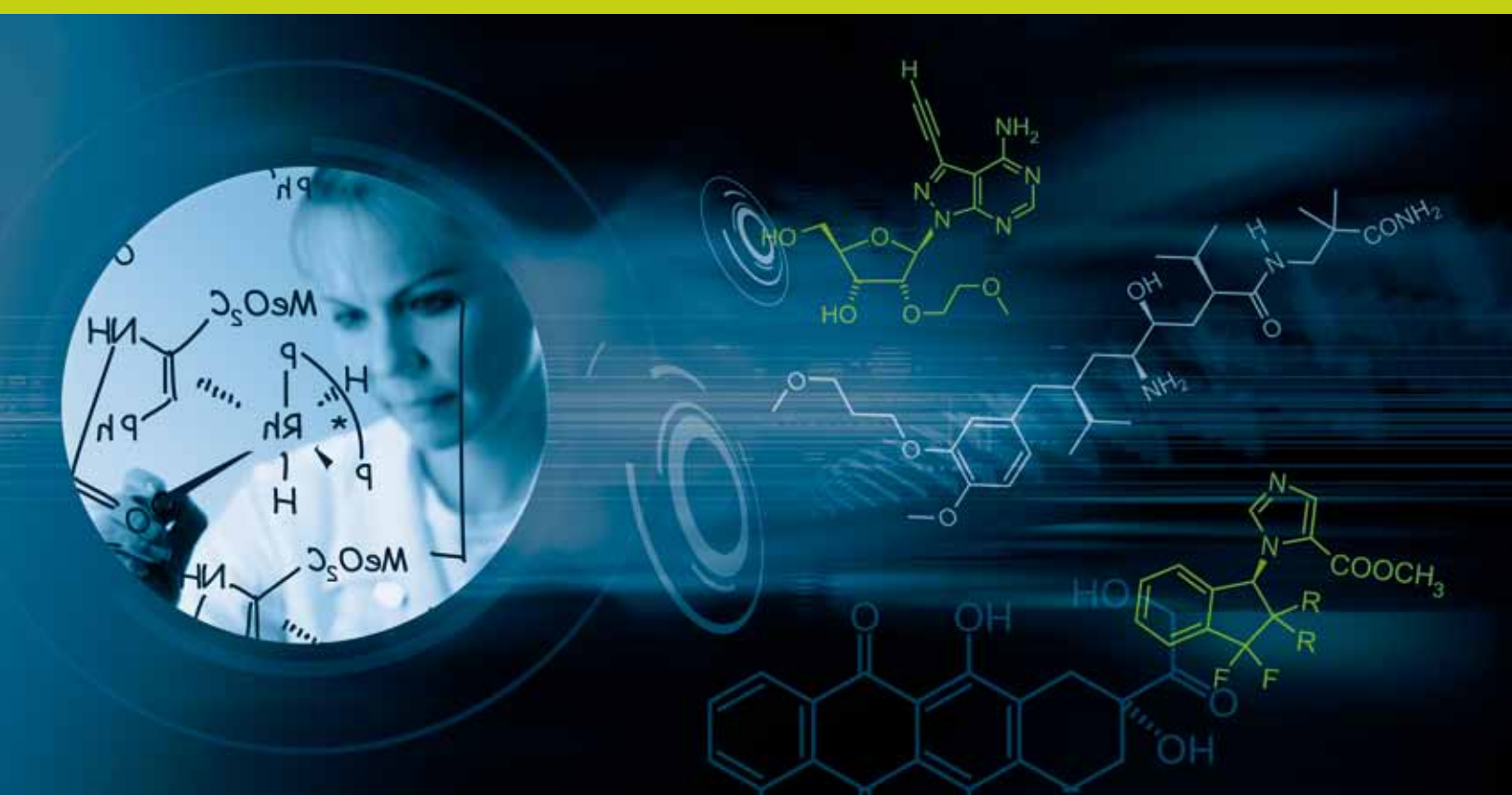


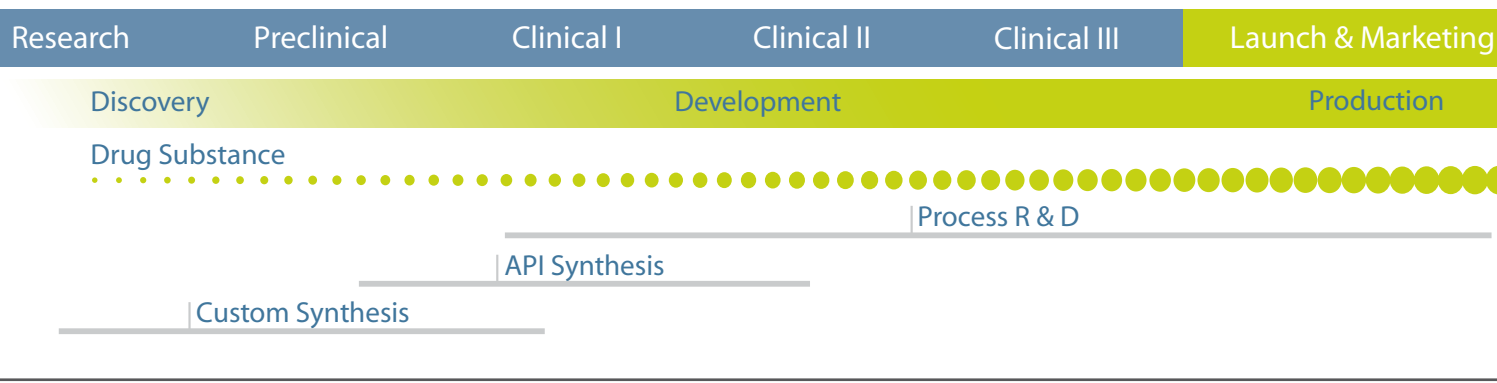
# Chemical Development and GMP Manufacturing



*Integrated Chemical Development Services for Early Drug Development*

# Solvias delivers...

Solvias provides you with a complete package of chemical and analytical services for your intermediates and pharmaceutical products. We can support you with a range of added-value activities – from custom synthesis of milligram to kilo scale (non-GMP) to process research and development and GMP kilo scale manufacturing of your APIs.



## ...your molecule...

Solvias offers custom synthesis, from milligram to kilo scale, of your small molecules.

### Our Expertise and Services

- Lead synthesis and optimization of pre-clinical candidates
- Synthesis, isolation and characterization of impurities, metabolites, degradants and reference compounds
- Supply of customized deuterated reference compounds
- Rapid scale-up and supply of scaffolds, building blocks and intermediates up to kilo scale (non-GMP) to support pre-clinical development

In addition, impurities, degradants or metabolites can be isolated by preparative HPLC and characterized by using state-of-the-art techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS), raman, infrared (FTIR) and ultra-violet (UV). Hyphenated techniques such as LC-MS/MS and LC-Accurate mass can also be applied to fully characterize your material.

## ...your process...

With more than 50 chemical development experts, we can rapidly develop scalable, robust and cost-effective chemical processes and optimize reaction conditions for your complex, often chiral, intermediates or APIs. Supported by more than 150 analytical chemists, we are a powerhouse for chemical and analytical development.

### Our Expertise and Services

- Consulting service for new route selection/prioritization and assistance in cost of goods analysis of your second generation process
- Evaluation, scouting and development of new manufacturing routes
- Optimization of reaction conditions to reduce manufacturing costs by classical methods or statistical design of experiments (DOE) – *Fit for purpose*
- On-line *in situ* monitoring of reactions using NIR spectroscopy
- Classification of hazardous raw materials, reaction mixtures and products by using differential scanning calorimetry (DSC) and reaction calorimetry (RC1)

