Batch Processing Solutions

for Oral Solid Dosage Forms

engineering for a better world

gea.com

Batch Processing Solutions

Making Science Work

GEA, a long-established supplier of pharmaceutical processing solutions, offers a comprehensive range of tableting technologies, from powder handling and granulation to drying, pelletizing, compression and coating. Whether batch or continuous, for contained production and/or direct compression applications, we have the know-how, equipment and expertise to optimize your oral solid dosage production.

Inspired by customer requirements and industry developments, innovation is at the heart of all our products; it's what makes them different. We understand your needs; we use our expertise and know-how to create solutions and optimize the processes that bring your products to market quickly.

GEA supplies standalone machinery, engineering services and completely integrated end-to-end process lines for even the most challenging products, including potent APIs, MUPS tablets, effervescents and/or multilayer pellets. Plus, as containment experts, we offer the largest selection of solutions for contained processing based on a thorough containment risk analysis. Our technology is world renowned for its reliability, flexibility and economy.

We offer truly rapid changeover solutions, increased productivity and safety. But it's much more than that; it's about how we work with you, the customer. We understand your needs; we use our expertise and know-how to develop solutions and optimize processes that bring your products to market quickly and provide the commercial advantage you need.

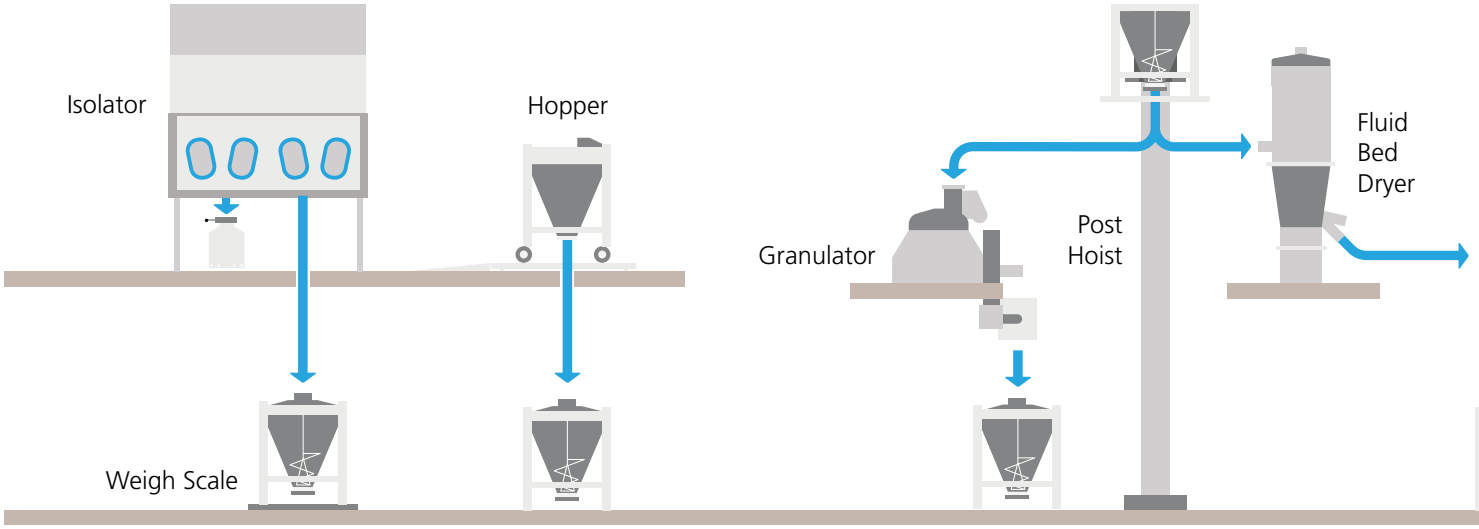
By Making Science Work, we have the right solution for your specific application.

From Powder to Coated Tablet

Experts in every aspect of batch processing, GEA offers a complete range of technologies for the production of solid dosage forms: from powder handling to granulating, drying, tablet compression and coating, including the first ever continuous high shear granulation, drying and tableting system.

Irrespective of the scope or complexity of your operation – from R&D through scale-up to commercial production – we have an unrivaled history of identifying the most appropriate solution for your specific application.

GEA's entire range of process equipment is designed with system integration in mind. A modular approach allows customers to select standard process modules to suit project needs.



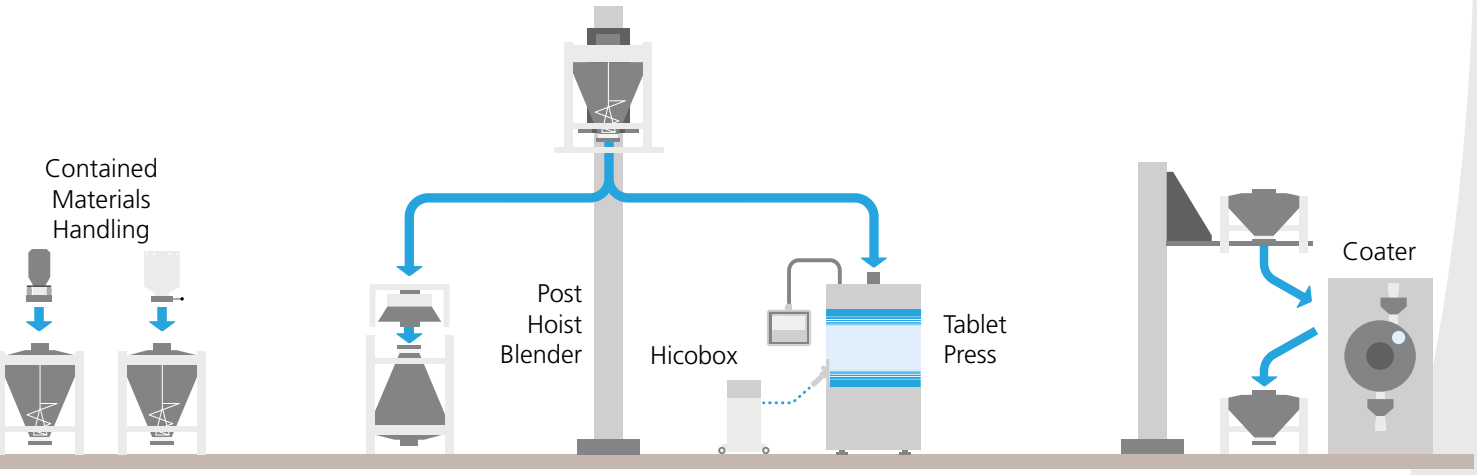
Dispensing

Granulation/Drying

MANUFACTURING SOLUTIONS THAT MAXIMIZE OPERATIONAL RELIABILITY AND PRODUCTIVITY

Fluid bed dryers and coaters can be combined with top-drive and bottom-drive high shear mixer/granulators, wet and dry milling facilities, product handling systems, binder and coating preparation units, filtration units, tablet presses, all designed for fully integrated systems.

