

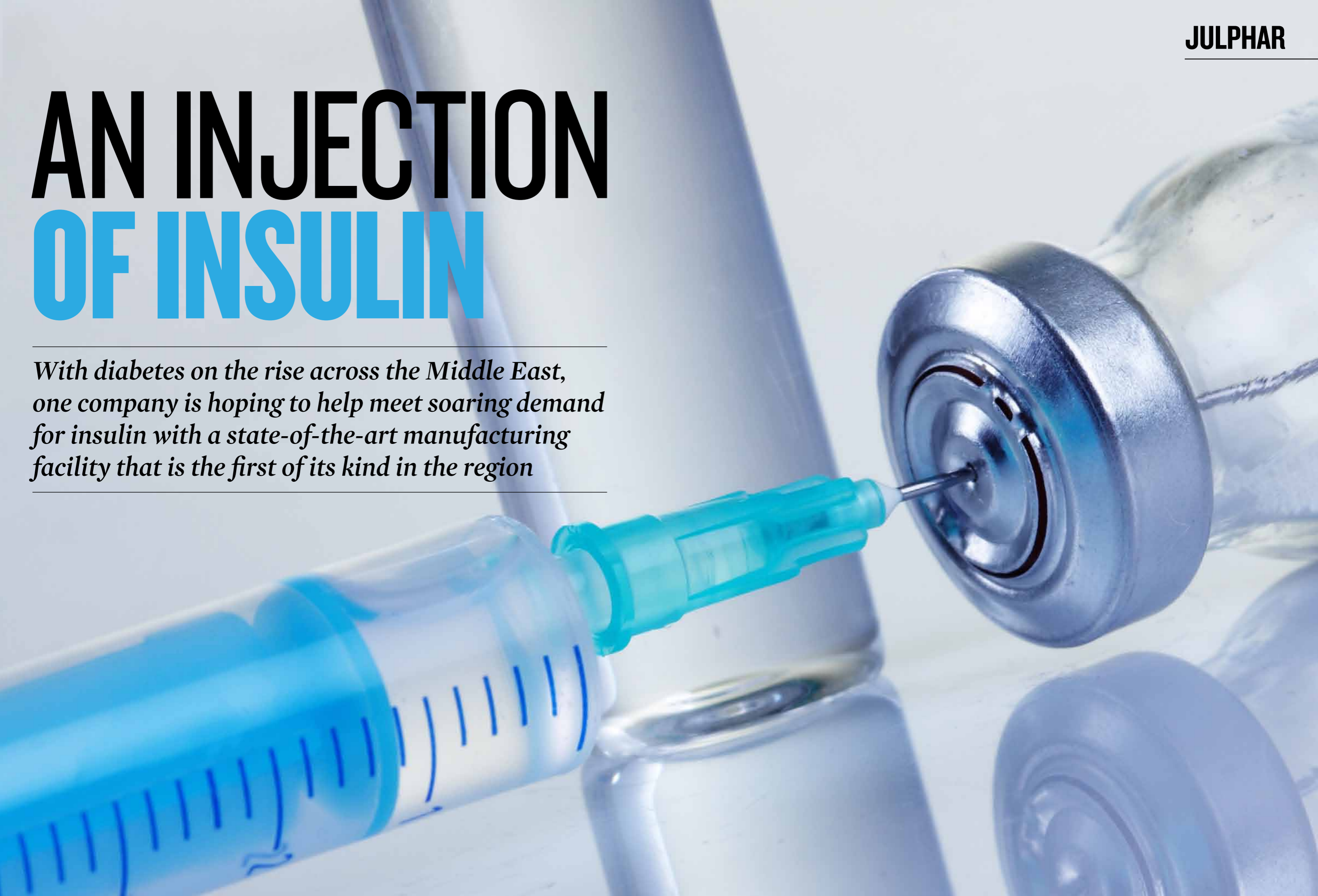
JULPHAR

www.jusline.ae | www.julphar.net



AN INJECTION OF INSULIN

With diabetes on the rise across the Middle East, one company is hoping to help meet soaring demand for insulin with a state-of-the-art manufacturing facility that is the first of its kind in the region



Obesity-related diabetes is on the rise in the Middle East. The World Health Organisation estimates that almost one-fifth of the region's population is affected by the disease. And the International Diabetes Federation believes that the number of diabetics in the UAE will soar by a staggering 80 per cent by 2030.

