

Natural stimulants for your success.

Gas solutions for the pharmaceutical
and biotech industries.



We design and deliver. From calibration mixtures to pharmaceutical plants.



In the complex world of today, the pharmaceutical industry continues to demand increasingly advanced products aimed at improving modern-day life. This is why Linde Gas has an in-depth understanding of the many regulations that govern the industry.

Gases are employed as “invisible helpers” in most areas of industry. Such areas include, for example, many processes in the manufacture of active pharmaceutical ingredients (API) and pharmaceuticals. This also includes research and development (R&D) as well as production and quality control. Linde Gas is not merely a supplier of gases and gas-related hardware. With our expertise and special abilities, we at Linde Gas are capable of doing so much more for you with regard to the safety, quality and productivity of your processes. We have extensive know-how and many years of consulting experience in dealing with a wide range of enterprises.

This profound knowledge of gas technology means that we can offer comprehensive, cost-effective solutions for both existing plants and new processes. Our expertise ranges from the design and construction of pharmaceutical plants all the way down to a single cylinder of calibration or high-purity gas and from bulk deliveries of nitrogen to sampling and analysis at your points of use. We always work in close cooperation with our customers and, no matter what product or solution is chosen, we will help you to ensure that it is suitable for your good manufacturing practice (GMP) requirements.

Tailor-made, tested and traceable. Gases to suit your every process need.

Whatever your gas consumption, be it large or small, Linde Gas can help you find the perfect supply solution. Our offering extends from single cylinders to extensive on-site gas production plants. Linde Gas has developed traceable gas concepts that help manufacturers comply with applicable GMP regulations. The use of traceable gases that have been tested to comply with pharmacopoeia monographs is a reliable way to increase safety in the manufacturing of pharmaceuticals or APIs.

VERISEQ® pharmaceutical grade gases

VERISEQ® Gases are traceable pharmaceutical grade gases for the production of pharmaceuticals and active pharmaceutical ingredients. VERISEQ® Gases are developed to suit the needs of the pharmaceuticals manufacturing industry. This unique range of gases helps manufacturers comply with the applicable regulations on gas used in pharmaceutical production. By turning to VERISEQ® Gases, producers of pharmaceuticals or active pharmaceutical ingredients are assured of the quality and integrity of the gas. In-house gas analysis can be reduced to a minimum, which means that stock turnover can be improved in the long run.

By choosing VERISEQ® Process Grade Gases from Linde Gas, the pharmaceutical producer uses guaranteed gases that conform to agreed and internationally harmonised specifications. The gases are analysed for identity and impurities using qualified analytical equipment. VERISEQ® Process Grade Gases fulfil the monograph requirements in the European, Japanese and United States Pharmacopoeias. The analytical methods are in accordance with the same monographs, or equivalent validated methods. When traceable pharmaceutical grade nitrogen with higher purities than the European, Japanese and U.S. Pharmacopoeias state are required, the VERISEQ® concept offers appropriate products with 5.0 purity, i.e. 99.999%, under the name VERISEQ® Research Nitrogen.

On-site supply

If you require large amounts of gas, Linde Gas can offer an on-site supply based on the ECOVAR® concept. On-site means that Linde Gas locates part of its production capacity at the site of the customer. ECOVAR® systems are designed to supply gas cost-efficiently and reliably – with less environmental impact and less transportation. The ECOVAR® portfolio from Linde Gas includes a full range of standard gas generation plants that are specially designed for remote on-site operation. Pharmaceutical manufacturers requiring large volumes of gas will particularly benefit from the CRYOSS® product line that generates nitrogen of cryogenic purity for inerting and purging. Linde Gas has gained experience from delivering ECOVAR® plants to customers who require full validation and FDA approval.

