

## Mixing and Granulation



*Collette Technologies*





# Product know-how

## Process expertise

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Collette has supplied mixing and granulation systems to various industries for more than a century, and to the pharmaceutical industry in particular for more than 50 years. Based on this experience, Collette supplies advanced solids processing systems for mixing, granulating and drying in the pharmaceutical industry. This includes small capacity systems designed for R&D as well as industrial size plants for batch and continuous production of pharmaceutical compounds under cGMP conditions.

Collette's plant and process expertise is based on experience and R&D. With more than 1000 plants installed around the world and literally thousands of tests performed, it has established a solid base of expertise related to the needs of the pharmaceutical manufacturing industry.

### **Delivering the right solutions**

Every Collette project begins with the customer's desire to create a product that will succeed in the market. In Collette, the customer finds a partner who will assist in meeting that goal. Collette's expertise lies in the processing of Active Pharmaceutical Ingredients into secondary pharmaceuticals using technologies such as blending, granulation, drying, pelletising and crystallization.

### **Plants customized for success**

Every pharmaceutical plant and system from Collette is a unique union of proven technology and individual solutions. The company supplies plants for cGMP production based on standard components configured to meet the customer's specific requirements.

### **Safety and the environment**

Collette offers a range of solutions, fully compliant with national, local and in-house regulations, to control product containment, explosion safety and solvent emission, including solvent recovery systems and full containment plants. Equipment can be supplied to meet explosion proof and pressure shock resistant standards as required.

### **A partnership in every perspective**

Working with Collette means working in a solid partnership every step of the way. From process testing and design, to specification of the software controlling the customer's plant. Collette's comprehensive after sales program ensures that the customer's return on investment is optimised throughout the lifetime of the plant.



## Process technologies

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Whether the customer's requirement is for mixing or granulation, Collette has a solution for every processing challenge and can help select the technology that is most suitable for the product and process.

### Dry mixing

Whatever the subsequent production steps, the formulation of an active compound and other excipients needs to be mixed homogeneously. High shear mixing uses a high intensity mixing blade resulting in a homogeneous blend. Other mixing and blending solutions are available from GEA Pharma Systems.

### High shear wet granulation

The high shear granulation process combines the components of the formulation using a high speed mixing blade and chopper. This process results in granules of a fixed composition, which avoids segregation in later processing steps. During the granulation process, density and compressibility of the product is modified to achieve the optimal flow and tableting properties.

### Melt granulation

In a melt granulation process, the binder solution of a standard wet granulation process is replaced with a meltable binder. This binder can be added in molten form, but the high shear process offers the benefit of allowing the binder to be added in its solid state. Melting is achieved by the energy added through the mixer friction and the heated jacket of the bowl.





# Built-in versatility

## **Effervescent production**

Producing effervescent granules can be achieved in many different ways. High shear granulation is suitable for both 2-step and 1-step granulation techniques. Even water can be used as granulation liquid when the granulator is integrated with a fluid bed dryer, or is equipped with its own drying techniques (Single Pot Processing).

## **Pelletizing**

The formation of pellets can be considered as granulation taken one step further, to achieve spherical granules. For high shear pelletization, a special mixing tool is available to optimise the process and maximise the output.

## **Substrate production for extrusion**

High Shear mixing is an excellent method of producing the wet substrate needed for an extrusion process and is often used as the first step before an extrusion spheronization line.



*More than a century of mixing experience*



## History

Collette nv was founded in Antwerp in 1892 as a manufacturer of mixers and kneaders for the baking industry. Over the years, the equipment range expanded and diversified to cover equipment for other industries and, from the early fifties, the pharmaceutical industry.

The major breakthrough in the pharmaceutical industry came with the introduction of the first High Shear Mixer Granulator (GRAL) in 1975. In 1980 the Single Pot concept was introduced with the TOPO-design and the GRAL-processor, and shortly afterwards, the Process Development Center opened, a test lab for the customers to explore this new technology.

With the introduction of the Vactron in 1990, Collette nv was one of the first machine manufacturers to promote microwave drying for pharmaceutical applications, emphasising its focus on this industry.

Within the pharmaceutical industry, Collette stands for innovation, new technologies, reliability, service and know-how. As part of the GEA Pharma Systems Group within GEA, Collette is able to offer many advantages in support and synergy including full process line design and turnkey project management.

