BRINGING YOUR SCIENCE TO LIFE
CARBOGEN AMCIS AG is a leading service provider, offering a portfolio of drug development and commercialization services to the pharmaceutical and biopharmaceutical industries at all stages of drug development. Our integrated services for Drug Substances (DS) and Drug Products (DP) provide innovative solutions to support timely and safe drug development.

Our flexible approach enables customers to benefit from tailored packages of work which balance their needs in terms of speed, cost and quality. CARBOGEN AMCIS also adapts communication and reporting to match customer-specific requirements and documentation.

CARBOGEN AMCIS has been part of Dishman Pharmaceuticals & Chemicals Ltd since 2006. Custom synthesis operations within the Dishman group include facilities in India and the Netherlands, as well as the seven facilities under the CARBOGEN AMCIS brand: four in Switzerland, one in the UK, one in China, and one in France.

CARBOGEN AMCIS employs almost 200 chemists, approximately 40 per cent of whom hold a PhD in Chemistry. Our staff regularly attend internal and external training sessions to keep abreast of the latest safety requirements and technology enhancements.

Quality is central to the CARBOGEN AMCIS business. State-of-the-art facilities operate to the highest standards of Good Laboratory Practice (GLP) and current Good Manufacturing Practice (cGMP). CARBOGEN AMCIS is routinely inspected by SwissMedic, the US Food and Drug Administration (FDA) and the French Health Authority (ANSM).

Process Research & Rapid Supply of APIs

Early Phase Active Pharmaceutical Ingredient (API) manufacture centers on the rapid synthesis of supplies necessary to perform both toxicology and early phase clinical trials. Typical batch sizes here range from 1 gram to 50 kg scale and are prepared in the highest standard of cGMP. CARBOGEN AMCIS has an extensive toolbox including micro-reactor technology, spray drying, lyophilisation, milling and wet-milling as well as a range of chromatography techniques (SMB, HPLC, MPLC, Biogel). The combination of tools and experienced personnel allows CARBOGEN AMCIS to solve complex chemistry issues and to provide rapid supply of initial quantities of APIs.

Process Optimization & cGMP Manufacturing

Process optimization skills are critical in ensuring a safe and efficient scale-up from development scale to routine cGMP and eventual commercial API manufacture. CARBOGEN AMCIS can offer experience with a broad range of organic chemistry reactions. This consists of a diverse selection of routine chemistries as well as a wide variety of sophisticated modern technologies, including low temperature and high pressure reactions, metallo-organic reactions, peptide synthesis and chiral synthesis.

Pharmaceutical Intermediates Supply

The CARBOGEN AMCIS Manchester facility focuses on process research and the synthesis of pharmaceutical intermediates. The large-scale production capacities (up to 4,500 L) allow the efficient production of non-cGMP intermediates that can be further processed at the CARBOGEN AMCIS Swiss facilities.

Fill & Finish of Drug Products

The CARBOGEN AMCIS in Riom (France) site offers aseptic formulations and the development or optimisation of lyophilisation cycles are also part of CARBOGEN AMCIS service offering.

Analytical Services

Analytics provides the foundation for process research and manufacturing activities. A thorough understanding of reactions is critical in process development and validation work. CARBOGEN AMCIS has always strived to provide a comprehensive range of tools and techniques to facilitate this work. Analytical chemistry services support both process control and material characterization for laboratory and production chemistry, from initial raw material release to the release of the final APIs. Our Laboratory Information Management System (LIMS) and efficient integrated data processing ensure that data is recorded and analyzed in a controlled and timely manner and that data integrity is assured.

Moving Toward Full-Scale API Manufacturing

The Shanghai facility can offer large scale production for API Manufacturing. Also, as part of the Dishman group, CARBOGEN AMCIS can provide solutions for internal technology transfer to FDA-approved large-scale production facilities in India.
CARBOGEN AMCIS provides services for the development and manufacture of highly potent drug substances (APIs) and drug products applying state-of-the-art containment technologies. All facilities operate to current Good Manufacturing Practice (cGMP) and can produce material for preclinical testing, clinical trials and commercial use. Our manufacturing sites are regularly inspected by the US Food and Drug Administration (FDA) and local regulatory bodies.

CARBOGEN AMCIS containment facilities are designed based on a containment concept utilizing barrier isolation technology and Rapid Transfer Ports (RTPs) as well as a strict zone concept with pressure cascades, airlocks and access controls. This allows the safe handling of highly potent compounds including cytotoxics.

