

Swiss for service

Solvias is investing heavily to meet demand for its analytical and chemical development service. **Andrew Warmington** visited the firm in Basel

Basel is one city where you cannot fail to be aware of the chemicals and related industries. On arrival at the airport, you learn that Clariant, Syngenta and Novartis are present there and that BASF has recently taken over Ciba. Take a tourist boat on the Rhine and you will find out all about the history of Novartis and Roche, whose facilities loom along the river.

Though much smaller, Solvias is very much part of the fabric of the industry. The firm stretches across three 'campuses' in central Basel and the Rosental campus contains the original laboratories of Traugott Sandmeyer (1854-1922), the creator of the eponymous reaction to synthesise aryl halides from aryl diazonium salts and the developer of several major dyes for the former J.R. Geigy & Cie.

Solvias emerged out of the restructuring of the Basel area chemicals industry in the 1990s. CEO Hansjörg Walther recalls "a push and pull situation" two years after the Ciba-Sandoz merger of 1996 that had created Novartis, Syngenta and what was until recently Ciba Specialty Chemicals. The old Ciba had always had a central services division, whereas Sandoz had not.

"A certain disagreement arose over whether to keep Novartis Scientific Services in its existing form, run it as a separate profit centre or sell it," Walther says. "In the end, the 'pull' won and the decision was to use it to provide services as a commercial business, in line with our experience within Ciba. We were convinced that there was an outside market."

Solvias is privately owned by a combination of the management, plus other investors, including Novartis Venture Fund and capital investment from Novartis and Ciba. BASF is expected to retain its stake. Co-founders Peter Loew and Ronald Haag both retired recently and Luzi von Bidder, who joined the board in 2008, was named president at



Laminar flow cabin and hastelloy pressure filter (above) and newly built cGMP kilo lab (below) at Solvias's site in Basel

the AGM in April, with Walther remaining in his position as delegate.

At the outset, Walther continues, Novartis, Syngenta and Ciba were inevitably the main customers, plus a few more in the Basel region, and sales were about €24 million/year. By 2008, there were over 500 active third party customers and sales were €44.1 million, with over half coming from outside Switzerland.

Western Europe is still the main market and all production is in Basel, but 10% of sales are in North America, where a sales subsidiary has been set up. A smaller volume goes into Japan and the company is looking at expansion elsewhere in Asia. The two main areas, analytical and chemical development

services - the latter mainly referring to catalysts - make up about 67% and 25% of sales respectively. The rest comes from specialities, such as patent services and in-process analytics.

Solvias mainly serves the pharmaceuticals market, from Big Pharma down to virtual pharma companies, generics companies and biotech; it does not break down the volume of business in any further detail. The agrochemicals and speciality chemicals industries are other - small - markets but there is no active marketing to them.

"We have generally enjoyed 5-10% year-on-year growth," notes Walther. "The first half of this year was much the same as the first half of 2008 - it's impossible to guess how the full year will go. We follow the same cycles as the market as a whole but, compared with what has been going on in the market as a whole, we are quite satisfied with our performance."

During the downturn, not surprisingly, analytical services have held up better. Chemical development projects and process analytical technologies have been more impacted by the downturn, as they tend to be longer-term investment projects.

"Customers are increasingly cautious and are delaying decisions, but they tell us that they still interested. Biotech, of course, have less to spend and that is impacting us - some are telling us they will do the project as soon as they have the money. There is always a lot of waiting around in this business."

The company hopes and expects to revert to 5-10%/year growth in the next couple of years, mainly based on organic growth. To provide the right infrastructure for this, it is building a €46 million new headquarters in nearby Kaiseraugst (see also SCM, June 2009, page 14), which is being financed by means of real estate leasing.

The foundation stone was ceremonially laid in May and the five-storey building is scheduled to be ready in 2010. During Q4, Solvias, will begin to move out from its rented space on Novartis and ex-Ciba sites in Basel to Kaiseraugst. Some synthesis laboratories in Basel will be retained but otherwise it will be a complete move.

This will give the company some 14,000 m² of office laboratory space and the scope for 6,800 m² more, thus enabling it to grow from 300 to 400 FTEs. This should, Walther believes, create enough space for the next 10-15 years of organic growth and maybe some small acquisitions as well, though none are planned.

Solvias generally spends 3-4% of its turnover on R&D for technology and services but this year will see significantly higher than average investment, with about €6.5 million being spent on a new GMP kilo lab and new capabilities in high throughput screening, polymorphism and crystallisation studies.