Containment solutions, digitalization and online monitoring systems can be incorporated into both manual and fully automated lines, and third-party equipment can also be accommodated to enhance your process, improve your production efficiency and deliver the ongoing support you need to make your business a success.



Blending/Sieving

Tablet Compression

Tablet Coating

EVERY GEA PLANT AND SYSTEM IS A UNIQUE UNION
OF PROVEN TECHNOLOGY AND INDIVIDUAL SOLUTIONS

Granulation Process

Granulation, which allows primary powder particles to adhere and form granules, is the single most important unit operation in drug manufacturing. A number of different granulation and compression technologies are available to pharmaceutical manufacturers, all of which have individual strengths and weaknesses depending on the specific application.

Whereas the use of a high shear granulator with a fluid bed dryer is still the most widely used combination, offering both high levels of productivity and versatility — particularly for large volume products and long campaigns — there are a number of granulation technologies available to pharmaceutical manufacturers.

Why Granulate?

Granulation involves smaller particles adhering to each other to produce larger particles or agglomerates and is often required to improve the flow of powders or the mechanical properties of tablets. It's also used to the improve flow, compressibility, bioavailability, homogeneity, electrostatic properties and stability of solid dosage forms.

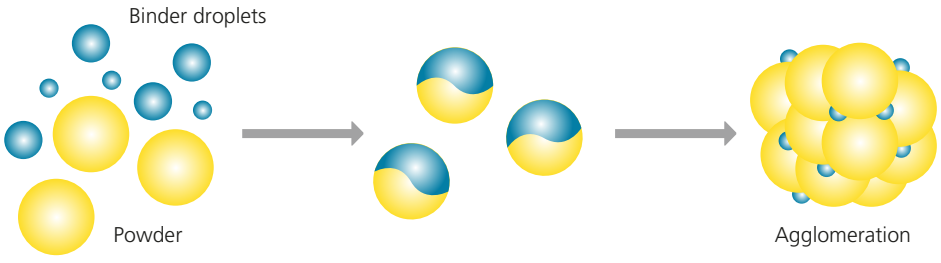
As granules are usually obtained by adding binders, either as solids or as liquid solutions, a working knowledge of the powder particle size is critical to ensure consistency. Plus, understanding and controlling the many variables in the granulation process is key to ensuring the repeatability and consistency of the finished product.

The GEA Advantage

Using strict scientific or cost-benefit criteria, GEA can help you to select the most appropriate equipment for your application. For example, single-pot technology offers numerous advantages; the machine can be cleaned in less than 2 hours; it's an extremely productive tool for short campaigns or those that require a large number of product changeovers; and, as a unit operation, it is perfectly suited for the PPE-free processing of potent substances.

The advantages of tangential spray systems were recognized by GEA and incorporated into the FlexStream™ multipurpose processor. Similarly, the ConsiGma® platform addresses the pharmaceutical industry's progressive implementation of continuous processing to improve production quality in an efficient and cost-effective way — and comply with increasingly stringent regulations.

Based on standard components, such as GEA high shear mixer granulators and fluid bed dryers, we supply plant for R&D, cGMP and commercial production — including emission control and solvent recovery options, outlet filters and containment solutions - that are configured to meet specific customer requirements. With projects completed around the world and literally thousands of tests performed, we have established a solid base of expertise related to the needs of the pharmaceutical manufacturing industry.



PMA™ & UltimaGral™ Granulators

High Shear Granulation

Offering small capacity systems designed for R&D as well as industrial-size plant for the batch and continuous production of pharmaceutical compounds under cGMP conditions, GEA high shear mixer and granulators — PMA™ and UltimaGral™ — are multipurpose processors that are equally suitable for the high speed dispersion of dry powders, aqueous or solvent granulations, effervescent products and melt pelletization applications.

The design of both the Gral™ and the PMA™ allows for different ways to setup a standalone machine in a GMP-compliant manner. And, whether your installation is standalone or fully integrated, several features are available to ensure completely contained processing, such as GEA high containment split butterfly valves, isolator boxes and vacuum transfer systems.

Contained processing also requires that the equipment can be cleaned without human intervention. Our high shear granulators can be equipped with a full CIP system that ensures cleaning-in-place of the product feed, product filter, bowl, lid and discharge valve. Even downstream equipment such as a mill can be incorporated in the CIP system.

Having established a credible pedigree of expert know-how in the pharmaceutical manufacturing industry, GEA provides optimal solutions for your applications: no other supplier offers such a complete range of granulation and drying equipment.

Integrated High Shear Granulation

This is the most common configuration used on an industrial scale for the production of pharmaceutical granules. This system allows full integration with upstream and downstream equipment, and even includes a wet mill between the granulator and dryer.

With modern control systems, it is easy to load, mix and granulate a second batch in the high shear granulator whilst drying the previous batch in the fluid bed prior to discharge. All equipment can be cleaned in place in a single automatic process.

WITH BOTH TOP AND BOTTOM DRIVE GRANULATORS AVAILABLE, GEA CAN HELP YOU TO SELECT THE TECHNOLOGY THAT IS MOST SUITABLE FOR YOUR PRODUCT

Fluid Bed Processing

Granulating, drying, pelletizing and coating

Fluid bed operations such as drying, granulation or particle coating are often major process steps in the production of solid dosage forms. And, even though fluid beds have been in use by pharmaceutical companies for more than 50 years, GEA continues to enhance existing designs, introduce new technologies to optimize performance and improve process understanding.

GEA offers a series of fluid bed processors that are suitable for the formulation, development and production of clinical material through to full-scale manufacture; this includes small capacity systems designed for R&D as well as industrial-size plants for the batch production of pharmaceutical compounds under cGMP conditions. The philosophy behind our approach is that a combination of standardised modules can be combined to meet specific requirements. As such, dryers of equal capacity may be completely different with respect to design, configuration and physical size.

For maximum process flexibility, GEA can supply a single fluid bed unit or the patented FlexStream™. Using proven GEA technology to achieve fluid bed granulation, drying and pellet coating (or tablet coating) in a single module, FlexStream™ is a multipurpose processor that addresses the current shortfalls of traditional fluid bed processing, including linear scale-up, fully contained loading and unloading, and superior product homogeneity for both LOD and PSD.