The test laboratories within the GEA Pharma Systems Group, the PDC in Belgium and the GPS Technology Centre in Switzerland, play a very important role in Collette's customer relationships by providing process development and process understanding within Collette's equipment range.



## High Shear Mixing Technology

With the Gral range, designed in the '70s Collette pioneered the market of top-driven High Shear Mixers Granulators. The workhorse of Collette went through various upgrades over the years and is still one of the most wanted High Shear Mixers in the market today. Collette offers today a state-of-the-art range of Grals with a wide range of bowl capacities to suit any production requirement. The equipment is built to comply with current cGMP standards and is recognized by companies worldwide as high quality, robust and reliable and low maintenance.

### Unique process design

The key to success is the unique design of vessel and mixing tools. The angled position of the mixing blades combined with the rounded edges at the bottom of the vessel guarantee the typical rope-type movement for optimal flow of product during granulation. Several binder liquid spray systems are available to suit your process. Bowl and mixing blades are shaped and mounted to minimize clearance for maximum yield, without locally overheating the product. During a discharge cycle, the centrifugal force created by the rotation of the mixing arm will push the product in a natural way to a proportionally regulated outlet valve at the side without compacting the wet granules. This way we can accurately dose the finished granules to a calibration unit, connected to the outlet.

### User-friendly operation

Many features of the Gral ensure that the equipment is easy to operate. Loading the powders can be executed by gravity. An inspection window is incorporated in the bowl cover for visual process monitoring. The height of the bowl outlet allows for an open discharge in the product vessel of the dryer or for an inline connection with a calibrating unit and vacuum transfer piece for closed transport of the wet granules to the

Fluid Bed Dryer. A bowl trolley is available for easy removal of the bowl. Process controls and automation are available by means of PLC and operating panel, with optional recipe control.

### Cleanability, safety and maintenance

The top driven design ensures that the shaft seals are not in contact with the product. The shaft seals are dry running and mounted in a cartridge, which eliminates cross-contamination and allows easy cleaning and inspection. The construction is extremely robust and requires hardly any maintenance. All mechanical and electrical parts are easily accessible from the technical area behind the machine. The machine can be executed as fully enclosed and free-standing in the room or can alternatively be built through-the-wall. The machine complies with the most stringent safety regulations and can be equipped for granulation with organic solvents.

### Flexibility

With bowl capacities of 10 to 1200-L (useful bowl content up to 2/3 of gross capacity) the Gral range of High Shear Mixer Granulators can cover all needs from lab scale to production scale. Special mixing tools are available for specific applications, as well as a jacketed bowl for temperature control during the process.

### 100% Compatible with the Ultima™ Range

As bowl shape, mixing tools and process parameters are exactly the same, all processes running on the Gral range can be immediately transferred to the UltimaGral™ and UltimaPro™ granulators without changing any parameters.



# High Shear Technology



Using proven standard components of the Gral range, Collette can supply both simplicity and flexibility in plant design with the Ultima™. User selected process options, control systems and liquid preparation units combine to exactly meet process requirements. This approach ensures that qualification and validation efforts are kept to a minimum.

## Through-the-wall configuration

Through-the-wall offers the best option in terms of cleanliness, maintenance and explosion protection. The through-the-wall configuration provides a sealed separation between technical and GMP space by the machine itself. This offers a clear containment concept including explosion area separation that fulfills the latest requirements like ATEX. By keeping technical components out of the process room, the equipment is much easier to clean.

Maintenance is carried out from the technical area, reducing the need for the maintenance engineer to work in a GMP area. This also reduces downtime and the risk of contamination. For ATEX, the design allows the technical area to be classified as safe.

## The UltimaGral™: stand alone or integrated?

### Stand alone UltimaGral™

Many applications of a high-shear mixer-granulator do not require integration with other equipment. The UltimaGral™ design allows for different ways of setting up a stand-alone machine in a GMP-compliant way: through-the-wall configuration or freestanding. With the freestanding method, all mechanical parts are completely covered and sealed, so the machine remains GMP compliant.

## Integrating the UltimaGral™

Collette nv has many years experience of integrating its equipment with other process units. Common integrations that have been supplied numerous times are the link between a granulator and a fluid bed dryer or IBC system.