CARBOGEN AMCIS offers services starting from laboratory scale for process research and development purposes up to large scale manufacturing in 1'600 L vessels. To support the API development process through all stages, a variety of high containment analytical and purification capabilities complements the chemistry service portfolio.

In addition to our process research and manufacturing services for the fast supply of highly potent APIs, CARBOGEN AMCIS offers conjugation services for Antibody Drug Conjugates (ADCs) as well as formulation and fill-and-finish services for drug products.

Highly Potent API Supply

The highest category in CARBOGEN AMCIS’ categorization system is category 4 with an Occupational Exposure Limit (OEL) range of 1 - 0.05 µg/m³. However, recent containment testing performed according to ISPE’s SMEPAC-guideline, has shown that CARBOGEN AMCIS can safely handle ultra-potent toxins with an OEL as low as 0.001 µg/m³ (10 ng/m³) 8hr-TWA. Very Highly Potent toxins with an OEL of 10 ng/m³ are often used as warheads for new generation targeted cancer treatments such as ADCs.

Safety and Product Quality

CARBOGEN AMCIS is fully committed to managing the risks associated with handling and producing highly potent and/or toxic materials. Safety and quality considerations encompass our personnel, our customers and patients using the materials we produce, as well as the environment and our neighbors. We are dedicated to maintaining and improving safety, environmental and health standards above and beyond the standard legal requirements. This remains the responsibility of both our management and individual employees. All processes follow our “protection cascade” of four increasing levels of containment technology systems and procedures, ensuring that worker safety and product quality are never compromised.

![Diagram showing containment levels](image-url)
CARBOGEN AMCIS exists to provide innovative solutions for drug development and supply to the pharmaceutical and biopharmaceutical industries that enable customers to bring new generation medicines to market.

Successful drug development is a balance between speed, risk, quality and costs. At CARBOGEN AMCIS we aim to offer our customers a choice of state-of-the-art tools combined with qualified and experienced staff in order to best meet these often changing priorities. CARBOGEN AMCIS has built up a portfolio of specialist services to give customers the highest degree of flexibility possible.

Chromatography

Chromatography often forms part of a fast route to producing initial quantities of material. CARBOGEN AMCIS offers customized chromatography solutions for the separation and purification of APIs and intermediates, including highly active APIs as well as impurity isolation. Our dedicated group of chemists has more than 50 years experience in the group expertise in method development and scale-up in a variety of different chromatographic techniques, all in accordance with Good Manufacturing Practice (cGMP) environment.

Cost-effective large-scale chromatography is also possible given the correct infrastructure. CARBOGEN AMCIS offers Flash Chromatography (Biotage), SMB and HPLC to effectively produce clinical trial quantities of APIs and commercial products.

Chromatography Services Gram to Kilogram

- 3x 10 cm systems (2 x Labomatic, 1 x Knauer) 10 cm ID (inner diameter) columns Multi-component separations 0.02 to 0.35 kg/day
- Preparative HPLC NovaSep 20cm (ID) column Multi-component separations 0.1 to 1.5 kg/day
- 2x SMB Licosep 10-50 Binary separations racemates 0.2 to 5 kg/day
- Preparative HPLC NovaSep 30cm and 45cm (ID) column Multi-component separations 0.4 to 4 kg/day
- Preparative MPLC Verdot/Armen large-scale normal phase 0.5 to 10 kg/day
- 2x Biotage systems 1 to 5 kg/day

Crystallization Services

Defining the best crystalline form of an Active Pharmaceutical Ingredient (API) is crucial in drug development, since it has a significant impact on its bioavailability and formulation properties. CARBOGEN AMCIS has established a service supporting our customers with crystallization investigations including solubility tests, salt screening, and optimization of the crystallization process and the solid/liquid separation in the API isolation process. Polymorphism screening complements the service portfolio. We offer online monitoring of critical parameters such as particle size, turbidity, temperature, and pH value, as well as analytical services dedicated to solid phase characterization including hot stage microscopy, differential scanning calorimetry, Dynamic Vapor Sorption (DVS) and x-ray powder diffraction.

To keep up with the increasing requirements of a diverse technology base for the more complex and time-pressured goals of our customers, CARBOGEN AMCIS has expanded its service portfolio by implementing new technologies.