FlexStream™

Requiring only one product container for all unit operations, the FlexStream™ reduces your build envelope (both height and footprint) and provides PAT-compatible inline particle growth measurement. The FlexStream™ concept has the additional advantage that no mechanical adjustment is necessary to switch between using the equipment as a dryer, a granulator or a coater. And, impressive test data prove that, in addition to these commercial benefits, FlexStream™ gives superior product quality when compared with conventional top spray granulation or Wurster coating.

Using recognized standard components, GEA makes plant design both simple and flexible. User-selected process modules, filters, control systems and air preparation units can be combined in a system that meets your process requirements exactly. This modular approach ensures that qualification and validation procedures are kept to a minimum.

AirConnect™

The multipurpose AirConnect™ from GEA delivers a range of fluid bed processing solutions for small-scale applications. A service unit provides the main air treatment and control facilities with exchangeable modules delivering an array of processing options, including fluid bed drying, granulation and both pellet and tablet coating.

The AirConnect™ has been developed by GEA to meet the pharmaceutical industry's requirements for unit operation flexibility and is based on the proven principle that a single core component can be used for numerous processes by interchanging a range of application-specific modules.

The ultimate fluid bed processor for small-scale research and production applications (from 100 g up to more than 10 kg), the AirConnect™ accelerates and optimizes product development by minimizing the amount of scale-up required to move from R&D-level batch processing to full-scale production systems.

THE MULTIPURPOSE AIRCONNECT™ DELIVERS A RANGE OF FLUID BED PROCESSING SOLUTIONS FOR SMALL-SCALE APPLICATIONS


GEA
GEA

UltimaPro™

Single-Pot Processing

With high-shear granulation technology at its core, single-pot processing relies on the application of a vacuum within the bowl to dry the wet mass. This technique allows pharmaceutical compounds to be dried at very low temperatures and, even if organic solvents are used during the granulation process, an efficient solvent recovery system means that environmental exhaust levels are minimal.

Single-pot processing is a very compact and flexible technology, achieved by incorporating several manufacturing steps into one machine. This reduces the capital cost of the equipment and, by reducing the cGMP and technical space required for granule production, the overall project cost.

The swinging bowl option enhances this flexibility even further by being able to process older formulations to a high quality standard. Quick product changeover is simple and efficient, and the equipment is clean-in-place (CIP)-compatible.

In addition, because of its very nature, a single-pot process is contained. No transfers are required between process steps, except to load the raw materials and unload the dry granules. This not only protects the operators from potent actives, it also prevents product being exposed to external influences such as heat, light or moisture.

A range of process control systems is available that offer maximum flexibility and functionality for process visualization, automation and data recording.

And, by combining process monitoring using online, PAT-compatible analyzers with solid process engineering principles and advanced process modeling techniques, we enable processes to be actively controlled to compensate for minor input variations (such as raw materials), so that the specifications for the final product will be closer to the ideal target.

PharmaConnect™

PharmaConnect™ combines a single control unit with a diverse range of process modules

This innovative plug-and-play system provides a unique benefit to the pharmaceutical development industry and enables a diverse range of process modules to be integrated with a single control unit.

Based on GEA's PMA™ and Gral™ granulation technologies, the PharmaConnect™ can process batch sizes of 25 kg or more, all from a single control system.

However, the PharmaConnect™ is not just limited to granulation; the unique design of the control unit allows any number of process technologies to be operated from the single operator interface, including high shear granulation, IBC blending and high shear blending.

Typically ranging from 1 to 60 L, standard capacities are available for each set of modules, with each unit being geometrically scalable.

In addition to the typical high shear granulation process, GEA also supplies PharmaConnect™ modules for its NICA™ extrusion and spheronization pelletizing system and for its TRV (Turbo Rapid Variable) high speed blender.

Through-the-Wall or Mobile Control Unit

Two versions of the control unit are available: a through-the-wall option and a mobile module. The unit also features a touchscreen user interface, a module drive motor and GEA's Module Recognition System (MRS), which automatically detects the type and capacity of the connected module, seamlessly displaying an image of the process on-screen and both enabling and defining the correct operational set points and parameters.

PharmaConnect™ is a truly PAT-compatible, cGMP-compliant, plug-and-play solution for the busy formulation scientist.

Mobile PharmaConnect® with 60-L PMA bowl

A COMPLETE RANGE OF TECHNOLOGIES FOR R&D

PharmaConnect™

Designed for specific applications, our R&D range covers every aspect of oral solid dosage production, from high shear mixers, fluid bed dryers and single pot systems to extruders and spheronizers, blenders and containment solutions, right through to tablet compression.

Bottom-Driven High Shear Granulation

Offering a wide range of processing capacities, standard module sizes for the bottom-driven PMA™ are set at 1, 3, 5, 10, 15, 20, 30 and 60 L, with each unit being geometrically scalable. Critically, each of these modules features its own impeller drive motor, maintaining a consistent energy input per unit volume and enabling true scale-up data to be generated, even at the 1 L level, for commercial expansion.

Top-Driven High Shear Granulation

The state-of-the-art Gral™ top-driven granulation system is renowned worldwide for its high quality, robust design and scalability. The UltimaGral™ comes with a 10 L bowl and can be scaled-up to provide 25 and 75 L capacities, facilitating the move to production-scale equipment. Furthermore, integration with the PharmaConnect™ control unit provides complete process flexibility.

Extrusion and Spheronization

Designed specifically as a pelletization system for the pharmaceutical industry and able to pelletize small batches (50 g) using the operating principles of larger pilot-scale and production machines, the NICA™ IPS-5 extruder and spheronizer is the perfect development partner for the PharmaConnect™.

IBC Blending Systems

Featuring the unique, removable Blending Prism™ and designed to handle a complete range of laboratory sized IBCs (3–75 L) using a single process module, NIR technology can also be applied to provide online blend homogeneity detection. The Prism™ adds low shear mixing to the rotating IBC, adding to the turbulence of the tumbling product and reducing the blend time.

Inhalable Fine Powder Processing

Inhalation is often the preferred drug delivery method for lung diseases, offering a number of advantages for both patients and medical professionals for the administration of vaccines and other biological drugs.

As well as a wide range of high quality homogenization equipment, GEA also offers production-scale mixing, blending, spray drying and micronization solutions for the manufacture of inhalable products (dry powders and suspensions), plus an unparalleled level of expertise in the design and layout of suitable plant: from vessel size dimensions to valves and 3D P&IDs, and from R&D to full-scale production.