Microbial contamination is not acceptable

Gas is normally sterilised with a filter at the point of use, but sometimes sterile liquid gas is required. Liquid nitrogen might be thought sterile in itself due to its low temperature. However, it is sometimes used to preserve living microorganisms. No conventional sterile filter can withstand cryogenic temperatures for very long. Linde Gas circumvents this by liquefying sterile filtered gas in its VERISEQ® Sterile Liquid Gas (SLG) system. The VERISEQ® SLG system belongs to the VERISEQ® PGC (Pharmaceutical Gas Concept). It has been designed for use in pharmaceutical production.



Bulk delivery of liquid nitrogen.



On-site supply with the ECOVAR® system.

Approved quality. Gas distribution and gas purity.

Gas distribution systems

The US Food and Drug Administration (FDA) encourages a science- and risk-based approach when designing, constructing, commissioning and qualifying utilities and equipment. The choice of materials for gas supply systems is determined by the gas to be distributed and the level of contamination that can be accepted in the gas. The inner surface finish of components is therefore of great importance to the final purity of the gas at the point of use. Gas system qualification includes performance testing, where gas samples are taken and then analysed according to relevant Critical Quality Attributes (CQAs), which in most cases will be those laid down in the pharmacopoeia monographs.

Linde Gas offers a wide range of gas distribution system installations, including:

- Industrial installations
- Specialty gas installations (laboratories)
- Specialty gas installations (GMP production)
- Ultra-high purity installations (semiconductor)

Gas purity

The quality and consistency of any gas is only as good as the distribution system. It is therefore essential that one of the goals in designing and building such a system should be the exclusion of impurities. Our extensive HiQ® specialty gas portfolio includes equipment for laboratory use, but also ensures equipment that offers traceability and proper documentation. Traceable equipment ranges from simple components such as valves and regulators to complex systems such as gas panels and points of use. All of these can be provided with certificates of conformity to prove compliance with the FDA. The BASELINE® cylinder regulators are Generally Recognized As Safe (GRAS) and are suitable for use with process gases in pharmaceutical production.

Because excellent products lead to excellent results. Specialty gases for laboratories.

A significant share of sales revenues from the pharmaceutical industry is reinvested in R&D, which is an area requiring a wide range of specialty gases for the development of chemical synthesis. Pharmaceutical laboratories use analytical instruments such as gas chromatographs with multiple detectors, liquid chromatographs, UV/VIS spectrometers and NMR spectrometers. These instruments need pure gases and gas mixtures with an accurately measured composition.

HiQ® specialty gas concept

The HiQ® specialty gas concept from Linde Gas meets many of the needs of the pharmaceutical and API industries. HiQ® is our word for pure and mixed gases and related gas equipment as well as services. This all rests on the combined global skill and knowledge of our HiQ® experts in the field, who have the software tools and networked information necessary to find the optimal solution for your specific needs.

Specialty gases

Linde Gas has the infrastructure – dedicated production facilities, accredited analytical laboratories, mobile analytical services, etc. – that puts the word “special” into HiQ® specialty gases. Needless to say, all gas products are quality-controlled and, wherever applicable, carry an analysis certificate. We make it our business to ensure that the gas or mixture you use in your business is the best one for the job.

Process chemicals – from lab to production

In addition to our standard assortment of industrial gases, Linde Gas supplies a range of gases that are specially tailored to the pharmaceutical industry. These products can be used at every stage of the development process: beginning at the lab bench, through process optimisation in the pilot plant, and on to the full production line. Typical applications and products are:

- **Amination:** ammonia (NH₃), mono, di & trimethylamine
- **Bromination:** hydrogen bromide (HBr)
- **Catalysis:** boron trichloride (BCl₃), boron trifluoride (BF₃)



