

HOSOKAWA ALPINE Aktiengesellschaft
P.O. Box 10 11 51
86001 Augsburg, Germany

Delivery address:
Peter-Dörfler-Straße 13 – 25
86199 Augsburg, Germany

Tel.: +49 821 5906-0
Fax: +49 821 5906-620
E-mail: pharma@alpine.hosokawa.com
Web: www.alpinehosokawa.com

Subject to change without notice.
All information in this brochure is purely
informative and non-binding. Our quotations
are authoritative with regard to orders.

ALPINE HIGH CONTAINMENT FULLY INTEGRATED SOLUTIONS



HOSOKAWA ALPINE Aktiengesellschaft

Hosokawa Alpine is a member of the Hosokawa Micron Group, a high-performance manufacturer of systems for powder and particle processing, systems for the confectionery industry as well as plastics processing machines and systems. The group is known and reputed the world over for its power of innovation, constant product care and market-oriented R&D. The most important group resources are R&D, engineering and manufacturing as well as customer service in all global markets.

© Hosokawa Alpine 2008. Printed in Germany.



HOSOKAWA ALPINE

PROCESS TECHNOLOGIES FOR TOMORROWSM

POWDER AND PARTICLE PROCESSING FOR THE PHARMACEUTICAL INDUSTRY

ONE OF OUR CORE BUSINESS ACTIVITIES



WE ARE YOUR COMPETENT PARTNERS



The Hosokawa Micron Group is the largest supplier of systems for powder and particle processing around the world. Renowned brands such as Alpine, Bepex, Stott, Vitalair, Rietz, Mikro, Micron and Vrieco-Nauta are included in the Group's product range.

PROCESS SOLUTIONS FOR THE PHARMACEUTICAL INDUSTRY

Hosokawa is a group of companies that is active and represented throughout the world with its sales networks, manufacturing facilities and testing centres. The pharmaceutical industry constitutes an extremely important business segment. Over the years, the Hosokawa companies have made a point of investing heavily in the further development and modernisation of its services for this sector.

As a result of this commitment, Hosokawa has built up an enormous fund of expertise and is thus able to offer pioneering technology and services. The Hosokawa Group is the global market leader when it comes to machines and systems for the production of fine powders, and is moreover highly innovative thanks to its R&D activities in testing centres in Europe, USA and Japan.

All machines and systems are manufactured on site in the individual Hosokawa companies. The concept of single-source supply means that complete systems with guaranteed process-technological parameters and validated documentation are supplied to the customers, whose planning and coordination complexity is thus reduced enormously.



Regardless of whether a production system, pilot plant or laboratory equipment, Hosokawa products and technologies are employed in numerous process stages:

- Mixing
- Vacuum drying
- Comminution
- Grinding and micronisation
- Agglomeration and compacting
- Classifying
- Isolators with integrated processes
- Hygienic product handling and weighing

Increasing occupational safety requirements and the use of highly active pharmaceutical substances force both manufacturer and processor to reassess their system concepts. This applies equally to new and existing systems. Above all in R&D, flexible containment systems have proved themselves as inexpensive solutions that can be realised quickly and easily. Whereas the type of mill is usually known when a system for grinding or micronising active substances is being designed, integration of the grinding technology into an isolator constitutes a new challenge.

Isolator manufacturers may be experts for product handling and transfer, but the specialised process-technological know-how needed for complex grinding/processing systems demands a more detailed knowledge of things such as the gas/air supply to the grind-

ing process, feed metering, product collection, safety concept and protection against pressure loss. And because the responsibility for the entire process should logically be taken by a manufacturer who masters both processes, Hosokawa Alpine decided in 1998 to develop and build integrated containment systems for its customers.

This strategy has proved itself to be a good one because of the significant advantages for the customers: they receive a complete solution from one single source, and the lack of interface problems between the isolator manufacturer and the manufacturer of the grinding system means that operational sequences are accelerated and costs are reduced. The successful installation of numerous integrated containment systems since then proves that Hosokawa Alpine is on the right track.

