behind the scenes

Newsletter Issue 2/07

Siegfried

Highlights

Semi-annual 2007: Siegfried Remains Focused

During the first half of 2007, the Siegfried Group attained revenues of CHF 157.8 million, an increase of 8.6 % over the same period last year. Operating profit (EBIT) reached CHF 21.4 million, 17.5 % more than in the first six months of 2006. Net profit of CHF 45.4 million were unusually high due to the sale of the Sidroga Division and other divestments.

The Siegfried Actives Business Unit, a manufacturer of active pharmaceutical ingredients, generated most of the revenue increase. During the first half of 2007, the Business Unit achieved revenues of CHF 108.9 million, an 11.2 % increase over 2006, thanks to growth in exclusive synthesis, controlled substances (in the U.S.A.), and other standard products. Both facilities – Zofingen and Pennsville – increased billings compared to the corresponding period last year. While the Business Unit won 15 new projects for all of 2006, the first half of 2007 saw already 11 new projects, well above our goals. In addition, the Business Unit developed three new opiate-based ingredients that are being prepared for a market launch in 2009.

For the rest of 2007, the Siegfried Group forecasts continued growth. Single-digit revenue growth is expected for 2007, with an operating margin of slightly more than 10 %.

Editorial

Dear partner,

Our semi-annual results confirm our strategic priorities, which are helping us to achieve our goals; Siegfried continues to grow in its core markets.

The sale of our medicinal tea division, Sidroga, has freed up additional resources to focus on consistent growth and invest further in our core businesses: exclusive synthesis (production of non-cGMP and cGMP intermediates and APIs for the pharmaceutical industry) and production and distribution of non patent protected APIs, e.g. controlled substances.

Siegfried is a technology leader in numerous areas. Our infrastructure for high potency APIs and cytotoxic drugs is being successively expanded. Our use of micro-reactors already at the pilot stage assures seamless control of critical chemical phases. In addition, Siegfried acquired patents for a new inhalation technology last year and built a new lab in Munich, Germany.

Soon, we'll all be at CPhl in Milan. I hope to see you there; my invitation is enclosed.

Sincerely,

Dr. Hubert Stückler
Head Business Unit Siegfried Actives

Content

A day in the life of
Head Development Actives

Microreactor (MRT)
Hans-Rudolf Marti
VP Science and Technology

Microreactor Technology (MRT)

1. General

A quick search for a definition of Microreactor technology (MRT) produces at least two versions. One is that from the viewpoint of the manufacturer of MRT devices:

...components produced by using microtechnology techniques with channels of diameters of smaller than 1 mm...

Or the viewpoint of the chemist:
A microsystem for chemical and biochemical reactions...as well as analytical systems. Its small reaction volumes and high heat and mass transfer rates allow for precise adjustment of process conditions, short response times, and defined residence times, resulting in greater process control and higher yields and selectivity. (citation from: www.answers.com).

It is in short a technology that couples the miniaturisation of chemical reactors with optimal reaction conditions and eliminating "classical" scale-up problems. By virtue of the small volume of reactants reacting at any given time safety concerns disappear, therefore minimizing the need for process risk analysis and allowing to carry out hazardous transformations otherwise not suitable for batch processing.

It is therefore easy to list the advantages of MRT
- The miniaturisation of the reactor allows to run demanding reactions under conditions that are impossible to perform on larger scale.
- It substantially expands the optimisation "range" of a reaction or even
- enables a large scale production of reactions not possible in standard batch reactors. E.g. if an initial conversion yields a reactive or unstable intermediate a (immediate) subsequent stabilisation step can be added
- better temperature control results in higher yields and cleaner conversions (selectivity)
- an optimisation can be done quite fast in an "on-line" mode by adjusting e.g. feed rate parameters
- an increased output can be reached by numbering up the reactors
- low investment even for industrial scale size for MRT devices

Still, MRT is a technique in development and it takes substantial efforts and quite some experience until it can be used like any other method in a companie's chemical "toolbox".

Of course only a part of the reactions are suited for MRT studies. Best candidates are

- fast
- mixing controlled
- exothermic reactions
- with a narrow temperature "window" and
- a high safety risk

Reactions that e.g. have to be performed now at very low temperatures to ensure the desired temperature in the mixing/reaction zone can be done at much higher temperature. We have even seen examples where reactions that need to be carried out at sub zero temperatures in a batch reactor can be run at ambient temperature, skipping the need for investments in cryogenic equipment.