This service has been expanded by collaborating with other companies from the same group, which deliver other key technologies such as; fluid bed dryers, tablet presses, handling and transport systems, and high containment valves. The advantage of being able to offer a complete processing line from within the GEA Pharma Systems group is obvious: no difficulties with contacts between vendors, the use of the same control systems, and only one contact person.



## Containment

Whether the UltimaGral™ is stand-alone, or integrated with other equipment; several features are available to ensure completely contained processing: For loading and unloading Buck high containment split butterfly valves can be mounted on the product feed and on the discharge valve. For processing highly toxic compounds, isolator boxes can be integrated into the design. Transfer of products in integrated systems is done using contained vacuum transfer systems. A sampling valve that allows the operator to take samples during the process without having to stop the machine, open the bowl, or even open a port in the lid, can be

# MicroGral™

## UltimaGral™

integrated into the processing vessel and adapted to different containment levels. The sample container is completely contained allowing the sample to be transported to the QC lab without exposure to the atmosphere.

### Moveable head

The UltimaGral™ can be equipped with a 'Movable Head' to enhance flexibility. This feature allows operators to lower the closed bowl to enable better accessibility and easy loading. The closed bowl can also be raised for dust free discharging. This option is extremely useful in height-constrained processing areas.

### Loading

Depending on the layout of the production area, several options for loading the powders are available. When the processing room is sufficiently high, gravity loading is applicable, using post hoists to lift the IBC on top of the UltimaGral™.

Alternatively gravity loading with the IBC located on a docking station on the floor above the machine is possible if a multiple floor installation is preferred. In height restricted areas however, vacuum loading can be used. In this case the product is sucked into the processing vessel from an IBC located close to the machine on the floor.

### Binder solution addition

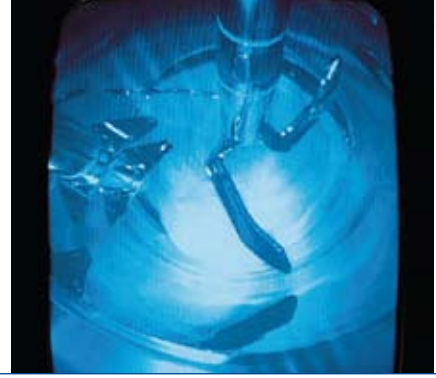
A range of binder addition systems is available to give the optimum binder liquid droplet size. This ensures an even distribution throughout the powder mass, for different viscosities. The liquid is transferred to the mixing bowl using a peristaltic pump or pressure vessel, while the rate and amount is controlled by a loss in weight system, or a mass flow meter.

### From R&D to large scale production

Collette is the perfect partner for the development of a granulation process from formulation up to full-scale production. In R&D, the MicroGral™ is the ideal equipment for the customer's formulation studies on granulation and pelletisation processes. It is suitable for batches from 100 g to 700 g by the availability of 2 interchangeable glass bowls of 1-L and 4-L. This table-top unit is equipped with an excellent process control system, including torque and temperature measurement, as well as a data logging system with the ability to export data. With capacities from 10-L to 1200-L, the UltimaGral™ range can cover all requirements after the formulation stage. From clinical batch production for scale-up trials to large scale production for marketed products.



# Understanding and controlling your process



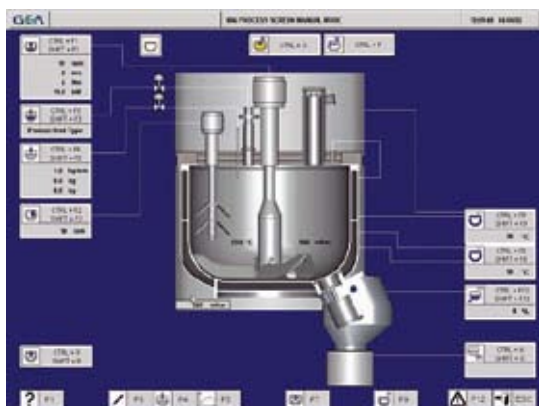
Collette has integrated its process knowledge and experience to help operators monitor and control the process in an easy and self explanatory way. Depending on the automation and reporting requirements, Collette can offer two different control systems both of which provide the operator with all necessary process information in a clear and easy to understand way.

## OP/ PLC control system

This control system provides basic functionality and process visualisation with data recording via a separate paperless recorder. It is designed to be FDA 21 CFR Part 11 compliant and provides a basic level of process automation with recipe control.