BASELINE C106 single stage cylinder regulator

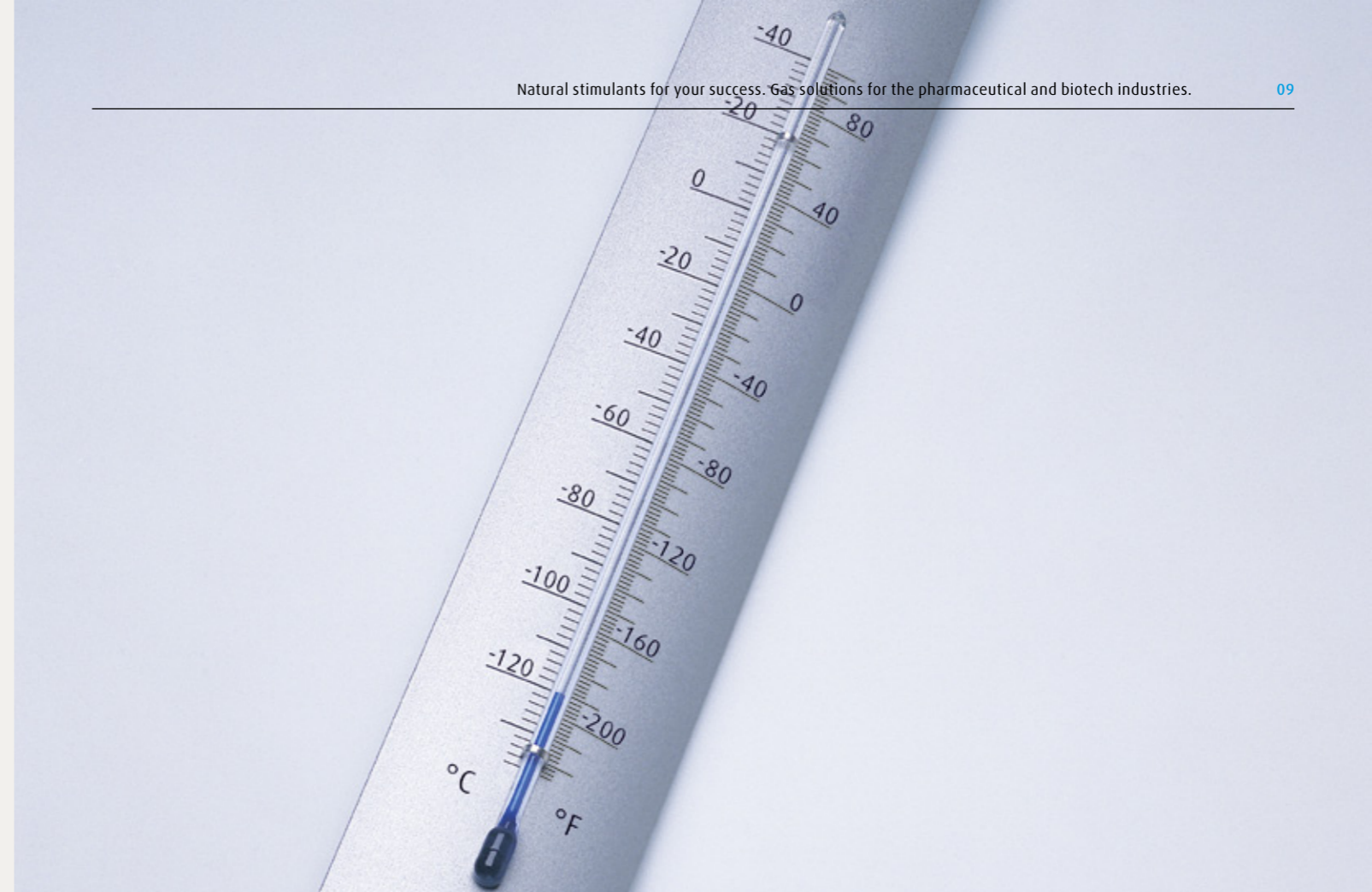
- **Chlorination:** hydrogen chloride (HCl), chlorine (Cl₂), silicon tetrachloride (SiCl₄)
- **Fluorination:** hydrogen fluoride (HF), nitrogen trifluoride (NF₃), sulphur tetrafluoride (SF₆)
- **General chemical:** carbon dioxide (CO₂), sulfur dioxide (SO₂), ethylene oxide (C₂H₄O), hydrocarbons
- **Insulation:** sulfur hexafluoride (SF₆)
- **Methylation:** methylbromide (CH₃Br), methylchloride (CH₃Cl)
- **Phosgenation:** carbon monoxide (CO), chlorine (Cl₂)
- **Propellants:** halocarbons, hydrocarbons.
- **Reduction:** hydrogen (H₂), diborane (B₂H₆)
- **Refrigeration:** halocarbons, ammonia (NH₃)
- **Thiolation:** hydrogen sulfide (H₂S), carbonyl sulfide (COS)