The ability to invest like this, says Walther, is one major advantage of private ownership.

Of the current 300 employees, 150 work in analytical services for small molecules with another 40 in analytical services for biopharmaceuticals. A further 60 work in chemical development and 27 in solid state management. "This is a great ratio, it means we never have a bottleneck in API development says," Dr Michael Quirnbach, product manager for synthesis.

Services the company offers range from full packages from toxicology testing materials to Phase II materials, which is mainly for biotech and small to medium-sized pharma companies, to specific analytical needs. Some customers want only solid state testing, hence the solid state team that is dedicated to working out crystallisation processes and transferring them to customer plants.

Quirnbach also stresses Solvias's unique project management system. There are a number of product managers in place for different areas - he is one himself, covering chemical development - all reporting direct to sector managers. This has proved highly successful, he says.

The **Analytical Services** offer follows the pharmaceutical value chain from pre-clinical testing to IND, Phases I-III, NDA and post-approval testing, covering a huge range of bases (Figure 1). The company has received BUWAL approval for GLP, Swissmedic and FDA approval for GMP and SQS accreditation to ISO 9001: 2000 standards.

Integrated programmes for drug substances and drug products include analytical method development, method development and validation, QC analyses, stability studies, reference standards, inhaler testing and various special services, such as

cleaning validations, leachables and extractables and general troubleshooting. All are done to customer specification; Solvias does not develop its own drugs.

The equipment currently at the Rosental campus in Basel reflects the need to cover all areas of analysis in drug development. They range from all kinds of HPLC, HPLC-MS, GC and GC-MS and less common forms of chromatography, like IC, SEC and TLC, to elemental and microanalysis techniques (XRF, ICP-MS, ICE-OES, Karl Fischer titration, etc.) and microbiology (aerobic count for yeast and moulds, efficacy of preservation, endotoxins, etc.).

Companies in this industry commonly claim to have the full range of analytical equipment. In Solvias's case, this may be true - certainly it is hard to think of a major capability that is not present somewhere in its laboratories. None has ever been dropped. Even where a major upgrade has taken place, the old equipment is still in use for more basic analytical needs, for instance cracking with heavy acids for sample preparation.

The scale of the recent investment is also very much in evidence on a tour through the Rosental campus. In the last two years, for example, capacity in the favoured technique of IC has been more than doubled, with the addition of new equipment from both market leader Dionex and Metrohm.

ICP-MS capacity has likewise been hugely increased via a new Agilent 7500 series machine. Combining this with AS, says Michael Becker, product manager for solid state, means that Solvias can analyse pretty much any element on the periodic table - iron cannot be analysed via ICP-MS.

Another unusual capability is the use of electron and other microscopy to look at crystals. This is

increasingly demanded by Japanese producers, whose quality standards are extremely stringent, but it also exemplifies the - costly - need to adapt techniques and equipment constantly in order to keep up with the internal capabilities of Big Pharma customers.

Within Analytical Services, the Solid State Development team can carry out salt and co-crystal selection, polymorphism screening, crystallisation optimisation and process development and the determination of polymorphic purity. Solvias describes this group as world class.

All solid state work and associated IP development take place on the second floor of the Rosental campus. This begins with seeding processes during crystallisation on Mettler Toledo equipment and the general definition of parameters before proceeding to synthesis. Reactions mostly take place on hundreds of milligrams scale, followed by screening in 96-well plates to check on, among other things, salt formation, before proof of concept work.

"The technology is quite basic. The real addition we make is the brains and experience of our people," comments Becker. Though there are hundreds of firms active in some degree in this field, Solvias is one of few with this level of capability, alongside SAFC subsidiary Pharmorphix, Avantium Technologies and SSCI, which is now part of Aptuit.

During the next stage, thermogravimetry comes into play, followed by Raman spectroscopy and XRFD - Becker adds that Solvias prefers to do it this way around, though others prefer the reverse, partly because it has a lot of Raman microscopes that can cope with 96-well plates. Having both techniques is necessary for confidence that a new compound is really new rather than just a mixture, he adds.