It comes as no surprise then, that insulin is one of the region's most sought-after medications. And one company looking to meet that demand by becoming the Middle East's first manufacturer of insulin is Gulf Pharmaceutical Industries, or Julphar, as it is more widely known.

Based in Ras Al Khaimah in the UAE, Julphar was established in 1980—the first pharmaceutical manufacturing company to be set up in the Arab Gulf States. Today it continues to be a leading pharmaceutical producer in the region, with nine production facilities located in the UAE.

Marketed across five continents, Julphar's 200-plus products target a number of major therapeutic areas, including anti-infection, the central nervous system, endocrinology, joints and the musculoskeletal system, the respiratory system, the oral cavity and gastrointestinal tract, immunosuppression, nutrition and blood, local anesthetics, skin, and para-medical products. The company, which is the largest drug manufacturer in the Middle East, has the capacity to produce a total of 4.8 billion units of various dosage forms each year.

Last year, Julphar announced record



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LINDE ENGINEERING DRESDEN



Linde Engineering in Germany, a leading contractor for process plants for the chemical, gas, biotechnology and pharmaceutical industries, also has a strong presence in the Middle East with well-established offices in the UAE and Saudi Arabia. Linde has more than 20 years of experience in the pharma and biotech industries. For Julphar's new recombinant insulin plant, Linde Engineering provided the basic and detail engineering, construction site coordination support, and services for commissioning and qualification. In 2009, Julphar Gulf Pharmaceuticals, a pharmaceuticals company based in the Emirate of Ras Al Khaimah, involved Linde to carry out the first engineering tasks for the new recombinant insulin plant in Ras Al Khaimah, UAE. Working closely with Julphar and the technology provider, the basic engineering was produced, then developed further during the detail engineering. A complete 3D CAD model of the new plant was generated, in which all equipment, pipes, cables, walls, cleanroom installations, HVAC systems and all main components were integrated and coordinated by an interdisciplinary team of experienced specialists.

The whole project was coordinated in the 3D model which enabled efficient installation on the construction site. The several package vendors were also integrated in the 3D CAD model coordination and the interfaces were defined early so that interferences and gaps were widely avoided, which saved construction time and material cost by

reducing waste material to the absolute minimum. Linde Engineering applies this interdisciplinary workflow and 3D CAD coordination to most projects, has broad experience with the related IT tools, and can carry out such engineering projects efficiently.

Linde's project team communicated closely with various installation contractors, whose construction activities were coordinated by utilisation of the 3D CAD model to a large extent. Commissioning of the new plant was planned early, also using the P&ID database system, linking the automation system and taking into account the IQ and OQ strategy for start-up of the plant. Linde's experienced process and commissioning specialists worked hand-in-hand with Julphar's Quality QA/QC/QM team and Julphar's experienced and newly trained operators, as they did in the planning and execution of start-up. The successful project execution proves that close teamwork between the client team, the engineering contractor, package vendors and specialist firms for the variety of systems in a modern biopharmaceutical plant such as cleanrooms, HVAC, automation and pure utilities can turn a complex and challenging project into a well-organised and focused project meeting the highest quality and PM standards. At over 20,000 square metres, this new state-of-the-art production facility is the largest biotechnological production plant in the whole of the Middle East.

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sales growth of 11.3 per cent, with sales of 186 branded generic products and 800 drug formulae to more than 40 countries reaching Dh1billion. The revenue even bolstered the UAE's exports balance sheet by an impressive Dh900 million.