Keep your cool with cryogenic gases. Innovations for cooling.

Gas products – such as liquid nitrogen, liquid carbon dioxide and dry ice – are used to cool various processes and equipment. Cryogenic cooling with gas offers an environmentally-friendly alternative when compared, for example, with mechanical cooling based on halogenated hydrocarbons (HCFCs and CFCs). Many pharmaceutical processes can be enhanced through the use of cryogenic cooling, e.g. grinding, milling, mixing, granulation, freezing, lyophilisation and several others. Temperature control can be integrated into existing processes or equipment to enhance both production and product quality. Some typical parameters are processing times, yield, selectivity, surface structure and particle size. Cooling may be obtained by either direct or indirect contact with a cold-gas flow or with a liquid gas. In cases where the pharmaceutical product must be in direct contact with the cooling medium, Linde Gas can provide sterile liquid gas.



Customer installation of a CUMULUS® PX20 unit.



Reactor cooling

The CUMULUS® Fluid Temperature Control (FTC) system is designed to control the temperature of a reactor or process liquid with exceptional accuracy – down to as low as -120 °C. The CUMULUS® FTC system will help you achieve higher yields, and the stable cooling process ensures easy repeatability. The extra-compact design of the system means a small footprint, which allows units to be installed in existing facilities and moved around to meet cooling requirements in different locations.

Cryogenic storage and transport

Thanks to the use of liquid nitrogen, cryo-preservation allows storage at a temperature sufficiently below any critical temperature. This means that biological material can be stored almost indefinitely, since the rate of decomposition is extremely low. Linde Gas offers a range of freezers and containers of all sizes, engineered to maintain specific temperatures between -150 °C and -196 °C, depending on whether the sample is in liquid or in vapour phase. When transporting frozen microscope specimens, biological matter or medicines, Linde Gas can provide specific services such as the management of dry ice, packaging, or product transportation requiring strict temperature control.

Freezing

At Linde Gas, we have developed sophisticated systems for freezing. Liquid nitrogen and liquid carbon dioxide are both versatile cooling agents. Excellent heat transfer is achieved through direct contact between the cryogenic refrigerant and the product. Our freezer systems ensure high-speed freezing for better product quality. Other benefits include a high degree of reliability, simple operation and minimal space requirements.

Laying the foundations for your success. Design and construction of pharmaceutical and biotech plants.

Linde-KCA-Dresden GmbH is a leading, full-service engineering contractor, well experienced in the design and construction of all kinds of pharmaceutical plants. More than 100 references in the past 10 years include projects for biotechnological or chemical production of active pharmaceutical ingredients, fractionation plants for blood plasma, facilities for pharmaceutical dosage forms, and plants for food additives. Linde-KCA-Dresden manages and executes projects

through all phases, from front-end studies or conceptual designs up to the hand-over of completed plants. At Linde-KCA-Dresden, we have the flexibility to provide either selected services or take on full responsibility for engineering, project management, procurement, construction management and commissioning – including all stages of qualification (DQ, IQ, OQ) and validation assistance.



Interior of a large-scale biopharmaceutical plant, designed and constructed by Linde-KCA-Dresden.

A win-win combination. Maximum safety while optimising production.

At Linde Gas, we have extensive know-how when it comes to working with inert gases – nitrogen, argon or carbon dioxide. Handling these gases requires caution, and Linde Gas can help you with training in the safe handling and storage of gases.

