industrial markets.