EVERYTHING FROM ONE SINGLE SOURCE ALSO MEANS CENTRAL RESPONSIBILITY



For OELs (occupational exposure levels) of down to 50 ng/m³

Over the last years, the trend towards isolator technology has increased in the pharmaceutical industry. In the case of process-technological applications such as the grinding or compaction of powders, protecting the operating personnel from active substances is a top priority. Isolators are employed in the implementation of high-containment applications. Practice has shown that every isolator must be adapted to suit not only the specific demands of a pharmaceutical product and its manufacturing process, but also the batch size and the technical environment in the production facility. In order to meet the requirements of a completely enclosed process configuration with a guaranteed OEL value, Hosokawa has refined

the technologies already available on the market sector of isolators and containment systems.

PERSONAL PROTECTION

Personal protection is understood here to be an arrangement of isolators operated under negative pressure which encapsulate the critical points of the process. The work steps that cannot be automated rationally are carried out via glove ports. This can, for example, be the filling of containers, the exchange of tools as well as the inspection or cleaning of equipment.

STERILE SYSTEMS

In the case of products such as antibiotics, their aseptic manufacture in a sterile system is a requirement. Dependent on the concept, the isolator is laid out for negative and/or overpressure and for SIP.

Dependent on the requirements, different isolator concepts can be realised:

- HIGH-END ISOLATOR

made of stainless steel with windows of safety glass, with safe-change filters in push-push design, with alpha/beta transfer systems, designed for WIP/CIP.

- GLOVEBOX

Glovebox(es) made of, for example, acrylic glass with simple filter and transfer systems.

- FLEXIBLE ISOLATOR

The isolator with flexible polymer skin and endless-liner-system.

Developed in response to the demands for an inexpensive, flexible encapsulation of systems used for handling of active material in the laboratories a flexible isolator offers excellent operator and product safety.



GRINDING PROCESS WITH GRAVIMETRIC FEED METERING AND IN-LINE PARTICLE ANALYSIS



FLEXIBLE ISOLATOR WITH DISPOSABLE SPIRAL JET MILL



ULTRAFINE MICRONISING WITH THE SPIRAL JET MILL AS



The integration of processing systems into isolators puts high demands on the engineering, and when customising the isolator, the following aspects must be paid particular attention to:

- Customer's product flow
- Transfer port system concept
- Operating comfort (ergonomics)
- Process safety
- Operator safety
- Product yield
- Cleanability
- Control concept

The isolator must be integrated into an existing product flow, meaning that special attention must be paid to the process steps upstream and downstream of the isolator. The type and the shape of the infeed or discharge containers have a decisive influence on the transfer port concept. Dependent on the batch size or OEL value, double-flap valve ports, RTPs or endless-liner-systems are available.

One of the greatest challenges when integrating processes into isolators is to ensure that the entire system can be operated comfortably, i.e. ergonomically. This simple statement puts extreme demands on the manufacturers of complex systems in terms of design of both the process components and isolators.

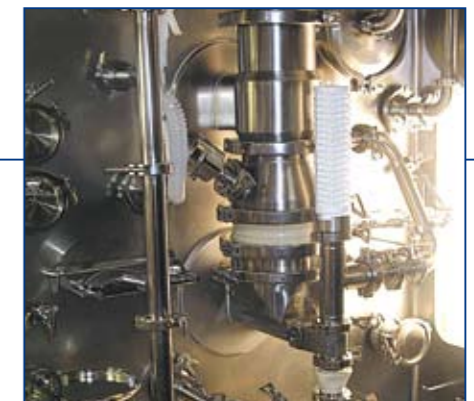
Advantages of the integrated Hosokawa Alpine solution:

- No interface between process or machine supplier and isolator manufacturer
- Optimum matching of system components and isolator
- Process safety
- Intelligent concept from the process and containment to cleaning and automation.

JET MILLING WITH THE ALPINE FLUIDISED BED OPPOSED JET MILL AFG WITH INTEGRATED AIR CLASSIFIER



PRE-CRUSHING WITH THE CONICAL SCREEN MILL BEXMILL BM 125





ONE ISOLATOR - SEVERAL GRINDING PROCESSES

Hosokawa Alpine builds isolators with integrated multi-processing systems for the optional operation of different grinding processes.