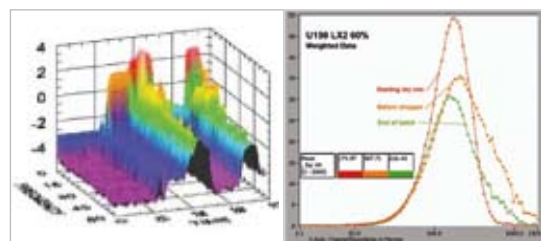
## Procoll pro control system

This SCADA based control system provides a maximum level of flexibility and functionality in terms of process visualisation, automation and data recording. It is designed for integration with customer MES systems for receiving and reporting GMP relevant data. This system is very much process orientated and guides using in-built intelligence the creation of recipes and automatic processing. All process data is stored in a relational database. The system is fully FDA 21 CFR Part 11 compliant and provides features like audit trail, including reporting and configurable graphs for process values. This batch control system is designed according to the S88.01 batch control standards.



## Process monitoring

A video camera installed in the head of the machine provides a complete view into the process vessel. This is the ideal tool for state of the art processing and gives the operator a clear indication of the product's behavior and flow while the vessel is closed. This feature provides a huge advantage for modern integrated and contained processing, both for development and production.



## PAT integration

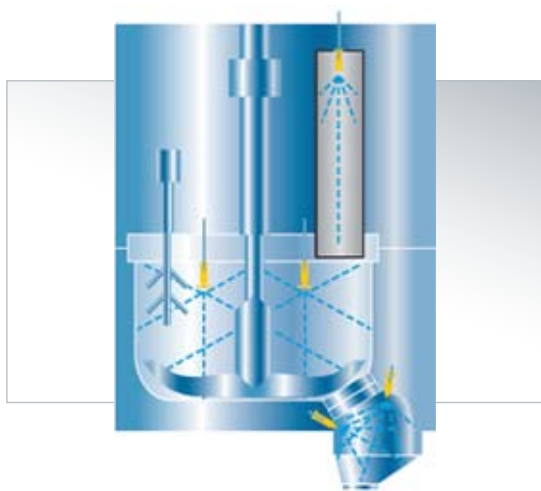
As well as the classical tools for monitoring and controlling processes like torque measurement or temperature for granulation control, Collette has developed innovative solutions for the integration of NIR (near infrared) and FBRM (focused beam reflectance measurement) sensors into its processes and controls. These advanced measurement tools are used for the direct measurement of product quality parameters such as moisture content, homogeneity of the mix, and particle size distribution, providing control parameters for direct release of the product.

# Design for cleanability & maintenance

Manufacturing compliance depends on efficient, effective cleaning. Automation of the cleaning process ensures repeatability, allows validation and minimises down-time. In recognition of the fundamental role played in today's advanced powder processing industry by automated clean-in-place procedures, Collette has developed a unique approach to CIP.

## Concealed services

The design of the UltimaGral™ ensures that lines and hoses for the utilities on the machine (water, electricity, hydraulics, etc.) are concealed in the machine encasement. This creates an uncluttered working space and avoids hoses being run to the machine within the process area.



## CIP and WIP

The UltimaGral™ can be supplied with a wide range of washing-in-place and fully automated cleaning-in-place options. These include spray nozzles adapted for most effective cleaning of product feed, product filter, bowl, lid and discharge valve (for example retractable spray nozzles for the lid). Even downstream equipment, such as a mill, can be incorporated in the cleaning system.

## Easy maintenance

Through the wall design of the UltimaGral™ ensures that technical interventions can be easily carried out without having to access the processing area and disturbing the clean environment. Even the concealed service lines can be easily accessed via sealed doors in the machine encasement.



# Optimum process efficiency

## Integration

Current good manufacturing practice increasingly requires that product is fully contained during processing to protect operators and the environment. Integrated process systems not only offer containment, but improved productivity through automation, increased yield, and efficient cleaning procedures.



### System integration

GEA Pharma Systems specialises in the design and manufacture of materials handling, fluid bed and high shear technology and is uniquely qualified to provide state-of-the-art integrated high-shear mixer-granulator and fluid bed drying technology, combined with the appropriate product handling.