The TRV is a high-speed blending unit that features a single, bottom-driven impeller drive. It is particularly suitable for the rapid batch blending of small quantities of APIs and excipients for inhalable products.

The modular design enables batches from as little as 200 g to be processed. And, with a range of bowl capacities up to 60 L — plus standalone systems integrated with isolators — the PharmaConnect™ system provides the ability to perform 1:10 scale-up procedures that are completely compliant with current regulatory requirements. Integrating GEA's BUCK®. containment valve technologies further enhances the system's capabilities.

PharmaConnect-PLUS™

Integrated small-scale granulation and drying

GEA has expanded its popular PharmaConnect™ system with the introduction of PharmaConnect-PLUS™, extending the unit's high shear granulation capacity to encompass batch sizes of up to 60 kg.

Designed for small-scale granulation and research and development applications, particularly with potent actives, the PharmaConnect-PLUS™ — based on the established combination of a single control unit with a diverse range of process modules — further benefits from both physical and control integration with GEA's fluidized bed processors: the MP2-Advanced and MP3-Advanced.

The modular design provides the opportunity to process batches from as little as 5 kg. With the new, increased maximum capacity, one integrated system now provides the ability to perform 1:10 scale-up procedures that are completely compliant with current regulatory requirements. Integrating GEA's BUCK® containment valve technologies further enhances the system's capabilities.

Both the BUCK® MC valve and the disposable Hicoflex® system are capable of delivering OEB 4 containment levels, facilitating the safe loading of raw materials and the collection of finished granulated product.

The high shear granulator discharges through an integrated wet mill with granules being conveyed directly into a fluid bed processor. After drying, the end product handling system utilises GEA's lean phase conveying technology to ensure the rapid, contained transfer of product through the dry mill and into the finished product IBC.


GEA

NICA™ System

Pharmaceutical Pellets for Optimized Release Characteristics

Specializing in the design, build and supply of equipment for the production and laboratory development of pharmaceutical pellets (spheroids) by extrusion and spheronization, powder and liquid layering, high shear pellet processing, and melt and wet granulation, GEA offers a complete engineering service from system design to process integration and optimization.

For example, the unique, modular concept of the NICA™ Pelletizing Plant enables us to meet your process requirements exactly, whereas mixer/granulator, extruder and spheronizer modules can be combined to create a completely integrated pellet production plant, or selected individually to suit specific requirements.

For maximum flexibility, the modules can be operated in either batch or continuous mode, and can be used as standalone products or integrated with other up- or downstream equipment (such as a fluid bed processor). Ideal for both product development and full-scale production applications, scale-up is easy; it's simply a factor of processing time.

Integrated Pellet Production Plants

Using our breakthrough technology and the experience gained during many successful installations, GEA provides seamlessly integrated pellet production plants. Our history of working with integrated systems is second to none and we continue to provide the highest quality and support for each of our core technologies.

With the advantage of being a single source of supply, GEA can supply a single fluid bed unit, such as an MP-Classic or MP-Advanced, or a FlexStream™ fluid bed processor that enables granulation, drying and pellet coating in one single unit.

The Benefits of Pellets

- Enhanced drug dissolution
- Ease of coating and improved aesthetic appearance
- Desirable release characteristics (sustained, controlled, delayed, site-specific or pulsatile delivery)
- Uniform packing
- Ease of capsule filling (improved flow properties)
- Even distribution in the GI tract and less irritation
- Flexible formulation development and manufacture
- Chemically incompatible products can be formulated into pellets and delivered in a single dosage form.

NICA IPS25 for extrusion and spheronisation – available for trials onsite and for rental

FLEXIBLE, EFFICIENT AND EASY TO FORMULATE MULTIPARTICULATE DRUG DELIVERY SYSTEMS

Capacities

PharmaConnect™ PMA

Size		1	3	5	10	15	20	30	60
Standard Capacity Range	Litres	0.4-0.8	1.2-2.4	2.0-4.0	4.0-8.0	6.0-12.0	8.0-16.0	12.0-24.0	24.0-48.0
Typical Batch Weight	kg	0.33	1.0	1.65	3.3	5.0	6.5	10	20

PharmaConnect-PLUS™ PMA

Size		15	20	30	60	90	120	150
Standard Capacity Range	Litres	6.0-12.0	8.0-16.0	12-24	24-48	36-72	48-96	60-120
Typical Batch Weight	kg	5.0	6.5	10	20	30	40	50

PMA™

Size		150	300	400	600	800	1200	1800
Standard Capacity Range	Litres	60-120	120-240	160-320	240-480	320-720	480-960	720-1440
Typical Batch Weight	kg	50	100	150	200	300	400	600

Gral™ / UltimaGral™

Size		10	25	75	150	300	400	600	900	1200
Standard Capacity Range	Litres	3.0-7.0	7.5-17.5	22.5-52.5	45-105	90-210	120-280	180-420	210-630	360-840
Typical Batch Weight	kg	3	11	30	60	120	160	240	350	480

UltimaPro™

Size		10	25	75	150	300	400	600	900	1200
Standard Capacity Range	Litres	3.0-7.0	7.5-17.5	22.5-52.5	45-105	90-210	120-280	180-420	210-630	360-840
Typical Batch Weight	kg	3	11	30	60	120	160	240	350	480

MP-Classic

Size		2	3	4	5	6	7	8	9
Standard Capacity Range	Litres	20-55	50-124	30-280	60-450	90-765	120-1060	180-1525	240-2135
Typical Batch Weight	kg	25	50	100	200	300	400	600	800

MP-Advanced

Size		2	3	4	5	6	7	8	9
Standard Capacity Range	Litres	10-80	18-160	30-225	60-450	90-600	120-900	180-1500	240-1920
Typical Batch Weight	kg	30	60	100	200	300	400	600	800

CONTAINMENT LINE FOR ANTICANCER DRUGS

GEA supplied a complete containment line to Ranbaxy Laboratories Limited (Gurgaon, India) to manufacture highly potent anticancer drugs with an OEL of 1–10 µg/m³. It was essential that the process prevented any cross-contamination in the production area and limited operator Real Daily Intake (RDI) of hazardous substances to well within the Acceptable Daily Intake (ADI).

During the selection process, several key equipment features were specified:

- all units had to provide full containment
- the entire process had to be contained in a single machine to avoid contamination and limit material handling
- the technology had to be flexible enough to adapt to different products and batch sizes
- the process should provide maximum yields with minimum wastage
- there should be a clear and straightforward documentation procedure.