Investigation of Siegfried's reaction portfolio as well as some literature references led to the conclusion that about one out of five conversions could be candidates for –and should perform advantageously with MRT- and maybe one out of ten would be worthwile to check on lab scale.

2. Siegfried and MRT

Upon initiation by Max Widmer 2003 Siegfried started studying MRT as a possible expansion of its technological toolbox. There were already several companies offering reactor units for industrial use or even complete computerized systems for the optimisation of chemical reactions. The companies offered to check the feasibility of our reaction candidates as a service and –to get started at all- we used it for a few of our candidates. However it quickly became clear that we needed our own MRT setup in house to develop expertise that would allow us to be able to rapidly check potential reactions from our customers. Having concrete examples are mandatory for convincing customers as well as our development and plant chemists – it is not enough to identify such opportunities just on paper! In 2005 we opened up the MRT laboratory headed by Dr. Beat Weber and operated by Norbert Schärer. The goal we set was to have one reaction candidate on industrial scale within the first year.

Finetuning a micro reactor

3. Build up of a new Technology in House

Of course we started with enthusiasm. However, in this particular case it was not quite sufficient. The hurdles we encountered were substantially higher than anticipated and resulted in setbacks. Chemical reactions are often quite sensitive to changes in reactant ratios. Therefore, feed rates of the small volume streams have to be controlled within very narrow margins over long periods of time. The challenge we encountered were:

- Quality control. To ensure continuous good quality conversions a fast in-line analysis of the reaction is necessary. Deviations from the optimal quality range have to be detected and corrective measures initiated immediately
- Engineering. Even if the reactors look like childrens playthings the ultimate goal is an efficient industrial process running 7 days/24 hours delivering tons. This has to be engineered more carefully than a large scale setup considering all the "micro problems" involved.
- Technial problems. Clogging pipes, leaking joints, decomposing sealings, gnawing corrosion, failing pumps, fluctuating flow rates.
- Good reaction candidates. During this set up phase we just did not have the necessary speed to compete with the (time) needs of our customers.

One of the big disadvantages of the available commercial reactor units was the material of construction used. Only a small part of the reaction candidates can be performed in stainless steel due to corrosion. In our usual batch chemistry reactors the material of construction is glass or glass lining to enable the use of corrosive reagents like hydrochloric acid, acid chlorides, sulfuric acid. All these reaction candidates were therefore excluded if we were only using steel reactors. These restrictions were too severe. We needed to expand the reactor material range to what we were used in batch chemistry. So we were very happy when we were approached by Corning SAS for a collaboration. Combining Corning's long standing experience working with glass with Siegfried's chemical expertise should yield in substantial progress to overcome many of the hurdles

mentioned above. Mid 2006 the two companies started an MRT program resulting in a growing professionalisation of the staff of both companies involved in the project. Working closely together during 2006 a number of reactions were checked on lab scale

- LDA deprotonation
- Nitration
- Demethylation
- Ring closure

culminating in the piloting of a nitration reaction. The result was a conversion with a similar selectivity as the batch reaction performed in the plant.

4. Examples

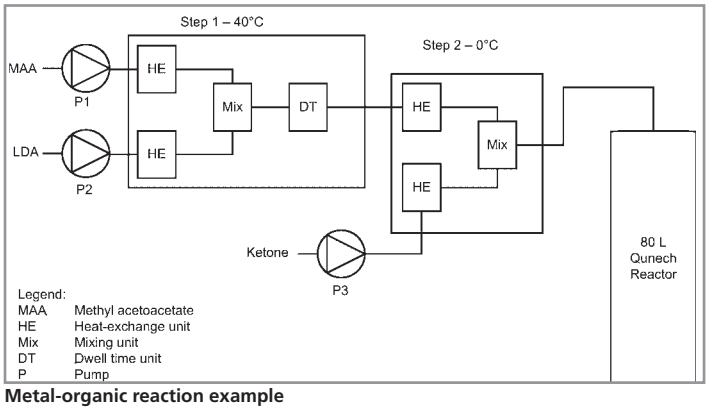
The nitration reaction run in MRT units immediately reached the benchmark set by the batch reaction results yield wise. In this case the main differentiating aspect of the MRT version is process safety. The inherently risky reaction conditions of a nitration reaction of an aromatic ring system can be easily controlled in the small reactor volumes due to excellent heat transfer in the MRT equipment. The reaction, performed in the MRT unit, can act as a lead example for future projects where the nitration of aromatic components is needed. We tested both types of equipment: glass equipment and a setup of stainless steel and Hastelloy (R) components. Conversion wise there was no difference, however we preferred Corning's glass equipment due to the fact that Corning's multi injection unit allows wider diameters, which tolerates easily some solid formation in the units.