And now, Julphar looks set to break yet more records with its new \$136 million insulin manufacturing facility in Ras Al Khaimah—a state-of-the-art biotechnological plant for the production of recombinant human insulin crystals.

Julphar first entered the insulin production market eight years ago, importing insulin crystals for the local production of Jusline (Julphar's recombinant human insulin). With regional demand for high-quality insulin now growing, Julphar is set to become the first company in the MENA region to produce recombinant DNA insulin in-house. Jusline has been approved by many regulatory

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“LAST YEAR, JULPHAR ANNOUNCED RECORD SALES GROWTH OF 11.3 PER CENT”



Julphar's products target a number of therapeutic areas



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GEA DIESEL



When a company exhibits at a trade show it's not always possible to identify direct business as a result. Often the benefits come much later and the link between a new contract and the attendance at the show is lost. But, for GEA Diessel, its attendance atACHEMA in the spring of 2006 was different.

GEA Diessel produces and supplies process systems for the production of liquid products for the pharmaceutical and biotechnological industries. Its sales teams were delighted when the managing director of Julphar, the UAE-based insulin manufacturer and one of the Middle East's largest pharmaceutical companies, walked onto the stand atACHEMA with a project to discuss.

Julphar and GEA Diessel were not strangers: the companies had worked together for many years to develop pharmaceutical plants, including the world's largest fully automated plant for the production of syrup and suspensions. However, despite being old friends the meeting was exciting and became more so when GEA Diessel discovered the nature of the enquiry. It was for a new plant for the production of insulin. In itself that was not extraordinary but what surprised even the seasoned engineers was the scale of the project. When complete the plant would produce 1,500kg of insulin a year, making it one of the largest of its type in the world.

In the autumn of 2006, GEA Diessel began work on the initial concepts and budget calculations. In 2007, the company worked on scaling up the systems from laboratory to production levels and determined important procedural parameters that would serve as a basis for the selection of process equipment. By 2009, all the plans and the engineering for the production plant had been completed.

The project was to provide all clean utility systems and to manage the process integration of all the main systems, including fermentation, harvesting, chromatography, filtration and freeze drying, for the new US\$136 million insulin plant at Ras Al Khaimah in the UAE. It was to be one of the most modern biotechnological plants designed for producing recombinant human insulin crystals. It was to have a floor space of 20,000 square metres including 5,000 square metres of clean rooms and around 17 kilometres of clean piping. It was a truly massive project. Ralph Schulze, head of Pharma and Biotechnology at GEA Diessel, takes up the story: "In autumn 2010, GEA Diessel started working on site. It was a big challenge for us," he explains. "We had to lead a team of 100 engineers and fitters, carefully managing them all in accordance with their abilities and expertise. We also had to maintain a high degree of flexibility as certain process areas had to be optimized and modified to meet specific requirements. By the end of 2011, all main work was completed."

Schulze added that the project was completed successfully and that he was very grateful for the excellent cooperation he had had from the Julphar technical team, especially Mr Hasan Jibreel, the director of projects; and Mr Essam Hammad, the director of the insulin plant. "We were able to complete the project in a very short time because of the experience the GEA Diessel and the Julphar engineers had in working together in the past," says Schulze. "We wish Julphar every success in the qualification of the biotechnological plant and with the insulin production."

www.diessel.com

GEA WESTFALIA SEPARATOR GROUP



In Ras Al Khaimah, Julphar uses the technology of recombinant DNA (r-DNA), by injecting the insulin gene into a suitable carrier substance, in this case Escherichia coli. Its genetic constitution is modified in such a way that it produces the human hormone insulin. In various stages, the bacteria then multiply in fermenters, and are subsequently recovered and purified in separators. Separators thus constitute the core processes in the production of insulin. Because GEA Westfalia Separator Group is known as the world-wide technology leader in the production of insulin, Julphar decided to use the know-how of the company from Oelde with centrifugal technology in its new plant.