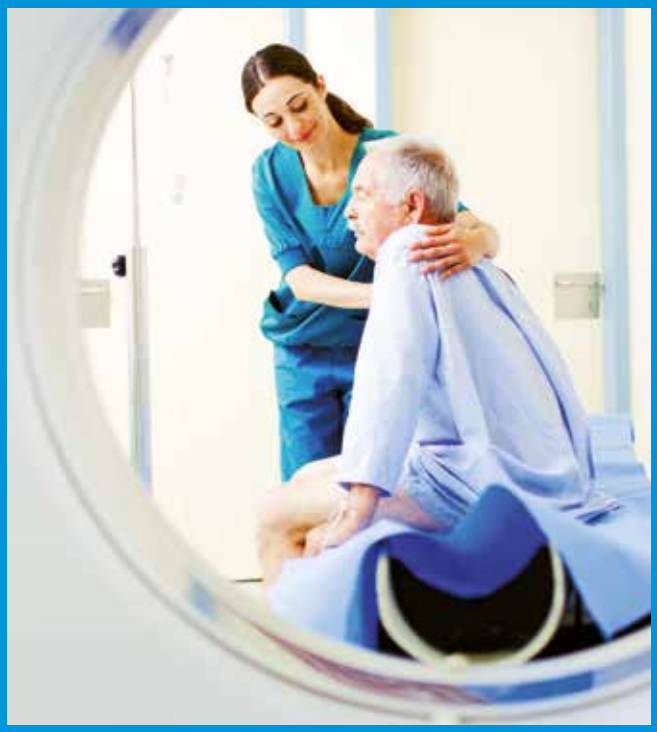
In addition, it was essential that the operators had an in-depth understanding of both the equipment and the relevant containment issues.

To meet the production, containment and whole life cost requirements, Ranbaxy chose two single-pot processors from GEA: the UltimaPro™ 10 and the UltimaPro™ 75 (10 L and 75 L processing bowl, respectively). The safe, low temperature, vacuum drying technology was augmented with microwaves or Transflo™ (gas-assisted vacuum drying); endpoint determination was achieved using a torque sensor (granulation) and NIR (end humidity); a built-in camera allowed operators to view the process without opening the lid; and cleaning was done by a comprehensive fully validated CIP system.

The new equipment has allowed the company to develop niche oncology products in a contained environment that protects its workforce and the wider environment from toxic compounds. Since installation, predicted levels of production, containment and operational efficiency have been achieved.

In addition, factors such as very effective microwave drying for aqueous feeds, more consistent granule sizes and much less operator intervention than had been anticipated have been cited as "areas of exceptional performance."

Lalit Sood, Projects Director for Ranbaxy, said: "The unit cost reduction has opened up the market and enabled the company to provide a hard-to-resist proposition worldwide. The GEA technology gives us security of outcome with the guaranteed quality and consistency we need."



Beyond the Granulator

Combining trusted technology with an ongoing program of innovation and price-performance leadership

Relationships matter, and we believe that by giving you access to the scientists and engineers who actually created our equipment and developed our technologies, you can invest with confidence, safe in the knowledge that GEA plant is designed to achieve its maximum potential and has been optimized for manufacturing excellence.

When compression problems occur, for example, it's all too easy — and common — to focus on the press. The root cause of the issue, however, is more than likely a consequence of upstream processing. Poorly granulated materials will not compress well and most fine pharmaceutical compounds require granulation to improve their flowability and processing properties prior to tableting. Likewise, poor mixing, granulating and drying will lead to issues with tableting that cannot be rectified by adjusting the press.

To cite a Japanese proverb: we learn little from victory and much from defeat. In pharmaceutical terms, this means selecting the most appropriate technology, using the equipment to its maximum capacity and keeping a strong focus on the total cost of ownership.

By delivering everything from technical know-how and process evaluation support to product development, expert-designed equipment, project management and the service you need to bring your plans to fruition, we supply the added value and the deep-rooted knowledge that counts.

Whether it's a single piece of equipment or a long-term strategic collaboration, our focus is on price-performance leadership, safety and quality. How do we do this? By making science work.

Tablet Compression

Our innovations include a unique dual control, PAT-compatible technology that monitors and controls tablet weight, hardness and density with an accuracy that cannot be achieved any other way.

Weight is controlled at pre-compression and hardness is controlled at main compression. As a result, weight and hardness can be controlled simultaneously and continuously on a standard tablet press.

GEA also offers adjustable dwell times at pre-compression (by up to 300%) without slowing the press: this functionality allows an increase in dwell time at pre-compression that's independent of machine speed, resulting in higher outputs and more consistent tablet quality.

In addition, constant dwell times while varying the machine speed can be used to match the production capacity of the line without influencing tablet quality.

Other unique features ensure a constant flow and equal distribution of powder that are without equal, as well as integrated data collection and analysis, and advanced process control.

Our MODUL™ tablet presses provide the fastest product changeover in the market, and our PERFORMA™ tablet presses provide the highest outputs. Plus, with the introduction of the ECM-based (Exchangeable Compression Module) MODUL™ rotary tablet press in 2002, GEA revolutionized the pharmaceutical industry.

The ECM succeeds in combining productivity, flexibility and safety — all in one — setting a new standard for pharmaceutical tablet production. A WOL-ECM (Wash-off-Line) version is available for the high-containment processing of potent and toxic formulations.

MUPS (Multiple Unit Pellet System) Production

MUPS tablets are a multiparticulate pharmaceutical solid dosage form produced by compressing a mixture of drug-containing pellets and powder excipients. The pellets have a spherical core that contains or is coated with the active ingredient, and have one or more protective layers (cellulosic and acrylic polymers) to control drug release.

Producing MUPS tablets using conventional bin blending to feed a tablet press is reported by many pharmaceutical manufacturers to pose significant challenges regarding productivity and batch content uniformity.

As a result, to increase process yield and guarantee tablet quality, an innovative continuous dosing, blending and compression system has been developed by GEA that eliminates these production inefficiencies and product quality risks. Segregation is kept to an absolute minimum and online process monitoring detects out-of-specification (OOS) tablets.

GEA OFFERS MANUAL AND FULLY AUTOMATIC ROTARY PRESSES FOR R&D, PILOT- AND FULL-SCALE PRODUCTION

Tablet Coating

Coating is used to add color, protect, mask the taste or create a modified release form in pharmaceutical production. GEA offers a range of standard, innovative batch coater systems for particles, powders, granules, crystals, pellets and tablets.

Coating is used extensively in the solid dosage industry for the application of non-functional or functional coats (aesthetic, protective or rate controlling polymer films) and for the deposition of active pharmaceutical ingredients (APIs) onto nonpareils (multiparticulate dosage forms).