The advantages of multi-mill systems are convincing:

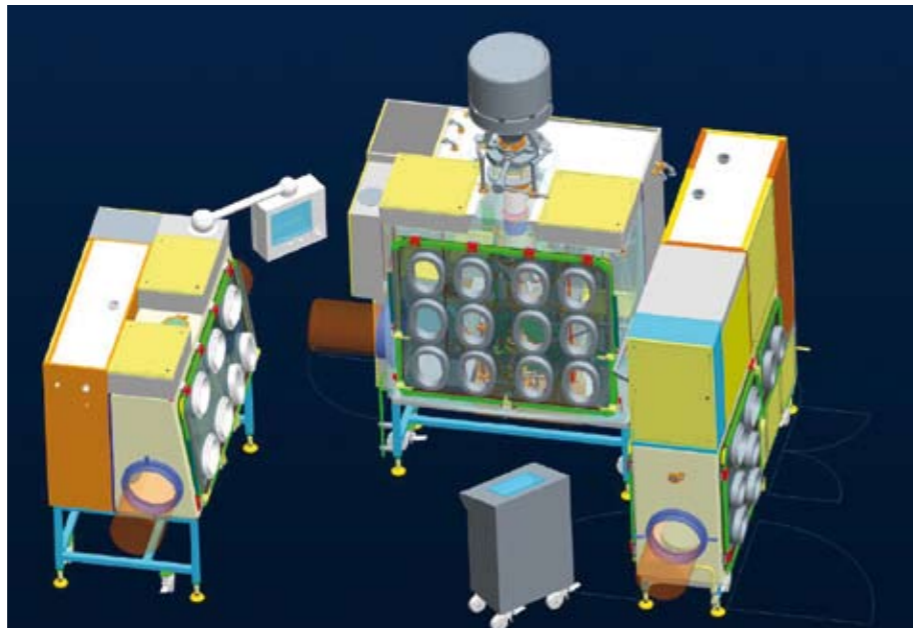
- One isolator, a number of different grinding systems
- Maximum flexibility
- Low space requirement (one clean room)
- Reduced capital expenditure
- Short cleaning times
- Optimum yield
- Flexible in terms of different batch sizes and containers.



ALPINE SPIRAL JET MILL AS CAN BE EXCHANGED FOR ALPINE FINE IMPACT MILL UPZ

An isolator system with several integrated grinding systems offers the user a high degree of flexibility, both for R&D applications (100 g to 5 kg) and for the production of large batches. The following machines are employed:

- A) Fluidised bed opposed jet mill AFG for fineness values down to 2 µm
- B) Ultrafine classifier ATP, separating range between 2 µm and 100 µm
- C) Classifier mill ZPS for fineness values down to 10 µm
- D) Spiral jet mill AS for fineness values of 5 µm to 30 µm
- E) Fine impact mill UPZ for fineness values down to 50 µm



MULTI-PROCESSING SYSTEM (4 MILL TYPES) WITH FILTER AND CLEANING ISOLATOR

NEW PICO SERIES

Combination possibilities				
AFG	ATP	ZPS	AS	UPZ
40	20	-	32	32
100	50	50	100	100
140	70	70	140	-
200	100	100	200	160



ALPINE SPIRAL JET MILL 50 AS WITH PMD PHARMA-DESIGN MICRO FEED SCREW



ALPINE SPIRAL JET MILL 100 AS WITH PHARMA-DESIGN METERING SCREW



ALPINE FINE IMPACT MILL 315 UPZ FINE GRINDING ON A PRODUCTION SCALE

RESEARCH AND PRODUCT DEVELOPMENT

Because at this stage of development, very little is known about the potency of the feed materials and the trend towards increasingly active pharmaceutical ingredients cannot be neglected, the protection of personnel and thus integration of the processing system into a containment system becomes a top priority.

PRODUCTION

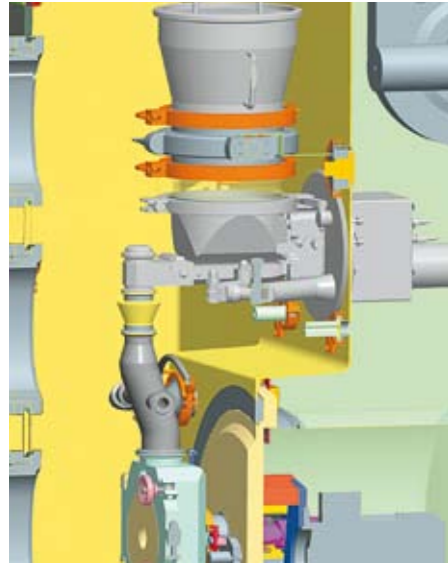
During production of large batches or the continuous production of highly active substances, the containment focus is on the system sections at which dust development can be expected:

- Filling and emptying process
 - Weighing and packing
 - Process components such as mill and feed metering unit, etc.
- In these cases, specially designed mills and system components are employed that permit handling in an isolator.