Inerting

Inerting is a common process in the pharmaceutical industry, where it is used to improve product quality by reducing water vapour or oxygen content, thereby avoiding unwanted reactions. It is also used to increase safety by inhibiting combustion or by preventing fire or explosions. Being inert, the gas cannot interact with the pharmaceutical substance in question. Inerting is frequently used with raw materials and with intermediate product storage as well as flammable solvent storage. The atmosphere within process reactors, for example, can be effectively purged of oxygen and moisture at the time of startup or shutdown with the help of nitrogen.

Linde Gas safety system

Not all combustible fuel mixtures ignite. It is only when the concentration of components falls within certain limits that ignition and a resulting fire or explosion is possible. Linde Gas has developed unique PC software to help you calculate flammability limits for almost any mixtures. The flammability triangle that is graphically presented makes it possible to determine how to alter the mixture so as to avoid ignition.

Process optimisation

The Process Application Management system (PAM) developed by Linde Gas can be successfully used for gas operations such as purging or blanketing. By using PAM, your Linde Gas contact will be able to calculate process data and estimate how much inert gas you will need for any application. The conveniently presented data will help you choose the optimal operational method.

Let nothing go to waste. Saving the environment for future generations.

It has been said that we have not inherited the earth from our ancestors, but that we borrow it from our children. This is why Linde Gas offers a range of products designed to help you minimise your impact on the environment. The very air you breathe is our raw material.

Innovations in cylinders

Anyone not wishing to discard empty compressed gas cylinders or not wanting to pay excessive disposal fees will value the benefits of ECOCYL[®], our Portable Calibration Gas (PCG) container. This has been designed to replace non-refillable or "disposable" cylinders that often end up as solid waste. ECOCYL[®] comprises a lightweight, high-capacity refillable cylinder with a cap-protected integral cylinder valve, a regulator and a variable, selectable flow meter to meet all your calibration-flow needs.

Air treatment

CIRRUS[®] Vapour Emission Control (VEC) systems from Linde Gas offer a flexible, compact and efficient air treatment solution to help you minimise the emission of Volatile Organic Compounds (VOC). Liquid nitrogen is used to condense the VOC vapour from gas streams. The ultimate aim is to prevent the unwanted release of VOCs into the atmosphere. For large-scale projects, Linde Gas is also able to offer customised cryocondensation.

Wastewater treatment

Pure oxygen is commonly used in biological wastewater treatment plants to improve aerobic activity, which reduces dissolved oxygen (DO) levels and unpleasant odours. Oxygen can also prevent the formation of hydrogen sulfide in buffer tanks, lagoon piping and sewerage systems. Where standard biological treatment is not applicable, Linde Gas also offers solutions employing wet oxidation.



Linde Gas received the 2004 Gases and Technology Magazine Product Innovation Award for gas delivery systems with ECOCYL[®] – a portable, refillable, integrated calibration gas cylinder and gas delivery system.



Cleaning and extraction with CO₂.

Dry ice blasting

The solid state of carbon dioxide is known as dry ice. It is similar in appearance to normal ice with a hardness close to plaster. At atmospheric pressure, it sublimates at a temperature of -78 °C. CRYOCLEAN[™] from Linde Gas is a dry ice blasting process that is easy to use and requires no electrical power. Furthermore, it leaves no cleaning agent residues, no wastewater, and no solvents.

Supercritical extraction

Carbon dioxide in its supercritical state is increasingly used for extraction. Such supercritical extraction is for example applied in the pharmaceutical industry to refine compounds and to extract active natural products from plants. Supercritical carbon dioxide is particularly interesting because its solubility properties can be changed by varying the pressure and temperature. It has a list of other benefits: it is non-toxic, taste-free, solvent-free and non-flammable. Linde Gas can supply carbon dioxide and other gases for supercritical extraction, fulfilling a range of specifications.

Not just a gas supplier. Safety, training, services and more – from Linde Gas.