Applications include taste masking, color modification, physical protection and/or to create modified release forms. Beyond efficient API layering techniques for multiparticulate systems, the pharmaceutical industry has an inherent need to accurately coat objects that are 3–30 mm in length (the most common size range for single-unit solid dosage forms) with APIs.

These include tablets for oral administration and other delivery methods (human implantation, for example). Existing coating methods in this size range have coating speed and accuracy/uniformity limitations, particularly for the deposition of low dose APIs onto single unit tablet dosage forms.

ConsiGma® Coater

The ConsiGma® coater from GEA is a revolutionary, high performance tablet coating technology that gently and accurately deposits controlled amounts of coating materials on tablet cores — even if they are extremely hygroscopic or friable.

The ConsiGma® coater is able to process small quantities of tablets at very high rates, offering improved heat and mass transfer.

PAT-compatible, the ConsiGma® coater is easy to clean and offers significant cost savings compared with conventional systems in terms of time, materials, downtime, process revalidation, stability testing, etc.

With a smaller technical space requirement than established technologies, less cleaning and a reduced plant area is needed. And, being a continuous production technology, no scale-up is required and the maximum batch size is almost infinite.


GEA

Contained Materials Handling

Tailor made containment for the pharmaceutical industry — for now and for the future

Taking an individual approach to each customer's needs and applying our extensive experience and know-how, we combine performance excellence with technological innovation to deliver long-term competitive advantages.

With thousands of installations worldwide, GEA has developed an outstanding reputation for quality and service to become the clear leader in contained materials handling technology, including powder handling, intermediate bulk container (IBC) systems, containment valves, container systems, in-container blending, tablet handling and IBC washing. Our distinctive specialization lies in the integration of BUCK® containment technology into complete solutions for pharmaceutical solid dosage form facilities.

How Much Containment?

Containment issues have become a vitally important aspect of solid dosage form production. Active pharmaceutical ingredients (APIs) are becoming increasingly effective, with more than 50% of all new chemical entities (NCEs) being classified as potent (OEL <10 µg/m³); at the same time, the health and protection of operators, all over the world, is being put under an ever more intense spotlight.

Why is the pharmaceutical industry interested in containment? For two reasons: operator exposure and the prevention or elimination of cross-contamination. But how much containment is required? "A key point," says David Johnson, Sales Manager, Containment Technology, GEA, "is that the required level of equipment and containment performance is not simply a matter of measuring the Occupational Exposure Limit (OEL) of the product. This is a common misconception and, as a result, there is a tendency within the industry to over specify."

He explains: "Selecting an overly complicated solution means that the system is more difficult to operate, difficult to clean and maintain and, of course, more expensive to buy. It can be problematic to show that a particular solution is 'good enough,' but it can be done. By understanding containment and looking at the product, the operator and the equipment, we can create well engineered and better value solutions."

Three main factors dictate how much containment is required and, therefore, which method of containment is best: the nature, especially the potency, of the API handled is of paramount importance; the type of process to be executed; and, lastly, the working regime of the operators.

In Summary

Containment is determined by the characteristics of the product, equipment performance and operator function. Operator exposure depends on the type of equipment being used, product dilution levels and frequency of operation.

As exposure can't be fully prevented, the employer must ensure that the operator's RDI of a hazardous substance doesn't exceed the product-specific ADE by using suitable equipment. The company should only implement additional personal preventive measures when this cannot be guaranteed by appropriate technical options, including

- eliminating the source of risk
- substituting the hazardous material with a less harmful one
- modifying the process
- using engineering controls to reduce exposure (contained handling)
- improving administrative procedures (SOPs).

The selection, placement and implementation of suitable containment equipment can be a daunting task; it requires an in depth understanding of the overall process, primarily to ensure that the chosen equipment performs at the necessary level, but also, from a financial point of view, to prevent any expensive and unnecessary investment into an over-performing solution.

GEA not only offers the largest variety of robust and compliant hardware solutions for contained materials handling, but it also boasts unrivaled expertise in identifying the most appropriate solution and a thorough understanding of containment risk analysis.

GEA can assist and advise you to determine what level of containment is required where and when, optimizing the manufacturing process and making it efficient, safe and cost-effective.

Digitalization

Multivariate monitoring and advanced process control (APC) solutions for batch and continuous pharmaceutical process units

The FDA's PAT (Process Analytical Technology) initiative has enabled GEA to combine its equipment design skills and process engineering know-how to integrate online (PAT) analyzers into its systems in a way that can provide real insight into the operation of the process and help customers to achieve key product quality targets.

The goal of the PAT initiative is to ensure that pharmaceutical products are manufactured using processes that are understood and monitored, so that the key quality characteristics of the products can be actively controlled.

Combining process monitoring with solid engineering principles and advanced modelling techniques will enable procedures to be actively controlled to compensate for minor input variations (raw materials), so that the specifications for the final product will be closer to ideal targets.

Plus, the continuous monitoring of product quality can prevent out-of-specification deviations and decrease production costs, as well as reducing final quality inspections by facilitating real-time release testing.

Built into its control systems, GEA has integrated its collective knowledge to help operators monitor and regulate their processes. For several steps, end-points based on process parameters are available, and guidelines are given depending on the set points entered. In addition, GEA has experience with integrating innovative analytical tools for process monitoring and control.

The Lighthouse Probe™

The novel Lighthouse Probe™ can be used with a range of spectroscopic techniques, including NIR and UV/Vis, to monitor moisture content and uniformity, determine end-points during drying and coat growth. It also overcomes the traditional problem of product sticking to the observation window.

INLINE CONTROL OF HIGH SHEAR GRANULATION

Sanofi Genzyme reduces probe fouling and improves NIR data using GEA's Lighthouse Probe™

Sanofi Genzyme was looking for a Process Analytical Technology (PAT) solution to control the high shear granulation of a formulation by measuring a critical product attribute. As opposed to relying on time-based processing or impeller blade loading, the company used an optimized Lighthouse Probe™ to obtain representative near infrared (NIR) data.

Genzyme's new drug was undergoing Phase III clinical trials. The active pharmaceutical ingredient (API) had a small particle size, but poor flow properties. This presented the company with a challenge when formulating a dosage for patient administration. To improve the flow characteristics, the API was to be combined with excipients and processed by high shear wet granulation.

Experimental Setup

The GEA Lighthouse Probe™ was attached to a Bruker Matrix-F spectrometer and inserted — through a customized opening in the granulator lid viewing window — into a PMA-1 10 L granulator bowl. Using a manufacturing process design of experiment (DoE), including five high shear wet granulation-related factors, 20 batches were analyzed.

