Maximising Drug Discovery by Simplifying Scale-up and Production

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Abstract

The pharmaceutical and biotech industries are heavily dependent on gases and chemicals, from high-purity gases for laboratory use to process gases for production processes such as chemical synthesis, sterilisation gases and gases to grow biological cultures. The Linde Group, a leading supplier of process and specialty gases and innovative engineering solutions to the pharmaceutical industry, has been successful in developing and providing solutions to meet the evolving needs of the pharmaceutical industry in terms of impact, commercial manufacture, good manufacturing practice (GMP) controls, scale-up issues and process validation. HiQ® solutions stand for the best Linde offers in pure gases, mixing accuracy, quality services, precision engineered supply systems and technologically advanced production facilities. With VERISEQ® pharmaceutical gases, Linde offers quality-assured gas solutions for the manufacturing of pharmaceuticals and active pharmaceutical ingredients (APIs). Maintaining the integrity of the gas from the product source to point of use is one of the biggest challenges. Therefore, it is essential that the supply system be designed and built with the goal of excluding impurities.

Keywords

Analytical service, application, certificate, chemical, gas equipment, pharmaceutical gas, process gas, specialty gas

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"I don't look to jump over seven-foot bars: I look around for one-foot bars that I can step over." Warren Buffett

The pharmaceutical and biotechnology fields are among the most complex and innovative industries in the world. It can take years of research and hundreds of millions of dollars to formulate a product that can safely and efficiently cure a patient. This is not the only challenge, as taking a laboratory-scale product to one that is commercially viable has its own set of problems. In many cases the company must build new manufacturing facilities or reconstruct existing ones because manufacturing processes vary from drug to drug. To add further complication, the drive to reduce risks associated with pharmaceutical treatments has resulted in stricter legislative requirements and increased regulatory burdens on pharmaceutical companies.

The Linde Group is a supplier of process and specialty gases and innovative engineering solutions to the pharmaceutical industry. It has succeeded in developing and providing solutions to meet the evolving needs of the pharmaceutical industry in terms of impact, commercial manufacture, good manufacturing practice (GMP) controls, scale-up issues and process validation. Pharmaceutical companies use gases in a variety of applications across all stages of the production chain – from research, development and quality control to production of active pharmaceutical ingredients (APIs) and final drugs. Previously, process gases used in pharmaceutical production were not subject to any particular attention from the authorities. Increasingly, however, process gases such as nitrogen used for inerting finished medicinal products are considered critical utilities.

Setting Standards

Pharmacopoeias promote public health by providing common standards that are recognised by health authorities and the medical community. This ensures the safe use of medicines by patients and consumers, and also ensures that trust is not broken between consumers and pharmaceutical manufacturers. VERISEQ® gases are a range of quality-assured pharmaceutical-grade gases. They are used in the manufacture of pharmaceuticals and APIs that leverage understanding of the complex regulatory background and diverse individual needs within the industry. By assisting in regulatory proof-of-compliance, the supplier verification process for customers is simplified considerably.

HiQ Specialty Gases

The pharmaceutical and biotech industries are heavily dependent on gas and chemicals – from high-purity gases for the laboratory to process gases for production processes, such as chemical synthesis, sterilisation gases and gases to grow biological cultures. HiQ solutions stand for the best Linde offers in pure gases, mixing accuracy, quality services, precision engineered supply systems and technologically advanced production facilities. Research, development, production and quality control laboratories all use gas-consuming analytical instruments, such as gas or liquid chromatographs, ultraviolet/visible spectroscopy (UV/VIS), nuclear magnetic resonance (NMR) or mass spectrometry. Gas quality can often affect the accuracy of measurements of these instruments. Carrier gases and calibration mixtures with known degrees of accuracy, purity and composition are an essential part of the HiQ specialty gases product programme. Where there is a demand for gas products in such areas as production, growth of biological cultures,