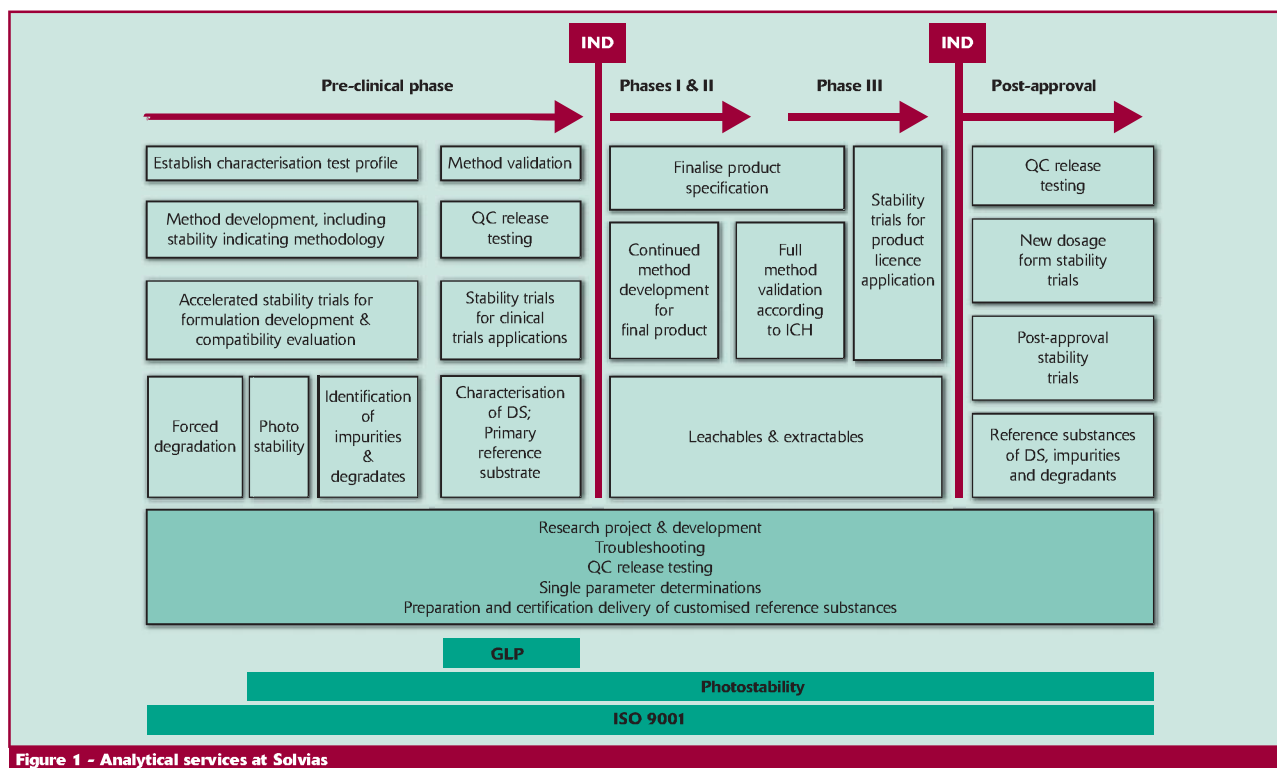


Figure 1 - Analytical services at Solvias

Finally, the Analytical Services department offers almost all the methods necessary for the analysis of highly potent and cytotoxic substances. In this area too, Solvias has invested recently to upgrade its capabilities, most notably in the form of a Panalytical X'pert Pro, which will be able to handle 96-well plates and thus operate ten times faster than the previous equipment.

It is through the services of the **Chemical Development** department that Solvias most interacts with the fine chemicals and pharmaceuticals industries. The firm has become known above all as a supplier of catalysts and process R&D services, but it has many other areas of expertise, notably:

- Asymmetric synthesis (α - and β -amino acids, small peptides, chiral intermediates etc.)
- Complex heterocycles (small rings, nucleosides, porphyrins, macrocycles, etc.)
- Challenging chemistry (high pressure chemistry, hazardous chemistry, fluorination, etc.), as discussed later

A non-GMP kilo laboratory carries out manufactures intermediates, building blocks and proprietary catalysts at multi-kilo scale. This operates at 10-100 litre scale and in the temperature range from -80 to +250°C.

Total volume in the lab is 850 litres in six fully equipped reactor trains, including filters, dryers and rotavaps, together with eight safety boxes for mobile pressure reactors, two containment laboratories, including external oxygen compressors, 20 kg of capacity for chromatographic separation. All of the trains feature heating and cooling in place.

Within this lab, three reactors of 8, 16 and 50 litres capacity operate at pressures of 300, \approx 200 and \approx 80 bar respectively. One remarkable feature here is the unusual range of materials used in the reactors: tantalum, Monel and PFA as well as the usual glass, stainless steel and Hastelloy B and C.