Ultrafiltration and Nanofiltration

This technique allows concentration of large chromatographic fractions under very mild conditions. In combination with lyophilization, this technique gives access to isolation of highly unstable compounds.

Micro-reactors

Micro-reactors and flow chemistry technology are currently used on a number of projects in parallel with conventional chemistry. Micro-reactors offer solutions where classical methods reach their limits. Examples are highly energetic reactions or unstable intermediates. Whilst the size of the vessels is small, the continuous processing allows this technique to produce material also at an intermediate scale.

Laboratory Information Management System

Analytics provides the foundation for process research and manufacturing activities. A thorough understanding of reactions is critical in process development and validation work. CARBOGEN AMCIS has always strived to provide a comprehensive range of tools and techniques to facilitate this work. Our Laboratory Information Management System (LIMS) and efficient integrated data processing are implemented at all cGMP sites. This system ensures that data is recorded and analyzed in a controlled and timely manner and that data integrity is assured. Customers can have direct real-time access to the LIMS system, thereby facilitating data exchange across the project team and aiding decision-making.
Technology Transfer Process

Complex, multi-step processes under both current Good Manufacturing Practice (cGMP) and non-GMP have been successfully transferred. For transfer outside of Switzerland, a specialist team follows an established three-stage procedure:

1. **Initiation:** the scope and goals are agreed upon by all parties – preparation of technology transfer master plan, definition of responsibilities, as well as preparation and transfer of technical information package;

2. **Piloting:** the process is trialled in the lab, analytical method transfer is completed, along with the key change review and pre-manufacturing review processes to ensure compliance with regulatory and quality standards. Finally trial batches are produced;

3. **Sign-off:** the trial campaign is reviewed in detail, any further learning implemented, and the transfer signed off. Routine production follows against established batch instructions.

A crucial element in successfully transferring technology across linguistic and cultural barriers is the quality of the communication between our experienced personnel, alongside clear definition of roles and responsibilities. Where it provides benefits, team members from the transferring site are present at the receiving site, for example for project kick-off, and during production start-up.

Case Study 1:
**Reduced lead time and cost with continuous local project management**

The first four steps of a an eight stage registered process, previously run in Switzerland on 1,600 L scale, were successfully transferred to operations in India within a timeframe of five months. The transfer was mainly driven by growth in product volume coupled to the need to reduce overall lead times. The process is now executed in India at 4 times the previous scale, allowing us to make significant reductions in both cost and lead time. The intermediate is sent to Switzerland for conversion to the final API with no measurable difference in quality.

This approach offers the customer flexibility in managing cost and quality demands without draining his own resources.

Case Study 2:
**Product lifecycle management**

A three-stage process to manufacture a launched API for a US customer had been successfully running in Switzerland for over 10 years. To support the customer in the generic market with lower costs, the exact process was transferred to India. Following regulatory approval of the change of site, the customer will benefit from a more economic source of the API with identical quality, while the supply chain is maintained with ongoing manufacture in Switzerland.

Case Study 3:
**Cost and feasibility aspects**

A multistage production process for a non-GMP intermediate was performed at CARBOGEN AMCIS’ Manchester site for a Japanese customer. Subsequent transfer to India was successfully accomplished, and the process was subsequently scaled up to 300 kg batches in a multi-ton campaign within 6 months. A chemist from Manchester supported the transfer on-site. In this case the transfer was driven mainly by the scale of production, but the customer also obtained a cost advantage from the increased scale at the new site.
CARBOGEN AMCIS delivers leading process research services that support the drug development process. Early Active Pharmaceutical Ingredient (API) manufacture centers on the rapid synthesis of supplies necessary to perform both toxicology and early-phase clinical trials. Typical batch sizes here range from from 1 gram to 50 kg scale and are prepared in the highest standard of Good Manufacturing Practice (cGMP).

CARBOGEN AMCIS has over 20 years of experience in the supply of APIs for clinical trials and commercial production and is specialized in the multi-step cGMP manufacture of low volume APIs (20 kg to 2000 kg). The goal is to supply our clients with market-ready quantities of APIs including drug master files and regulatory documentation. Our services are tailored to the individual needs of each client from initial route finding through to cGMP production.

**Process Research & Development**

We currently have more than 100 hoods available for PR&D and production support activities. The state-of-the-art infrastructure including double jacket reactors, lab automation and micro-reactor capabilities ensures an efficient and comfortable working atmosphere. Our chromatography and crystallization services provide an invaluable resource in producing & isolating early-phase material without recourse to excessive development time or costs.