ISOLATOR AND PROCESS COMPONENTS



Alpine offers a completely integrated volumetric or gravimetric feed screw which requires no cables, no load cell and no weighing platform inside the isolator.



PROCESSING AREA AND TECHNICAL AREA COMPLETELY SEPARATE FROM EACH OTHER



FEED METERING UNIT (OPEN)



FEED METERING UNIT (CLOSED)

TOTALLY INTEGRATED FEED METERING

With Alpine's pharma-design feed metering screw, it is only the actual process components that are installed inside the isolator chamber.

GRAVIMETRIC / VOLUMETRIC

- Totally integrated solution
- Drive in the technical area
- Gravimetric feed screw with weighing platform also in technical area
- Decoupling achieved by means of highly flexible Alpine EZConnect expansion joints and special sleeves
- Only process components inside the isolator, no components that are difficult to clean inside the isolator

INNOVATIVE INTEGRATED FILTER (PATENT PENDING)



- Swivel arms for weights > 8 kg
- All components can be dismantled, cleaned and reassembled with the isolator closed
- Consistently ergonomic concept

FILTER

Innovative solution (patent pending) of a completely integrated automatic filter. Can be operated as:

- Automatic reverse jet filter for large batches or continuous operation
- Static filter for mini batches
- Simple and optimum adaptation to the respective batch size
- Optimisation of processing times, yield and cleaning times
- Filter can be dismantled inside the isolator without having to open it



CUSTOMISED SOLUTIONS FROM ONE SOURCE

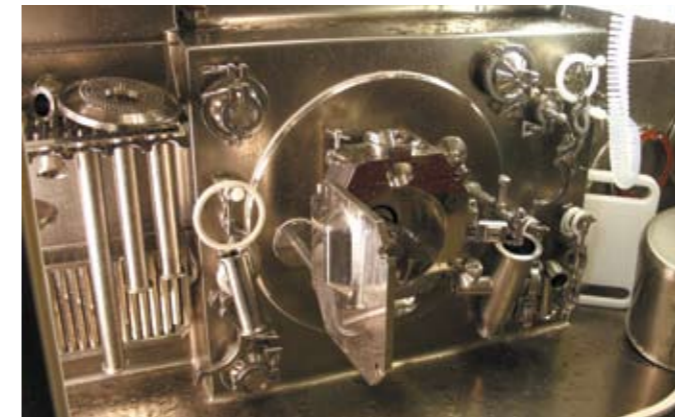


It's often the little things that count when it comes to ergonomic handling in the isolator



INTEGRATED WIP/CIP SYSTEM (AUTOMATED DRYING ALSO AVAILABLE TO ORDER) OPTION: SIP

DISMANTLED PIN MILL AFTER THE WIP PROCESS



WELL THOUGHT OUT - RIGHT DOWN TO THE LAST DETAIL

- A specific bracket permits easy and ergonomic installation of the filter cone
- Hygienic design of vibrator at product cone
- Special illumination inside the isolator
- Shelf for all parts such as ductings and clamps needed for dismantling and cleaning
- Design and work sequences optimised during mock-up operation.



ATEX-CERTIFIED DESIGN

- Installation in Ex-zone, if necessary with purging or overpressure encapsulation
- Selection of suitable instruments
- Complete potential equalisation of system including gloves



THE TECHNICAL ZONE IS AN INTEGRAL PART OF THE ISOLATOR

The following functions and units are accommodated in the technical zone:

- Process gas distribution
- Separate routing of process gas and isolator air
- Instrumentation
- Inerting
- HEPA safety filter
- Drives
- Cables
- Complete control system
- Supply lines for WIP system

ADVANTAGES OF TECHNICAL ZONE

- Compact set-up
- Mobile unit
- Delivery of a complete "Plug and Play" system that is ready for operation
- No exposed instruments or drives in clean room



Our systems can be equipped with an on-line particle size analysis unit to optimise process management



The User Requirement Specification (URS) informs us of the fundamental system specifications and thus of the requirements placed on the grinding system.