At Linde Gas, we offer various value-added services along with our products. We have many years of experience with situations similar to or exactly like yours. We can, for instance, simplify your qualification process through correct documentation, and we can perform factory and site acceptance tests (FAT and SAT). We can also help you with installation and operational qualifications (IQ and OQ) of our equipment.

Safety first

Safety consciousness is an overriding aspect of our company culture at Linde Gas, and it is given top priority in all gas installations. Any risks connected with potentially hazardous gas, the gas supply system, collection or disposal are minimised through preventive action. Linde Gas offers extensive security and maintenance services, and we can, in some areas, offer qualified on-site personnel and the security of an emergency response team.



Education and training

Linde Gas can recommend, and assist in, the development, implementation, control and follow-up of appropriate safety measures and procedures such as enhancing awareness and the training of personnel. Education and training in applicable processes is considered to be of the utmost performance in GMP. Linde Gas can assist you in your educational requirements concerning gases and gas-related applications.

Sampling and analysing

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. Our analytical services involve Linde Gas personnel regularly taking gas samples from the factory's gas system and analysing them in accordance with appropriate regulations.

Automatic gas ordering

Thanks to our sophisticated logistics and management systems, we are able to offer cylinder tracking and follow-up services under the name ACCURA®. We also offer SECCURA™ – our fully-automated gas supply service – to ensure that you will never run out of gas.

Total gas management

Our total gas management solution aims to meet all the needs of the customer, thus allowing you to focus on your core business. Total gas management spans everything from inventory control to remote monitoring, covering everything from automatic ordering and cylinder replacement to incoming inspections.

Our quest for quality goes on. Get the most out of innovations in gas technology.

Linde Gas, founded over 125 years ago, today represents the first choice for more than 1.5 million customers in more than 55 countries, all of whom benefit from our gas application technology, wide range of hardware and proven specialist services.

With business segments such as Linde-KCA-Dresden in its portfolio, Linde is a valuable partner, providing extensive know-how and state-of-the-art applications for the pharmaceutical and biotech industries. Another subsidiary, Linde Gas Therapeutics, is itself a pharmaceutical manufacturer, so it has its own store of in-house knowledge.

At Linde Gas, several engineers concentrate solely on gas-related innovations for pharmaceutical manufacturers. Our ongoing R&D activity converts ideas into new technologies to help you, our customer, secure competitive advantages and open new market opportunities.

We at Linde Gas strive to simplify your GMP compliance by providing you with the right products and the right services – right on time. Both the pharmaceutical industry and the biotechnology industry set very high standards for safety and quality. This is reflected in the demands placed on gases and on their applications. Which is why we offer more than mere catalogue content. Your local Linde Gas representative will help you find out more about how your company can get the most out of our expertise and innovative solutions.



Getting ahead through innovation.

With its innovative concepts, Linde is playing a pioneering role in the global market. As a technology leader, it is our task to constantly raise the bar. Traditionally driven by entrepreneurship, we are working steadily on new high-quality products and innovative processes.

Linde offers more. We create added value, clearly discernible competitive advantages, and greater profitability. Each concept is tailored specifically to meet our customers' requirements – offering standardized as well as customized solutions. This applies to all industries and all companies regardless of their size.

If you want to keep pace with tomorrow's competition, you need a partner by your side for whom top quality, process optimization, and enhanced productivity are part of daily business. However, we define partnership not merely as being there for you but being with you. After all, joint activities form the core of commercial success.

Linde – ideas become solutions.

Linde AG

Linde Gases Division, Seitnerstrasse 70, 82049 Pullach, Germany

Phone +49.89.7446-1661, Fax +49.89.7446-2071, hiq@linde-gas.com, <http://hiq.linde-gas.com>

CRYOCLEAN™ and SECCURA™ are trademarks of the Linde Group. HIQ®, VERISEQ®, ECOVAR®, CRYOSS®, CUMULUS®, CIRRRUS®, ECOCYL®, BASELINE® and ACCURA® are registered trademarks of the Linde Group.