Further down the chain, Solvias has also developed a wide range of capabilities for process R&D (process redesign and optimisation, rapid screening of reactions on a Symyx platform, in situ monitoring by NIR spectroscopy, analytical development, crystallisation optimisation, scale-up and tech transfer) and API synthesis. Following a three-phase route, it claims to be able to offer API synthesis from pre-clinical to clinical in 24-36 weeks (Figure 2).

The Symyx platform, in place since 2004, is also used for high-throughput screening of catalysts, incidentally. It runs four 96-well plates at up to 100 bar with a capacity of 200 reactions/day, depending on the substrate. Features include fully inert handling, robotics for dispensing and analytics and single-software handling.)

The most important recent development from the Chemical Development department has been the construction of a cGMP kilo lab. This cost €1 million and was completed in June 2009 after a year of planning and four months of building. Swissmedic approval was received on 14 July and the first customers have signed up for projects.

Key features here include HEPA filtered air, laminar flow cabins and a joint-less floor using Pharmaterrazzo flooring. The multi-purpose 30-100 litre glass-lined and stainless steel reactors feature



Hazardous and high-pressure chemistry are core to Solvias

QVF and De Dietrich process systems and operate in the range from -80 to +160°C, supported by 30 and 50 litre PTFE filtration units, 50-150 litre separation units and a GMP dishwasher. It is run by a PhD facility manager with eight years of experience, aided three to five technicians, and it is QA-audited internally and externally.

"We were often asked in the past why we didn't invest in a small-scale cGMP plant," Quimbach recalls. "When we started out, we did a lot of process R&D for transfer but then customers increasingly wanted other things, such as toxicology material or even full service packages."

The company therefore started making the toxicology material to non-GMP standards and subcontracting the GMP campaigns out to third parties. In time, however, it decided that doing this in-house was preferable and it therefore invested to be able to offer the whole package.

"There is clearly a lot of capacity like this out there, but in Phase I there are a lot of things that need to be fixed. Our skill at process R&D gives us the ability to fix problems coming out of medchem, so it was a logical small step to add small-scale manufacturing to our repertoire," adds Quimbach. He doubts that Solvias will ever get into large-scale manufacturing, however.

"Customers have come to us to sort out issues in Phase I-II before transferring to other large-scale manufacturers. In our experience, biotech and Medium Pharma generally firms sell their projects on to Big Pharma after Phase II and there are plenty of good manufacturers in India and China who can take on Phase III projects once the process has been sorted out."

Nor have customers really put any pressure on Solvias to invest in Phase III. "They like the fact that we are open and that large-scale CMOs can come and see how we run processes," says Quimbach, "It isn't a competitive situation with them and we don't form strategic partnerships. We will work with anyone, including the big Swiss CMOs."

The list of technologies Solvias uses is immensely long, but there are six areas of focused work where it has the critical mass to contribute to an API development project. First and foremost is the rapid screening, process optimisation and scale-up of C-X coupling reactions, using DoE on Stavex software.

The firm claims to have the most comprehensive set of proprietary and non-proprietary industrially relevant catalysts and ligands on the market. These include Josiphos, palladacycles of all kinds and, most recently, CataCXium, which was licensed in exclusively from Evonik along with the CatASium family, and has been used in a wide variety of C-X coupling reactions.

Based on all this, Solvias claims world-class expertise in such reaction as Buchwald-Hartwig amination, cyanation, hydroformylation, carbonylation, Malonodinitile coupling, Sonogashira coupling, Suzuki-Miyaura reactions and vinylation. It has been involved in over ten commercial manufacturing processes using C-X coupling reactions, such as Syngenta's Exceed (prosulufuron) and Axial (pinoxeden).

The second key capability is selective heterogeneous hydrogenation. The company has developed broad capabilities in the major transformations of this kind, including its own technology for selective NO₂ hydrogenation using vanadium-modified platinum on carbon, chemoselective C=C hydrogenation, diastereoselective hydrogenation of α -hydroxyketone, reductive amination and others.