**Production and cGMP Manufacturing**

We are highly experienced and equipped for handling a broad range of organic reactions embracing sophisticated modern technologies including low temperature reactions, organometallic reactions, chiral synthesis and hydrogenation at elevated temperatures. Our purification capabilities applying chromatography or distillation allow an efficient synthesis of your compounds.

Our equipment includes:

- 70 multi-purpose reactors from 6 L to 4'500 L, glass-lined, hastelloy, and stainless steel in a temperature range from -100°C to +160°C
- More than 10 filter dryers (0.25 m² to 1 m² hastelloy)
- 400 L temperature-controlled pressure filter dryer (hastelloy)
- High temperature reactor (200 L) in a temperature range from -120°C to +350°C
- High-Pressure autoclaves, pressure range up to 20 bar
- High vacuum distillation, 200 L to 900 L, 40 theoretical plates
- 6 cryogenic reactors 10 L to 3,000 L (< -70°C)
- Horizontal Pharma-Peeler Centrifuge, Diameter 630mm
- Lab automation system
- Micro reactors / continuous systems (Ehrfeld system with micro agitators, tubular reactor system, glass microreactors and H-cube)
- Milling and wet-milling
- Micronization
- Freeze dryers up to 30 kg ice per run
We internally optimize each site with all the equipment necessary to help your project to become a success. We provide unparalleled analytical support for research, development and commercial production of late-stage intermediates and APIs, including pre-formulation studies to support drug product development.

Our equipment at CARBOGEN AMCIS includes:

- 3 NMR (400 MHz; H, C, P, F, N)
- 84 HPLC (DAD, ECD, ELSD, RI, MALLS, VWD, CAD, Polarimeter)
- 3 UHPLC
- 4 HPLC-MS (single Quad)
- 2 HPLC-MS/MS (ion trap) AAPI, APCI, ESI
- 24 GC (ECD, FID, NPD, TCD, Head Space)
- 1 GC-MS (single Quad)
- 1 GC-MS/MS (ion trap)
- 3 DSC
- 2 RCI
- 4 FTIR (ATR, DRIFT)
- 4 UV-Spectrophotometers
- 2 TGA
- 3 Polarimeters
- 2 Particle Sizer
- 4 Ion Chromatographs (conductivity) – 3 anionic and 1 cationic
- 6 Automated Titrators
- 2 Densitymeters
- 3 Refractometers
- 1 XRPD
- 1 ICP-OES
- 1 Capillary Electrophoresis
- 1 ICP/OES for metal analyses
- 1 Small scale jet mill
- 1 Water activity and moisture analysing instrument
- 1 Dynamic vapour sorption analyzer
- 1 Dissolution testing equipment
- 1 Disintegration testing equipment
- 2 Microscopes

ICH Stability studies:

- 25°C / 60% r. H.
- 30°C / 65% r. H.
- 40°C / 75% r. H.
- 5°C
  - - 20°C
  - - 80°C
Clean Room for Antibody Drug Conjugates (ADCs)

Our state-of-the-art infrastructure includes process research and development (PR&D) laboratories and, one laboratory dedicated to conjugation of small and large molecules and manufacturing capabilities.

The specialized laboratories and kilo-scale manufacturing equipment for small batch sizes of up to 15 kg are designed to operate safely at 0.05 µg/m³ OEL. This performance allows safe handling of highly potent compounds, including cytotoxic warheads applied in antibody drug conjugates (ADC). Our intermediate and large scale manufacturing equipment currently operates down to 1 µg/m³ OEL (Switzerland) or down to 0.05 µg/m³ OEL (India) on a scale up to 1’600 L producing batches in the 200 kg range.