Figure 1: REDLINE Semi-automatic Gas Panel A208

Figure 2: Liquid Oxygen Tank Used for VERISEQ Gases

environmental mixtures, sterilisation or chemicals, Linde offers the right product for the right application. In some cases cylinder gas might be unsuitable. This may be for safety reasons or due to difficulty in cylinder transportation. Linde has a range of small and reliable gas generators for such situations. These generators produce gas on-site for instant use. The main advantage of this is that because the gas is produced on site, it allows complete control over gas production. This could be essential if there is a power failure – particularly if the gas being produced is hydrogen. Another advantage is that there is no need to store large amounts of compressed gas as there is instant access to newly produced gas. Gas generators are small and allow for flexibility in laboratory set-up and streamlining of lab rearrangements. Due to their compactness, laboratory space can be saved. The HiQ specialty gas generator programme includes high-purity no-maintenance hydrogen generators (99.9999% purity), liquid chromatography or mass spectrometry (LC/MS) nitrogen generators and Ultra Zero air generators.

Specialty Gases Distribution Equipment

Maintaining the integrity of gas from the product source to point of use is one of the biggest challenges facing every specialty gas user. The quality and consistency of the gas is only as good as the quality of the distribution system. Therefore, it is essential that the supply system is designed and built with the goal of excluding impurities. The REDLINE® gas supply equipment range is designed to ensure the highest standard of quality, design and performance. Coupling REDLINE equipment with our extensive in-house expertise in system design, construction, installation and operator training enables us to deliver complete, customised supply solutions for pharmaceutical and biotech applications. For pharmaceutical applications, Linde offers REDLINE stainless steel regulators that are traceable and come with a material certificate to fulfil US Food and Drug Administration (FDA) requirements (see *Figure 1*).

Analytical Services

Custom analytical services are developed for manufacturers of pharmaceuticals and APIs who use gas distribution systems in their production processes. These manufacturers set very high standards for safety and quality. This is also reflected in the standards set for gases and their distribution systems. To verify the contents of gas systems at factories operating under GMP requirements, a complete gas analysis should be carried out at least once a year. This is especially important where the gas comes into contact with finished products. The gas samples can be regularly taken by either qualified personnel or the customer. The sampling is performed by applying set routines and is transferred to specially designed cylinders for testing. Linde specialty gas laboratories are capable of carrying out standard analyses in accordance with the requirements of the common pharmacopoeias, as well as completely unique gas analyses by arrangement.

VERISEQ Pharmaceutical Gas Concept

With VERISEQ pharmaceutical-grade gases, Linde offers quality-assured gas solutions for the manufacturing of pharmaceuticals and APIs to meet the increasingly stringent requirements of European, US and Japanese pharmacopoeias, and the FDA and other authorities. Linde has been broadening its portfolio of pharmaceutical-grade gases in the VERISEQ product portfolio with the goal of these products enabling pharmaceutical manufacturers to swiftly commercialise operations by quickly complying with all necessary specifications. Consequently, documentation, traceability and reliability are just some of the gas demands of the pharmaceutical industry. VERISEQ gases are analysed for identity and impurities using analytical equipment that fulfils the monograph requirements of European, US and Japanese pharmacopoeias. Although nitrogen is the most commonly supplied gas, used as an inert gas for the conditioning, transport and storage of pharmaceutical products, VERISEQ gases also include gases such as carbon dioxide, helium and oxygen. These are tested to comply with the requirements in the pharmacopoeia monographs and can be supplied in cylinders or bulk. Based on individual requirements, Linde selects a custom solution from this product range to suit specific needs. These solutions include a broad, proven portfolio of cost-effective services targeted to meet the environmental, compliance and productivity enhancement needs of each specific customer (see *Figure 2*).

Yield Enhancement Through Low-temperature Cooling

One of the challenges in scale-up is minimising side reactions that generate unwanted compounds or isomers in the process that are not seen in the laboratory-scale process. By cooling the reaction to a very low temperature, the preferred or desired product may be made in greater quantity and the formation of undesired side products minimised or eliminated. As drugs become increasingly complex, the demand for synthesis and crystallisation at very low temperatures also grows. The low temperature cooling of process fluids is both necessary and beneficial to achieve a high degree of process control and stability to increase product quality, yield and selectivity. The CUMULUS® fluid temperature control (FTC) system is the optimal solution for rapidly bringing the process down to temperatures between -120 and -30°C, with unchallenged accuracy. The system uses liquid nitrogen as a cooling medium to automatically cool process fluids in a highly

controlled manner. The CUMULUS FTC system is a patented method for cooling process liquids in a controlled manner without the risk of freezing. With the use of liquid nitrogen as a coolant, fluid streams can be chilled to extreme temperatures. Common fluids cooled by the system within the pharmaceutical and chemical process industries are methanol, toluene, SYLTHERM™ XLT, brine and many others.

