Chemical development and GMP manufacturing

Integrated chemical development services for early drug development

Amazing where you can go
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
• Rapid scale-up and supply of scaffolds, building blocks and intermediates up to kilo scale (non-GMP) to support preclinical development
• Synthesis, isolation and characterization of reference compounds using state-of-the-art techniques such as NMR, MS, Raman and FTIR. Techniques such as LC-MS/MS and LC-MS using accurate mass measurement can also be applied to fully characterize your material

...YOUR PROCESS...

With a dedicated team of 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 a large team of analytical chemists, we are the right partner for your chemical and analytical development.

OUR EXPERTISE AND SERVICES

• 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
• Rapid screening of reaction conditions (e.g. homogeneous and heterogeneous hydrogenation, carbonylation, C-X 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 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 III (GMP)

...RELIABLE, COST-EFFECTIVE AND ON TIME.

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

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 >400 employees
- Dedicated project team
- On average >10 years industry experience
• Process research and development
• Salt and co-crystal screening
• Process optimization – Fit for purpose
• Reference substance supply
• Scale-up – Proof of concept
• Polymorph screening
• Crystallization development
• Manufacturing of non-GMP / GMP tox material
• GMP starting materials – API for clinical phases I-III
• Comprehensive development report
• Batch records (English / German)

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

C-X coupling
• Carbonylation
• Heck reaction
• Suzuki-Miyaura coupling
• Sonogashira coupling
• Buchwald-Hartwig amination
• Direct CN coupling with ammonia
• CS coupling
• Asymmetric CC bond formation

Ligands and catalysts
• >600 chiral ligands on stock
• Most prominent and successful ligand families such as Josiphos, Walphos, Mandyphos, Taniaphos available
• Comprehensive set of industrial relevant catalysts available incl. cataCXium®, palladacycles, Josiphos
• 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 NO₂-hydrogenation technology (Vanadium-modified Pt / C)
• Chemoselective C=C double bond hydrogenation
• Diastereoselective hydrogenation of β-hydroxyketone
• Reductive amination
• Rosemund reduction of acid chlorides
• Nitrile reduction
• Removal of benzyl protecting groups

High-pressure chemistry
• Homogeneous and heterogeneous hydrogenation
• Hydroformylation
• Carbonylation
• Amination
• Vinylation
CASE STUDY: NCB5 FOR PIQUR
Leveraging experience into innovation

STARTING POINT
- Lab route and 1 g API

TASKS
- Process optimization
- Catalyst screening for coupling step
- Synthesis of 100 g reference standard
- Isolation and characterization of major impurities
- HPLC-method development and validation
- Preliminary polymorphism study
- ISO-manufacture 250 g
- GMP-manufacture of 1.5–2.0 kg of API
- Certificate of analysis

MAIN ISSUES OF INITIAL CONDITIONS
- Incompatibility of THF / NBS
- iPrMgCl x LiCl (turbo Grignard) needed
- Chromatographic isolation of boronate
- Suzuki coupling: PdCl2(dppf) x DCM THF / aq. Cs2CO3
- Low yield in last step

MAIN CHANGES / FINAL CONDITIONS
- Use of 2 Me-THF instead of THF
- Intermediate SOL22064 not isolated (results in higher yield)
- iPrMgCl (standard Grignard) used
- Cheaper catalyst Pd(OAc)2 / PPh3 used
- Higher yield in Suzuki step without column chromatography
- Pd removal implemented

PROJECT TIMELINE (IN WEEKS)

|   | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
|   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sourcing |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Process development |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| ISO batch |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Analytics |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Polymorphism |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Polymorphism |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| GMP batch |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

DELIVERABLES
- ISO batch
- GMP batch
- Fully characterized
- Methods validated
- Certificate of analysis
- One final report
- Forced degradation
- Stability studies started

Novel manufacturing process for triazine, pyrimidine and pyridine derivatives, University Basel / Piqur Therapeutics AG
Paul Hebeisen, Florent Beaufils, Jeanbaptiste Langlois, 2015, WO2015162084 A1