GEA Westfalia Separator Group has installed a total of five separators in Ras Al Khaimah, to the north of Dubai. A nozzle-type separator CFA 65 with viscon® technology is used for separating the coli bacteria from the fermentation broth; in this solution, the solids are continuously discharged with a constant concentration. Following the homogenisation stage, two self-cleaning separators of the type CSE 80 separate the inclusion bodies from the cell fractions and wash them. Following

the precipitation of the insulin crystals in the clean room, two chamber-type separators BKA 28 are then used to separate the crystals and thus produce concentrated insulin. Whereas the separators in the first two stages were supplied as compact package units, the chamber-type separators are standalone machines with the corresponding valve blocks and control unit. After GEA Westfalia Separator Group has provided intense training to the operating personnel, operations in Ras Al Khaimah will start providing product in mid-2012.

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Julphar Insulin Plant

health authorities and is registered in more than 14 countries worldwide.

“This new facility strengthens Julphar’s commitment to diabetes management, not only in the UAE, but also on an international scale,” says Dr Ayman Sahli, CEO of Julphar.

A clinically-validated recombinant DNA insulin, Jusline is available in 10ml vials of 100 u/ml in three different formulations:

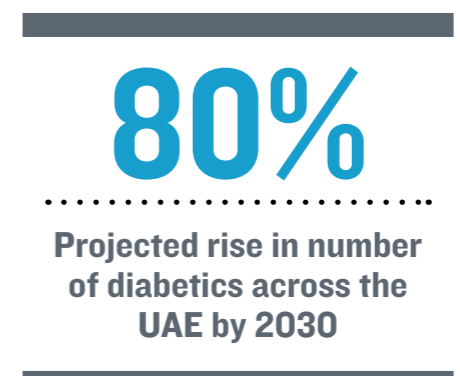
Jusline R (regular), Jusline N (basal) and Jusline 30/70 (biphasic), covering all insulin requirements for diabetic patients. Julphar says that Jusline offers high quality recombinant human insulin to healthcare providers and patients at an

accessible price, and also supports regional governments with a strategic solution to reducing the diabetes burden and increasing the accessibility of insulin therapy.

Julphar hopes that the factory, which has the capacity to produce up to 50 million vials of the raw material for insulin each year, will fill a gap in the local market, where over 90 per cent of pharmaceuticals

are currently imported. At the time of writing, the plant was just weeks away from commencing production.

All sub plants within the new complex are supplied through centrally connected corridors, technical shafts and underground tunnels,



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In addition to a broad and innovative product portfolio, Siemens offers services and competencies from dedicated engineering services to a multi-disciplinary optimisation approach throughout bio and pharmaceutical manufacturing to address the key issues of the industry and improve business. This covers not only state-of-the-art technology but also work on strategic, long-term and comprehensive concepts to benefit the customer's business worldwide. Siemens is a trusted partner for Julphar in automation projects. Several production facilities are already equipped with Simatic controllers and automation solutions e.g. the "Julphar VI" multipurpose manufacturing plant for liquid and semi solid pharmaceutical dosage forms. The new insulin production plant "Julphar XI" is one of the most modern biotechnological plants designed for producing recombinant human insulin crystals. Siemens' first class knowledge and experience in biopharmaceuticals combined with innovative automation products and solutions were the main reason that Julphar decided for the Siemens automation solution based on Simatic PCS 7, including Batch and Route Control. According to Dr.

Ayman, General Manager of Julphar, this is the start of a long-term relationship, initially focused on successfully completing what Julphar considers to be one of their most strategic projects during recent years.