Solvias now has a database of 33,000 transformations in heterogeneous hydrogenation. These techniques it used in developing a generic process

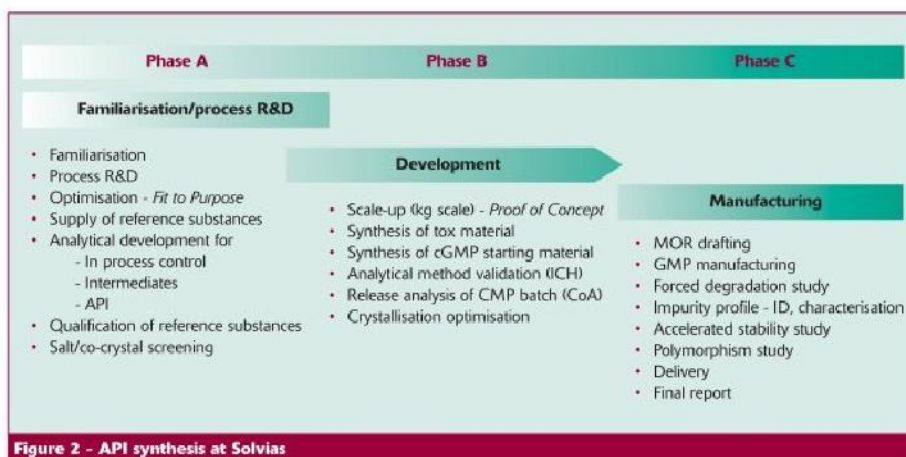


Figure 2 - API synthesis at Solvias

for Zoloft/Sutral (sertraline) with Ciba and Inspire/Rebin (butafenacil) with Syngenta.

Asymmetric homogeneous catalysis, based in large part on the expertise of chief technology officer Hans-Ulrich Blaser, Felix Spindler and other well-known scientists, is another key capability. Solvias can use chemocatalysis, asymmetric synthesis and diastereomeric crystallisation alike to find routes to chiral intermediates and APIs. It has developed 15 commercial processes, including the single largest asymmetric hydrogenation process in use today.

Examples include the last chemical step to Merck & Co.'s potential diabetes blockbuster Januvia (sitagliptin) and the fast-track development of a compound from milligram to 300 kg in two months in partnership with RohnerChem. The company was also involved in developing Dextrometophan with Lonza and Roche, Biotin with DSM and S-Dual (metacholor) with Syngenta using these technologies.

The company has a stock of over 600 **chiral ligands and catalysts** for screening, process optimisation, scale-up and manufacturing. Of these, 65% are its own, 20% are licensed-in and 15% are patent-free. As well as the aforementioned Josiphos and CataCXium and CatASium, these include such families as Walphos, Mandypfos, Taniaphos and others. These can be supplied for commercial manufacturing or used in-house under various licensing models.

Solvias has over 40 years of experience in the use of **hazardous and high pressure chemistry** from process R&D to kilo-scale production. It has dedicated laboratories and containment facilities to handle dangerous reactants at kilo scale. The in-house database runs to 10,000 different reactions.

Key hazardous reactions include cyanation, chlorination and bromination, methyl triflate, nitration, organolithium and Grignard reactions, ozonolysis and phosgenation. The latter "is not often called for but is nice to have," Quirnbach comments. High pressure reactions include heterogeneous and homogeneous hydrogenations at up to 300 bar, hydroformylation, vinylation, carbonylation and amidation.

For safety reasons, all of these reactions are carried out on the top floor of the Rosental campus, as are all **fluorination** reactions. There are dedicated fluorination laboratories for process R&D and kilo-scale production and the firm claims both proficiency in handling all kinds of fluorination reagents and all the main chemoselective fluorination methods.

Solvias offers the regioselective introduction of fluorine or fluorine-containing functional groups, like CF₃, into intermediates and APIs, as well as deoxofluorination, the Halax and Schiemann reactions and electrophilic and nucleophilic reactions. It can work with elemental fluorine and even SF₄, as well as HF.

The company cites several case studies where different aspects of this range of expertise came

into play. One good example is Rasilez (tekturna, SPP-100 or aliskiren), the first renin inhibitor which is licensed by Speedel Pharma to its now owner, Novartis. Solvias used its chiral chemistry, process R&D and full chemical and analytical development capabilities. Chronologically, this involved:

1. Milligram batch & laboratory procedure
2. Developing analytical methods, including validation
3. Broad polymorphism screening for the API
4. cGMP production with a custom manufacturer
5. Synthesising all of the isomers and reference standards

"We started out with a big analytical department and some catalysis capabilities, then we realised the need for kilo-scale manufacture - that is where we are now," Quirnbach says. "The key message is the breadth of services in chemical development and how we differentiate our services through technology and working in close internal collaboration."

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