The experience we gained with the first pilot trial, encouraged us to expand the technology and apply MRT for a next typically fast reaction class: metal-organics. We selected the addition of double de-protonated methyl acetoacetate to a ketone as candidate. The tasks to be solved by the MRT were:

- Run the cryogenic addition reaction at moderate temperature
- Keep the amount of reactive and potentially risky double de-protonated methyl acetoacetate as small as possible
- Identify reaction conditions where the yield of product is maximized

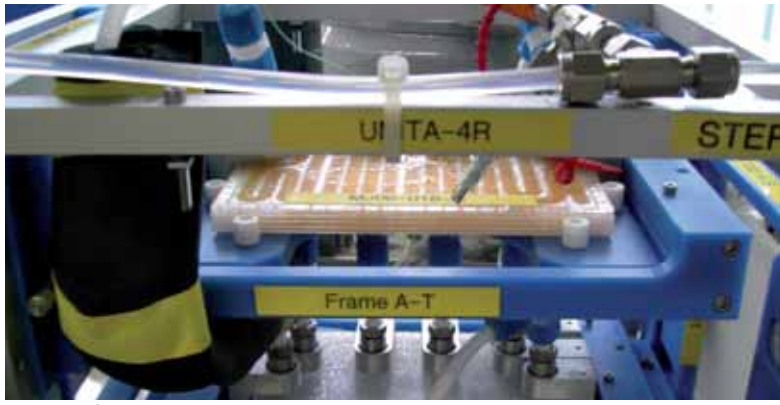
To address these tasks we designed the reactor set-up as follows: In a first MRT unit LDA and methyl acetoacetate were combined at 40°C forming the double de-protonated species. A dwell time loop with 30 seconds residence time allows the de-protonation to come to completion. A second MRT unit mixes the so formed species with the ketone at 0°C. The outlet of this second unit was piped to an 80 litre pilot reactor for an immediate aqueous quench and subseqent work-up. This set-up allows multi-kg production during a one day shift. The three tasks as defined above were well met:

- Reaction can be run at 40°C and 0°C for the individual steps
- Volume of the reactive intermediate is only a few mL
- Yield is >80% (typical batch reaction is 70-80%)

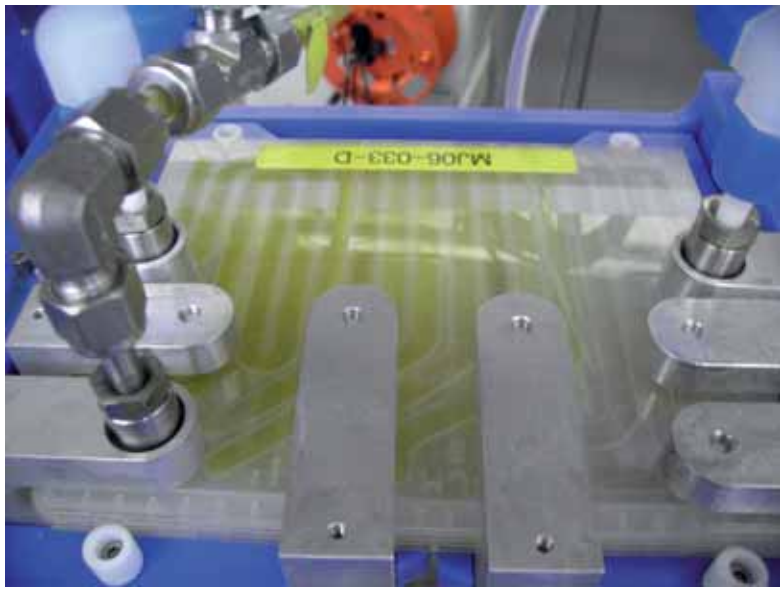


Metal-organic reaction example

The overview: The MRT is nearly invisible within the infrastructure



The core of a MRT unit: The reactor and the heating/cooling coil attachments



Double de-protonation of methyl-acetoacetate.
The progress of the de-protonation can be seen by the brown color of the solution.