NIR spectra were collected from the granulation process at a scanning speed of approximately one spectra every 5 seconds. The last six spectra collected from each granulation step were averaged and correlated against granule attributes such as water content, particle size and density of the final blended product.

The wet granules were subsequently tray dried, milled and blended with a lubricant. Principle component analysis was done throughout the granulation process to assess any changes taking place.

Conclusions

The Lighthouse Probe™ showed that it is well suited to monitoring a high shear wet granulation process when used as the sample interface with an NIR spectrometer (Figure 1). It minimizes probe fouling — based on its 360° window — and allows for the maximum absorbance of light from the spectrometer, which facilitates signal detection.

The Lighthouse Probe™ enabled satisfactory models to be produced for key granule attributes such as water content, particle size and bulk tapped density. This study proved the viability of Lighthouse Probe™ technology to monitor and control a high shear wet granulation process.

Figure 1: A Hotelling's T2 plot shows that the process time for the first batch was shorter than second batch because less water was added at a higher spray rate. The plot inflexions could be related to the point at which sufficient water is present to activate the binder in the formulation.

Cleaning

Process optimization depends on efficient, effective cleaning

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

And, today's increased demands for customized design, special construction materials, surface treatments, advanced control systems, compliant production and process validation have resulted in continuous improvements in solid dosage plant design for the pharmaceutical industry.

Automation of the cleaning process ensures repeatability, allows validation and minimizes downtime. In recognition of the fundamental role played in today's advanced powder processing industry by automated clean-in-place procedures, GEA has developed a unique approach to CIP.

Concealed Services

The integrated design ensures that all lines and hoses for the utilities of the plant (water, electricity, hydraulics, etc.) are concealed. This creates a safe and uncluttered working space.

CIP and WIP Systems

More efficient cleaning is one of the key advantages of system integration. We provide validated cleaning with minimal downtime. GEA offers CIP-by-design features in all of its processes. Every aspect of the integrated plant, from inlet to discharge, has been value-engineered for optimum cleanability. Spray system, tanks cleaners, nozzles and seals are an integral part of our equipment design.

IBC Washing

Although it is important to handle and transfer powders in a contained way to prevent operator exposure, it is equally important to be able to wash the IBC and the containment valves in place — without the need for operator intervention to strip and clean the valve.

Tablet Press Cleaning

Thanks to its inherently closed design, the ECM model significantly reduces the concentration of airborne particles in the tablet compression room and contributes to the protection of equipment operators and supervisors.

Easy and Safe Single-Pot Processor Cleaning

To verify the CIP approach, a cleaning validation study was done on a single-pot processor using both a water-soluble (theophylline) and a water-insoluble (mebendazole) material. The results showed that the CIP system is capable of removing both products to a level well below the generally accepted acceptance criteria.

Using our unique CIP approach, a product changeover can take place in 2–3 hours, reducing the downtime of the equipment (depending on the product characteristics and the cleaning program used). As the whole CIP cycle takes place automatically, it is also possible to start the cleaning in the evening, allowing it to run overnight and prepare the equipment for a new production run in the morning.

OPTIMIZING HIGHLY POTENT DRUG PRODUCTION

After conducting extensive market research, Penn Pharma (now PCI Pharma Services) identified an increased need in the solid dose oncology market for the outsourced development and production of high quality, highly toxic drugs. Initiating an investment project to upgrade its site capabilities to support this market need, the aim was to create a new multiple active pharmaceutical ingredient (API) facility that could produce 1–120 kg batches using full containment according to ISPE guidelines.

Its production site had been manufacturing potent solid dosage products for more than 20 years but needed additional capacity. Without both innovation and investment to provide better solid dosage technology, and dispense with the cumbersome isolation suits that restricted development and were uncomfortable for operators, Penn would not be capable of achieving the production levels required by international pharmaceutical companies and business would only grow at the same pace as the global outsourcing market.

To take advantage of the opportunity identified by its research, Penn would require a totally new concept in plant design, incorporating leading technology, the latest techniques and the ability to upscale operations from research and development, through pilot-scale testing up to full production, all under one roof.

Penn Pharma elected to work with GEA because of its proven track record in containment technology and expertise in creating fully integrated production lines. GEA's approach was to eliminate the use of isolation suits in favor of containment interfaces (BUCK® MC high-containment valves and Hicoflex®).

These would not only interface with GEA's advanced granulation, containment and compression technologies, but also with third-party equipment such as the powder dispensing isolator and, further downstream, the tablet filling and tablet coating elements to produce a fully contained, powder-to-capsule facility, in an open working environment.

The new plant now includes the first commercial PharmaConnect™ "through the wall" system in Europe. The contained R&D line for wet granulation also includes the dispensing of excipients and potent powders, GEA's PMA™ 150 and FlexStream™ 1000 for granulation and drying, dry milling, granule collection and blending, tablet compression using a MODUL™ P tablet press with a Wash-off-Line ECM (exchangeable compression module) and pellet coating.

The plant also has a contained R&D line for direct compression and a separate production line that offers containment interfaces for powders, API and excipient dispensing, dry milling and powder collection and blending. Penn Pharma is now a single source for the development and production of highly toxic drugs at one of the world's most advanced and efficient plants.

The project has significantly increased their capacity and the company can now manufacture approximately 500 additional batches during a standard two-shift operation.

PROJECT OBJECTIVES

Safety
The facility was designed to handle multiple APIs with occupational exposure limits (OELs) down to 0.01 µm/m^3, based on an 8-hour time weighted average (TWA). The approach was somewhat unconventional, as it started with a negative pressure equipment philosophy that would eliminate the need for personal protective equipment in routine operations.

Quality
The new contained manufacturing operation had to meet the regulatory needs of the global markets supported from the site, including the USA, Japan, South America and Europe.

Delivery
The facility was designed to be flexible enough to support customers through development, early phase and commercial supply. It had an accelerated timescale and aimed to turn a car park into an operational facility in 12 months.

Cost
Nothing could be compromised on quality or safety; successful equipment sourcing was key. A robust FMEA selection process and commercial bid analysis was done to secure leading edge equipment at a competitive market price.

People
With an initial team of five project members, supported by an external project design and construction team, the focus was on speed to market. Armed with a full complement of formulation, quality, validation, engineering, regulatory and operational skills, and budgetary control, everything was put in place to create a unique, market-leading facilit

GEA Pharma Solids Center

Offering a full range of batch and continuous manufacturing technologies for the testing, development and optimization of oral solid dosage forms

With a total footprint of 1100 m², including 200 m² of technical space, the GPSC epitomizes the state-of-the-art in oral solid dosage (OSD) form testing, development and optimization, and offers a full range of batch and continuous manufacturing technologies.