Drawing on its world-class expertise, GEA Pharma Systems offers fully integrated turnkey installations. This service includes: design, installation assistance, commissioning, process validation, as well as training and technical support. Installation, operation qualification and documentation are carried out according to FDA / GAMP guidelines.

# Continuous improvement

## Safety

### Safety and the environment

For full compliance with national, local and in-house regulations, GEA Pharma Systems offers a range of emission control options including solvent recovery systems, outlet filters and full containment plants. Equipment can be supplied to meet explosion-proof and pressure shock standards as required.

### Improved safety for integrated granulation and drying suites

Extensive safety testing confirms pressure enhancement effects and identifies safe design limits for integrated systems. GEA Pharma Systems in conjunction with the FSA, the safety specialist centre in Germany, have carried out an extensive test programme involving over 100 test explosions. This research has shown conclusively that should an explosion occur during the transfer operation in an integrated system where a granulator is connected directly to a fluid bed dryer without an explosion isolation valve, the secondary explosion pressures in the granulator can be significantly higher than in the fluid bed. These tests have enabled GEA Pharma Systems to gain full EC type approval for a range of pressure shock resistant integrated systems and 16-bar pressure shock resistant high shear granulators.

### Safety when using organic solvents

The tests were carried out with hybrid mixtures that behave in the same way as pharmaceutical products containing organic solvents and showed that the final explosion pressure in the granulator is dependent on the volumes of the two vessels and that the length and diameter of the interconnecting duct is critical in ensuring that the pressure remains within safe limits.

The tests showed that where the fluid bed is designed in accordance with VDI 2263 part 5 (i.e.: for a 10-bar explosion pressure, which the standard considers to be adequate for all pharmaceutical

powders and organic solvent combinations), then the granulator must be able to withstand an over pressure of at least 16 bar to provide a range of transfer duct configurations which are both practical and safe.

Where the fluid bed is required to handle materials with explosion pressures greater than 10 bar (e.g.: metal powders) - and hence is designed outside of the VDI standard - or where the configuration of the interconnecting duct is outside the safe design parameters, then either the granulator must be designed to a higher pressure shock resistance or a hygienic fast acting valve, or some other form of protection, is essential. The test program showed that the pressure enhancement effects are caused by the difference in the propagation speed between the pressure wave and the flame front. The worst cases are when the pressure in the granulator is able to rise significantly before the flame can reach it and ignite the pre-compressed material.

For the range of transfer duct configurations to be used with the 16-bar granulator design, the presence of bends and obstructions such as mills was not seen to affect the increase in pressure.

For plant processing powders, or mixtures that are not flammable at the time of transfer between the granulator and the fluid bed, then the risk of explosion is eliminated and hence a wider range of transfer duct designs can be used safely. This extensive research program has significantly advanced the state of the art in safety technology for pharmaceutical plants and confirms GEA Pharma Systems' commitment to introducing new products which are based on sound research and development using solid process know how and understanding.



# The complete partnership

Entering a partnership with Collette means entering a partnership that does not end until the customer is completely satisfied. From the moment requirements are specified until the plant has been put into service and has been qualified, Collette's trained staff work closely with the customer during every step of the process to create the components that will result in a finished plant.

## Project management

The expertise of the Collette engineering team is available to help customers find the optimum solution for their individual processing needs. The company assists with single phases of a project, or takes full responsibility for design and installation of a complete turnkey plant.

In case of joint GEA Pharma Systems projects, one GPS project manager is appointed to oversee the whole project and co-ordinate the project between the customer and the GEA Pharma System companies.