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Siemens AG (Berlin and Munich) is a global powerhouse in electronics and electrical engineering, operating in the fields of industry, energy and healthcare as well as providing infrastructure solutions, primarily for cities and metropolitan areas. For over 160 years, Siemens has stood for technological excellence, innovation, quality, reliability and internationality. The company is the world's largest provider of environmental technologies. Around 40 percent of its total revenue stems from green products and solutions. In fiscal 2011, which ended on September 30, 2011, revenue from continuing operations totaled €73.5 billion and income from continuing operations €7.0 billion. At the end of September 2011, Siemens had around 360,000 employees worldwide on the basis of continuing operations. Further information is available on the Internet at:

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Manufacturing operations are divided between six suites. Bulk media is formulated in the media preparation room before inoculation and up-filling to pre-fermentation vessels for fermentation. Bulk buffers are formulated in the buffers preparation area before up-filling to storage vessels in the buffer hold suite; and in the fermentation suite, four seed fermentors and four 5,000-litre production fermentors produce 10,000 litres of bacterial broth per batch. In the recovery area, the E.coli is killed and broken down to harvest the pre-proinsulin.

The pre-proinsulin is then separated out from the cell debris by centrifugation and filtration, prior to further refolding reactions, where it is treated with buffers to assist it in attaining the correct structure. In the downstream initial purification suite, the pre-proinsulin is purified to



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“QUALITY IS OF THE UTMOST IMPORTANCE TO JULPHAR, AND HYGIENE PROCESSES HAVE BEEN CONSIDERED AND CATERED FOR DURING EVERY STAGE OF THE PLANT’S DEVELOPMENT”

get rid of attached peptides; and in the downstream final purification suite, the pre-proinsulin is cleaved using CPB to modify its primary structure and then separated by chromatography and finally, crystallized.

Quality is of the utmost importance to Julphar, and hygiene processes have been considered and catered for during every stage of the plant's design and development. The chromatographic process is monitored by protein-specific analysis using enzyme-immunological methods that make it possible to detect even the smallest possible by-products. The purity of the insulin is measured at every intermediate stage of production by the in-process control (IPC) laboratory. And all stages of the process use deionized and purified water, with microbiological and physical chemical quality monitored routinely and ozone removed with UV light before it is used.

All raw materials and auxiliary materials (such as solvents, acids, bases, salts and buffers) are of pharmaceutical quality or meet internal plant specifications and are checked regularly; and the nitrogen used for inerting is purified through high-efficiency particulate filters before use to prevent contamination by particles. As a rule, all stages of the process are carried out in closed tanks with solid pipe connections, and



A group of high level officials from Saqr Hospital visit Julphar

manual handling of the product is reduced to a minimum. The material used for the tanks and connecting pipes is corrosion-resistant stainless steel with defined surface roughness (internally electropolished for critical process steps), which ensures thorough and complete cleaning.

At the plant's core is a high-capacity process control system, which processes about 10,000 items of input and output information and monitors and controls the

entire manufacturing process. All quality-related instruments are calibrated upon putting into service, which is repeated regularly at appropriate intervals.

To achieve its world-class vision, Julphar has worked with a number of world-class suppliers. The architects for the plant were Julphar's Projects and Engineering Department in collaboration with leading engineering consultants LINDE-KCA. Process piping and installation of the plant equipment was undertaken by GEA Diessel of Germany; cleanrooms were provided and installed by Isocap of Belgium; and automation of the plant and control systems along with instrument validation was carried out by Siemens. Main process equipment suppliers included

GE Healthcare for chromatography purification systems; Pall for tangential flow filtration systems; GEA Westfalia for cell separators; Abec for fermentors and process vessels; Martin Christ for lyophilization; Fedegari for autoclaves; and Veolia for the RO system, WFI distiller and clean steam generator.

Julphar hopes that the new plant will mark the start of a new era in healthcare for the Middle East, where access to the most important medications is improved and high quality does not have to cost the earth. **BE**

“TO ACHIEVE ITS WORLD-CLASS VISION, JULPHAR HAS WORKED WITH A NUMBER OF WORLD-CLASS SUPPLIERS”

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