- Rapid screening of reaction conditions (e.g. homogeneous and heterogeneous hydrogenation, carbonylation, CX coupling, transition metal catalyzed reactions) using a Symyx platform
- Development of reliable analytical methods for in-process control, intermediates and APIs
- Scale-up of new and existing routes in glass reactors (10-30L) and fixed reactors (up to 100L capacity) – *Proof of concept*
- Development of robust and scalable crystallization procedures for intermediates and APIs

Our world class expertise in process research and development is reflected in the launch of numerous production processes designed by Solvias on behalf of our customers.

The processes can be readily transferred to our kilo lab in the form of a proof of concept study, or for scale-up and delivery of material to support your pre-clinical studies. We can also enable you to transfer the process to a custom manufacturer of your choice.

...your API...

We provide rapid and comprehensive support for your pre-clinical and early-phase drug development program.

### Our Expertise and Services

- Process research and development
- Full analytical method development and validation according to ICH guidelines
- Solid-state development including salt screening, selection of optimal final salt formation and polymorphism study
- Synthesis of APIs for pre-clinical and clinical studies up to phase II (GMP)

...reliable, cost-effective and on time.

We deliver gram to kilogram quantities of your API required for pre-clinical to phase II clinical studies. This includes robust, scalable syntheses with purification and quality control procedures.



# Areas of Expertise

Leveraging Experience into Innovation

## Hazardous and High-Pressure Chemistry

We master a wide range of chemistry including cryogenic ( $-80^{\circ}\text{C}$ ) high-temperature ( $350^{\circ}\text{C}$ ), hazardous and high-pressure chemistry (up to 300 bar) on scale. This enables us to conduct process research and development for your challenging chemistry, and to rapidly manufacture your intermediates and APIs. Our dedicated laboratories and containment facilities are well equipped to handle toxic, noxious, corrosive or metastable reactants on kilo scale.