Reduction of Volatile Organic Compound Emissions

The safety of the products produced within a factory is just one aspect of manufacturing. Strict environmental legislation also places pressure on manufacturers to purify exhaust gas and recover volatile organic compounds (VOCs) that create health and environmental hazards. These emissions are strictly regulated by law. CIRRUS® vapour emission control (VEC) systems from Linde constitute a complete and comprehensive approach to minimising or totally restricting the release of VOC, using liquid nitrogen to condense the VOC vapour from gas streams. The cryogenic process is chlorofluorocarbon (CFC)-free and generates no wastewater. Furthermore, there is no secondary pollution in the form of nitrogen oxides (NO_X), acids, gases and dioxins. The inert nitrogen does not come into direct contact with the VOC, which means the condensed VOC and evaporated nitrogen can be recycled and re-used for other purposes in a pharmaceutical company's process. Nitrogen recycling and chemical recovery are extremely cost-effective, thus significantly reducing pharmaceutical company's operating costs. This technology has proved to be effective for recovering VOCs such as acetone, methanol, toluene, dichloromethane and other hydrocarbons – either as pure compounds or as mixtures. CIRRUS VEC systems are therefore an ideal solution for VOC control in the pharmaceutical industries. The CIRRUS VEC modular system has been developed to provide flexible, compact and efficient solutions for air treatment problems.

Safe Production of Sterile Liquid Gas on Location

The VERISEQ sterile liquid gas (SLG) system provides sterile liquid nitrogen by liquefying sterile filtered gas. The system is fully automatic and may be operated batch-wise or continuously within the normal operating time for the sterile filter. The filter is the barrier that ensures a sterile result during operation. The system is prepared for non-destructive integrity testing of the sterile filter in place and is aseptically engineered to allow steaming in place (SIP) for sterilisation of the entire system prior to operation. Due to the system being automatic, any risk of contamination is eliminated. The SIP process has been functionally qualified both thermally and with biological indicators. The specifications used for the VERISEQ SLG system are acknowledged within GMP, for example system requirement specification, functional specification and design specification. All systems are subjected to a thorough pre-delivery inspection (PDI) before release. Commissioning and validation services are available. With VERISEQ pharmaceutical-grade gases, Linde Gases Division offers quality-assured gas solutions for the manufacturing of pharmaceuticals and APIs. Coupling REDLINE equipment with expertise in system design, construction, installation and operator training enables Linde Gases Division to deliver complete solutions for pharmaceutical and biotech applications. ■

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Drug Development

Drug Development • Volume 4

Welcome to *Drug Development*

Successful drug development can be summarised through the use of three main pillars: great protocols, great operational execution and great statistical and medical interpretation of results. This year's edition of *Drug Development* contains important contributions in all three pillars of excellence.

Within these pages, Ken Getz reports on his groundbreaking research into the effects of protocol design on clinical trial performance, Pravin Jadhav and team provide insight from the Center for Drug Evaluation and Research (CDER) into paediatric development, Laurie Burke reviews regulatory concerns regarding the use of patient-recorded outcomes in trials and Lisa Chatterjee discusses a protocol representation model. Operationally, Zoran Antonijevic provides insight into how dose selection affects the likelihood of success in phase III trials and Michael Branson supercedes trial design to discuss utility scenarios. To balance this edition, strategic thinking has been provided by Bruce Pratt into a new collaborative model for pharmaceutical development, and Elna van der Ryst shares her learnings in the development of HIV therapies. Finally, insights into regulatory and validation concerns are provided by Siegfried Schmitt regarding the process validation of biologicals, and Patrick Cellis discusses the views of the European Medicines Agency on the certification procedure for advance therapies.

For those of us who share a passion for drug development, this edition should be a thought-provoking treat. Enjoy!

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