## After sales

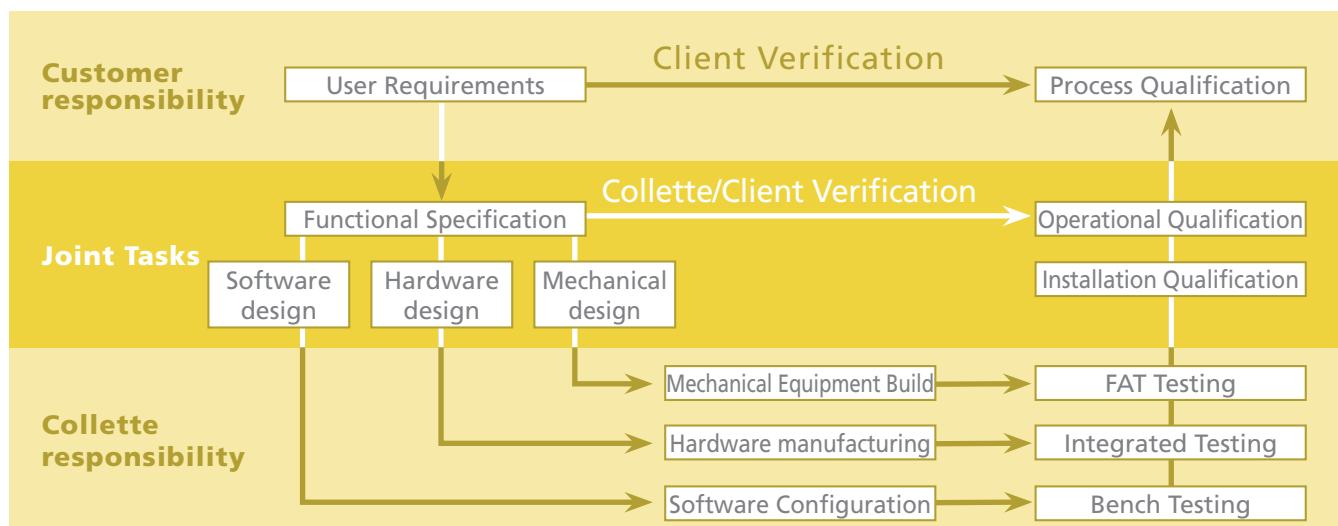
Regular maintenance is essential to ensure equipment operates to maximum efficiency. Fully trained engineers can carry out on-site servicing and calibration of equipment, either as part of a planned maintenance programme or in response to customer need. Replacement parts can be supplied from stock or manufactured to order. To avoid the expense of equipment replacement, Collette can upgrade existing systems and plant to meet different operational parameters, to comply with changing regulations, or to modify for use at another location.

## Training

Finally, operators of Collette equipment can undergo training to help them maximise efficiency, either at the time of installation or periodically as required.

## ...Every step of the way

Based on years of experience, equipment qualification will be carried out according to an agreed plan based on documents prepared by Collette. Collette's engineers will contribute to a successful qualification of the equipment in close co-operation with the customer's validation staff.



# The Process Development Center

## Proven process

The Process Development Centre (PDC) plays a major role in the partnership between the customer and Collette nv. This fully equipped laboratory offers the opportunity to benefit from Collette's years of experience in wet granulation, pelletising and drying processes in High Shear Mixers and Single Pot Processors.

The staff of the PDC consists of very experienced and dedicated people with a background in engineering, chemistry and pharmacy. They will assist customers with all questions concerning processes in Collette equipment.

A fixed, through-the-wall installation of an UltimaPro™ 75 High Shear Processor is at the disposal of Collette's customers to test the equipment with their own products. Also, 2 mobile units, an UltimaPro™ 10 and 25 High Shear Processors are available to rent, for customers who prefer to



perform tests in their own facilities. Finally, the PDC also has one or more MicroGrals available for testing small-scale batches or for rent. This enables processing batches between 100 g and 30 kg in the Collette PDC.

Next to the high-shear mixer/processors, a wide range of analytical equipment is available for characteristics of granulate and tablets.

The Collette high shear technology can also be tested in the GPS Technology Centre in Switzerland, where a MicroGral™, an UltimaGral™ 75 and 300 are available.

In this test centre, the high shear technology is integrated with fluid bed technology from Aeromatic-Fieldler for testing transfer and drying issues. Small scale trials can furthermore be executed in the GPS laboratories in Singapore and the US.



### Central know-how on a global scale

Based on a strong commitment to research and development, pharmaceutical technology centres in Belgium, Denmark, Switzerland, the UK, Singapore, and USA provide global technical support and know-how to the pharmaceutical industry.

These centres of excellence give customers

access to a range of test facilities and expert teams with technical and process know-how. Our teams work closely with our customers to optimise processes and evaluate their products, enabling them to achieve their process and production goals.



### Contracting profitable experience

A world leader in supplying pharmaceutical equipment, GEA Pharma Systems offers manufacturers all over the world the opportunity to enter into a profitable partnership for development and contract. GPS combine advanced in-house technology with a thorough

understanding of the pharmaceutical industry to help customers maximize their development results.



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