With our in-house database covering more than 10 000 different reactions handling critical reagents, we are ready to support you.

Our infrastructure covers a variety of different reactor materials ranging from glass, glass-lined steel, stainless steel, PTFE, Tantalum, Monel to Hastelloy B and C to accommodate your chemistry. Together with our dedicated and experienced staff – with over 40 years of experience in handling critical reagents and our in-house database covering more than 10 000 different reactions performed in this area – we are ready to support you.



### Hazardous Chemistry

- Cyanation (HCN)
- Chlorination, bromination
- Methyl triflate
- Nitration
- Organolithium and Grignard reactions
- Ozonolysis
- Phosgenation

### Fluorination Chemistry

- Deoxofluorination ( $\text{SF}_4$ )
- Halex reaction (HF)
- Schiemann reaction (HF)
- Electrophilic and nucleophilic fluorination

### High-Pressure Chemistry

- Homogeneous and heterogenous hydrogenation
- Hydroformylation
- Carbonylation
- Amination
- Vinylation

# API Synthesis

Integrated Chemical and Analytical Development Services for  
Your Preclinical and Early Drug Development Program (Phase I/II)

## Our Quality

- ISO 9001-certified QM system SQS
- Swissmedic approved GMP facility
- FDA inspected test facility for the analysis of pharmaceutical products
- Successfully inspected/rated by more than 300 customers

## Our People

- Total headcount >280 employees
- 47% graduates/Ph.D.
- Dedicated project management team
- On average >8 years industry experience

Analytical Development

- Analytical development:
  - In-process control
  - Intermediates
  - API
- Reference standard qualification
- Method validation according to ICH guidelines
- GMP release (CoA)
- Forced degradation study (ICH)
- API impurity ID/characterization
- Accelerated stability study

Technologies

- CX coupling technology
- Selective heterogeneous hydrogenation
- Asymmetric homogeneous catalysis
- Chiral ligands and catalysts
- Hazardous and high-pressure chemistry
- Fluorination



## Chemical Development

- Process research and development
- Salt and co-crystal screening
- Process optimization – Fit for purpose
- Reference substance supply
- Scale-up – Proof of concept
- Polymorph screening
- Manufacturing of  
- tox material (non-GMP/GMP)
- GMP starting materials  
- API for clinical phases I/II
- Comprehensive development report
- Batch records

# Technologies

Accelerating Your Development

## Homogeneous Catalysis

From screening to process optimization and subsequent kilo scale production, Solvias employs innovative strategies and modern scalable methods for the successful manufacturing of chiral and non-chiral intermediates and APIs. We rapidly implement transition metal catalysis, asymmetric synthesis or diastereomeric crystallization steps to enable the fast and cost-effective development of your chiral target molecules.

### Asymmetric Catalysis

- Homogeneous hydrogenation
- Asymmetric ring opening
- Transfer hydrogenation
- Pd-catalyzed allylic substitution
- Michael addition of Grignard reagents

### CX Coupling

- Carbonylation
- Heck reaction
- Suzuki-Miyaura coupling
- Sonogashira coupling
- Buchwald-Hartwig amination
- Direct CN coupling with ammonia
- CS coupling
- Comprehensive set of industrial relevant catalysts available incl. cataCXium<sup>®</sup>, palladacycles, Josiphos

### Chiral Ligands and Catalysts

- >600 chiral (non-)proprietary ligands on stock
- Most prominent and successful ligand families such as Josiphos, Walphos, Mandyphos, Taniaphos, catASium<sup>®</sup> available
- Supply of ligands/catalysts for commercial manufacturing
- Toll manufacturing and development of new ligands
- IP-included kilo price or other licencing models

## Selective Heterogeneous Hydrogenation

For decades we have been known for our top-end expertise in the development of cost-effective heterogeneous hydrogenation processes. We have hydrogenated more than 33 000 different substrates with a very high success rate and have a broad range of commercially available heterogeneous catalysts on stock.

From initial screening through development and scale-up, Solvias can assist you in all phases of process development according to your specific needs and requirements. We help you to find the optimal heterogeneous catalyst system in the shortest time possible.

We have contributed to the successful development >50 pilot plant and 15 commercial processes including the world's largest asymmetric hydrogenation process.

### Heterogeneous Hydrogenation

- Selective NO<sub>2</sub>-hydrogenation technology (Vanadium-modified Pt/C)
- Chemoselective C=C double bond hydrogenation
- Diastereoselective hydrogenation of  $\beta$ -hydroxyketone
- Reductive amination
- Rosemund reduction of acid chlorides
- Nitrile reduction
- Removal of benzyl protecting groups

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