MOCK-UP

PLEXVIEW - THE PROCESS VISUALISATION MODULE

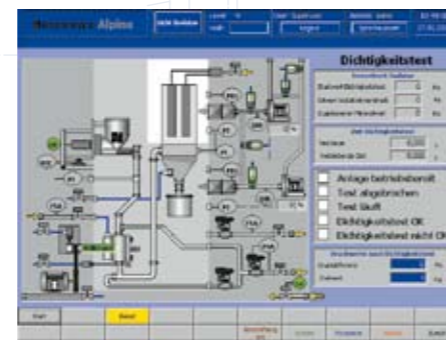
The process sequence and the process parameters are represented graphically on screen. The system flowchart forms the basis for visualisation, and is formatted, animated and supplied with the requisite process parameters for representation on screen. Process operation is also carried out with the visualisation unit. The user interface has a clear design; the operator is guided intuitively through the hierarchical menus. This prevents operating errors and avoids the necessity of additional training measures.

System automation brings convincing advantages:

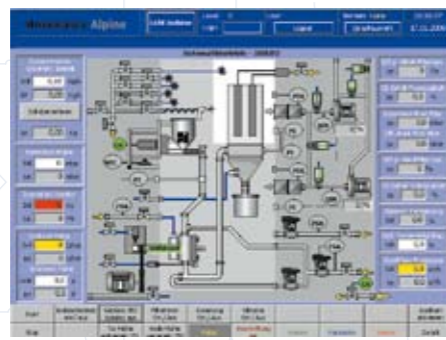
- Control of the grinding process and of the isolator in one system
- Constant status display of the complete system
- Menu-guidance through the different operating modes
 - * Leakage test
 - * Inerting
 - * Processing mode
 - * Cleaning mode
 - * Drying
- Storage of process data
- Trend visualisation
- Error message/alarm archiving
- Password management
- Recipe management
- Design as defined in GAMP 4/5 and 21 CFR Part 11



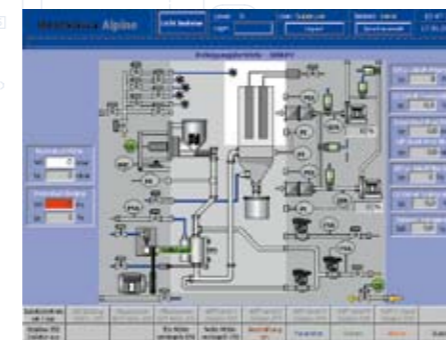
UPZ OPERATING MODE SELECTION



UPZ LEAKAGE TEST



UPZ AUTOMATIC MODE



UPZ CLEANING MODE

Upon receipt of the URS, the characteristic process data such as the end-product fineness and throughput rate, etc. are determined, and the system-specific parameters such as construction materials and surface qualities, etc. are defined. The resultant system configuration is checked during the subsequent qualification phase for agreement with the URS.



MOCK-UP

PROJECT REALISATION:

ALPINE RENTAL ISOLATOR

With our rental isolator, we offer our customers the possibility of gathering experience with an integrated isolator system and of generating an optimum URS.

3D DESIGN STUDY

Based on our experience and in close collaboration with the customer, we develop a 3D system concept which serves to graphically illustrate the ergonomic issues.

MOCK-UP

To permit assessment of the design study, we make a 1:1 wooden model that allows all the important process steps to be simulated with the original components wherever possible. In this project phase, the final positions and dimensions of the system components and of the glove ports, etc. are determined and the ergonomics are checked.

3D DESIGN STUDY

DETAILED DESIGN

On the basis of the mock-up, manufacturing drawings are prepared and special solutions are developed where necessary.

MANUFACTURE/ASSEMBLY

Manufacture, assembly, wiring and connection to the control unit all take place on Alpine's premises, thus ensuring that all interfaces are optimally matched to each other.

FAT/SAT

The executed quality of the system is checked by means of the factory and site acceptance tests (FAT/SAT). Compact systems are assembled completely on Alpine's premises and subjected to a FAT, which reduces the effort for the SAT to a minimum.

COMMISSIONING/TRAINING

Alpine supports its customers during system commissioning and provides training for the operating personnel.



FAT/SAT