From cost assurance and process enhancement to real-life simulations and test and loan machines, we provide a unique range of services that are designed to improve production and expedite time-to-market.

The GPSC Offers

- customer demonstrations and trials on our batch and continuous equipment
- training sessions and classes
- hands-on laboratory experience
- pharmaceutical product development assistance
- CQA evaluation support
- testing of new concepts (equipment and advanced controls)
- scale-up from laboratory to production (1:10)
- process development/refinement to increase the understanding and capability of GEA equipment.

The company combines advanced in-house technology with a thorough understanding of the processing industries to help customers maximize their development results, gain more know-how and discover additional opportunities for their applications.

GEA's centers of excellence provide access to a full range of test facilities and teams of experts, all of whom work closely with their customers to optimize procedures and evaluate their products, enabling them to achieve their process and production goals.

Batch Processing Technologies

The GPSC enables you to investigate all the batch-based solid dosage production techniques offered by GEA, in lab-, pilot- or production scale.

- IBC blending
- High Shear Granulation
- Fluid Bed FlexStream® Granulation
- Fluid Bed Top Spray Granulation
- Single-Pot Processing
- Fluid Bed FlexStream® Drying
- Fluid Bed FlexStream® Coating
- Fluid Bed Precision Coating
- Extrusion/Spheronization
- Tablet Compression
- Milling/Calibration

To discover more or organize a test, demonstration or training session, contact our dedicated, passionate and experienced team. With a long history of solid dosage form expertise, including more than 125 formulations on CM equipment, everyone at the GPSC is committed to going the extra mile to meet customer expectations. Wherever you are in the world, whatever your application, we'll take you further, faster.

WE HAVE THE EXPERIENCE AND EXPERTISE TO TRANSFORM A WIDE RANGE OF TECHNOLOGIES AND PROCESSES INTO VIABLE SOLUTIONS

Continuous Manufacturing

The greatest paradigm shift in pharma processing since validation and qualification systems were introduced

With 14 years of continuous learning, GEA has firmly established its longevity in the CM market. And having completed more than 70 projects involving a variety of filed and authorized products, including the first ever FDA-approved breakthrough therapy developed and manufactured using the ConsiGma platform, no other company has as much experience and done more to pioneer continuous manufacturing (CM) for the pharmaceutical industry.

ConsiGma® is a Six Sigma-inspired manufacturing platform, incorporating different technologies to produce oral solid dosage forms in a continuous, cost-efficient way:

- by collecting more information during R&D with less product
- by excluding risky, time- and product-consuming scale-up exercises
- by introducing online measurement and targeting real-time release (Six Sigma production), reducing waste to zero
- by incorporating flexible batch size (JIT production), reducing inventory
- by decreasing the energy cost per tablet, reducing environmental impact.

ConsiGma® was developed in compliance with the FDA's QbD initiative. It satisfies the industry's need for reduced risk and higher quality while avoiding lengthy and costly validation and scale-up to bring products to market much faster. This flexibility enables the production of products to meet demand, keeps expensive cleanroom space to a minimum and reduces inventory costs.

ConsiGma® continuous oral solid dosage tableting lines (granulation, drying, tablet compression) are designed for plug-flow, first-in first-out (FIFO) production, avoiding back-mixing, providing a consistent quality and allowing for the inline control of critical quality attributes. ConsiGma® ticks all the pharmaceutical industry's boxes:

- broad opportunity, ethical and generic, worldwide
- R&D: flexible batch size, no scale-up, fast DOE
- reduced investment and running costs:
- easy to install, reduced use of utilities, parametric release, reduced quality cost
- time-to-market: fast deployment, full flexibility with modular construction, POD-based installations possible.

Looking to the Future

GEA has been successfully demonstrating its late-stage development-to-manufacturing capabilities for many years. With the portable, continuous, miniature and modular (PCMM) pod-based mini factories, for example, GEA and its partners are leading the way toward smaller, more flexible, continuous processing technologies that have the potential to transform the future of pharmaceutical development and manufacturing — and deliver customized quantities of drugs to patients in need in a quick and efficient way.

GEA Service – For your continued success

GEA Service partners with our pharma and biotech customers, supporting them throughout the entire lifecycle of their plant and equipment to ensure business success. To guarantee optimum performance and operational excellence, we provide a wide range of services to maintain and improve your plant and equipment.

Getting you started: seamless support for instant productivity and performance

From installation onwards, our GEA Service teams will work with you to get the best out of your plant and equipment. As a supportive and committed partner for life, we start as we mean to go on.

We plan and build according to individual needs, sharing process knowledge, training staff and supporting operators to get you up and running and deliver a smooth, seamless and ongoing service for optimum performance and safety.

Keeping it running: the cost-efficient way to ensure safety and reliability

Regular maintenance is not a cost, it's an investment. By implementing corrective and preventive maintenance techniques, we ensure high performance, availability and quality — as well as maximizing the lifecycle of your equipment or plant.

To ensure you benefit from continuous production and minimal downtime, we provide fast support and top quality spare parts, whenever and wherever they're needed.

Constantly improving: sharing our knowledge to safeguard your investment

To meet your production requirements — today and tomorrow — GEA works with you to keep your equipment up to date and optimized.

We safeguard your investments by constantly looking ahead, by upgrading or modernizing equipment and enhancing processes to meet changing needs and new market demands. We are always working to increase production efficiency and ensure peak performance.

Together with you: enduring commitment to you and your business

By integrating the latest automation and control solutions, we boost your output and efficiency, reduce waste and minimize both resource use and the need for manual intervention.

Our commitment to you and your business means investing in your objectives, your risks and your future success. We collaborate with you to provide ongoing systems audits and on-site support, and to generate improved performance through innovative new service models.

We supply the added value and the deep-rooted knowledge that counts

KEEPING IT RUNNING

FOR BETTER BUSINESS SUCCESS

GEA Service partners with our pharma and biotech customers, supporting them throughout the entire lifecycle of their plant and equipment to ensure business success.

engineering for
a better world

We live our values.

Excellence • Passion • Integrity • Responsibility • GEA-versity

GEA is a global technology company with multi-billion euro sales operations in more than 50 countries. Founded in 1881 the company is one of the largest providers of innovative equipment and process technology. GEA is listed in the STOXX® Europe 600 Index. In addition, the company is included in selected MSCI Global Sustainability Indexes.

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