Bubendorf, Switzerland
- 4 PR&D laboratories proven to operate below 0.05 µg/m³ OEL (grade D)
- Conjugation laboratory with Grade C and D areas designed to operate below 0.05 µg/m³ OEL
- Kilo-scale manufacturing facility designed to operate below 0.05 µg/m³ OEL Air Cleanliness Class ISO 7 (Class 10,000)
- 4 Reactors from 100 L to 250 L (hastelloy and glass-lined), temperature range from -100°C to +160°C, pressure up to 12 bar
- Hastelloy Filter Dryer with glove box (0.125 m²)
- Hastelloy Filter Dryer with glove box (0.22 m²)
- Intermediate-scale production facility designed to operate down to 1 µg/m³ OEL by utilizing Rapid Transfer Ports (RTPs), barrier isolation technology and flexible containment of technology

Key equipment:
- Reactors from 250 L to 1000 L, temperature range from -100°C to +160°C, pressure up to 20 bar
- Hastelloy Filter Dryers (0.25 and 0.4 m²)

Hunzenschwil (Neuland), Switzerland
- PR&D laboratory designed to operate down to 1 µg/m³ OEL
- Intermediate-scale production facility designed to operate down to 1 µg/m³ OEL
- 4 Glass-lined reactors of 630 L (2x) and to 160 L (2x), pressure up to 6 bar
- 2 Filters (0.28 m² and 0.16 m²)

Dishman, India
- 2 PR&D laboratory designed to operate below 0.05 µg/m³ OEL
- Large-scale production facility designed to operate at 0.05 µg/m³ OEL utilizing barrier isolation technology:
  - 6 Reactors from 630 L to 1’600 L
- Hastelloy Filter Dryer (1.0 m²) fitted with a discharging isolator
- Hastelloy Filter Dryer (0.6 m²) fitted with a discharging isolator
- 6 Isolators dedicated to charging and one to dispensing
- Isolator for milling/micronization (Nara Pin Mill, Quadro)

Vionnaz, Switzerland
- PR&D labs designed to operate down to 0.05 µg/m³ OEL
- Pilot plant unit (10, 15 and 30 L) designed to operate down to 0.05 µg/m³ OEL (up to about 1 kg)

Under construction: Kilo-scale manufacturing facility designed to operate below 0.1 µg/m³, Air Cleanliness Class ISO 8 (Class 100,000) including:
- 3 Reactors from 80 L to 50 L (hastelloy and glass-lined), temperature range from -80°C to +160°C, pressure up to 10 bar
- Hastelloy Filter Dryer (0.1 m²)

Analytics of Highly Potent APIs
- NMR
- HPLC (SEC-UV, GPC-MALLS, HPLC-MS)
- GC (FID, Headspace)
- pH meter
- UV/VIS
- IR (KBr pellet)
- KF-determination
- DSC (closed pan only)
- Heavy metals
- Residue on ignition
- Optical rotation
- RC1
- Access to crystallization development and screening for metastable zones in closed vials
- Access to powder X-ray diffraction and particle size determination
- Malvern particle size distribution (PSD)

Purification of Highly Potent APIs (Bubendorf)
- Chromatography suite dedicated to highly potent APIs
- 3 Multipurpose Walk-in-Barrier Hoods
- Preparative HPLC 5-20 cm columns
- Tangential Flow Filtration for macromolecules from 10’s to 100’s of kilo Dalton
- Gel Permeation Chromatography for the removal of aggregates and higher molecular impurities
In addition to pre-formulation services, solid state and crystallization services, and analytical support for physico-chemical characterization and method validation, CARBOGEN AMCIS offers a complete range of formulation services for parenteral APIs and highly-potent APIs. Our formulation and aseptic drug products services are performed at our Riom, France site, which is exclusively dedicated to the development of parenteral products and to the fast supply of batches for clinical trials.

Our pre-formulation and formulation equipment includes:

- 2 aseptic filling isolators (running under class A)
- Semi-automated dosing Xcelolab from Capsugel
- Non-GMP jet mill and GMP jet mill (up to 50 grams)
- Water activity and moisture analysing instrument
- Dynamic vapour sorption system
- Dissolution testing equipment
- Disintegration testing equipment
- Powder, closed-loop weight dispenser
- Glovebox (2.4 square meters) for the formulation of new highly-potent compounds
- Segregated (0.6 square meters) Telstar lyophilizer and Telstar LyoBeta 20
- Terruzzi freeze dryer (1.2 square meters) with CIP and SIP for GMP production
- Autoclave for sterilization
- Dry heat oven
- Biological safety cabinet
- Incubators

The aseptic process is validated by media fill testing, microbiological and analytical controls and 100% visual inspection.
CARBOGEN AMCIS AG is a leading service provider, offering a portfolio of drug-development and commercialization services to the pharmaceutical and biopharmaceutical industry at all stages of drug development. The integrated services provide innovative chemistry solutions to support timely and safe drug development allowing customers to make the best use of available resources.

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