5. Expectations and Outlook

With the build up of in an house expertise Siegfried is now able to offer expanded reaction possibilities. The new tools help us to solve several shortcomings of classical development and scale up work

- skipping critical parameters originating from scale up.
- increase the selectivity of chemical reactions by a more precise reaction control
- faster scale up. Just run a reaction performing well in a micro reactor during 7/24 and collect the product.
- runaway reactions are no problem anymore if they can be run with MRT. Only a few grams are "active" at a given time.
- small investments compared with a new batch reactor. Often the same reactors can be used for very differen reactions
- broader reaction possibilities
- highly reactive intermediates can be manufactured and immediately converted to stable intermediates. This is not possible in a batch reaction
- mix – heat – react – cool – quench in seconds, even with pressure reactions!

To make best use of the new technique the chemists involved have to be made aware of its potential. They have to think broader than in test tubes, glass bulbs or chemical reactors. It is therefore our hope and expectation that with growing know-how the application of MRT at Siegfried will become a standard tool. Thus we need to educate our development chemists to think outside the box of classical batch reactors, and to consider reactions they'd otherwise deemed to dangerous or challenging.

Hans-Rudolf Marti, VP Science and Technology

The team from left to right:
Norbert Schärer, Patrick Limacher, René Grindat

Siegfried Symposium in conjunction with the University of Zurich

Organic Chemistry Institute
New Methods in Process Chemistry
September 4th, 2008, at the University of Zurich

and awarding of the Siegfried Medal 2008

Please reserve this date.

Process Chemistry

Process chemistry drives much of the chemical industry but receives fewer than its share of recognition. The Siegfried company and the University of Zurich jointly sponsor this third in a series of award symposia showcasing the importance of process chemistry. The event will be held at the university's Irchel campus on **September 4th, 2008**. Representatives of the leading laboratories of the world will present important aspects of process chemistry.

- **Prof. Matthias Beller**, Rostock Institute for Catalysis
- **Prof. Anthony GM Barrett**, Imperial College London
- **Dr. Michael Lipton**, Schering Plough
- **Dr. Thomas Bader**, LPF-Zurich
- **Dr. Michael K. Levis**, Siegfried Ltd
- **Symposium Medalist**

The Siegfried Medal

This distinguished award was established in 2004 jointly by the University of Zurich and Siegfried Ltd, Zofingen, Switzerland to recognize original research in chemical processes carried out in academic and/or industrial laboratories. The third biannual prize will be awarded at the 2008 Siegfried Symposium and consists of a gold medal and an honorarium.

Final invitation to follow in January 2008.

If you are interested in receiving more detailed information on this free symposium, please contact

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Dr. Regina Thiergardt, Head Development Actives

Regina Thiergardt, Head of Development Actives, looks back on eventful times and 13 years with the Siegfried Group. But let's start back at the beginning...

Born and raised in northern Germany near the Danish border, Regina had a goal; she wanted to move south to explore a different lifestyle. That's why she headed south after college to the picturesque town Freiburg im Breisgau to study chemistry – at a time when women were rare in organic synthesis.

Her professional career began across the border in Basel at the pharmaceutical research division of Ciba-Geigy (today Novartis). One day, a colleague from her lab who was born in Zofingen, urged her to come for a visit to the medieval town and – without further ado – apply for a job at Siegfried!

No sooner said than done. As it turned out, Siegfried was looking for a Development Chemist. According to Regina, she "hit the jackpot" and won the job, where she worked for the next five years.

The time as a Development Chemist came to a sudden end in 1999. Regina was transferred to the U.S. to help turn around the Siegfried facility in New Jersey. As the Head of Development, she played a key role in merging the two US-sites and she created a Development team that would cooperate closely with Production in Pennsville and Development in Zofingen. As part of the management team, she worked hard and endured intense periods of work to make the site fit for the next FDA inspection.

In those days only little time remained for her beloved outdoor activities, such as hiking and skiing, but together with her partner, who also worked at Siegfried in the U.S., she was able to travel across the country and explore Hawaii.

In 2001, she returned to Switzerland to take on a whole new challenge: as Head of Management Development and Training for all of Siegfried. Once there, she build up this newly built department and established a comprehensive leadership program for Siegfried management.
"At Siegfried I was able to change my focus from hard facts of developing molecules towards soft factors of developing people. This would have been difficult in any other company," recalls Regina. "It was a fascinating time."

In 2004, she was promoted to Head of Development Actives, one of the most important jobs in our company. The start in her new position had its surprises: Before she could even take up her work, a fundamental re-organization and restructuring project was started. Therefore she found herself as a full-time member of a task force of the leading managers in Siegfried to realize ambitious reorganization goals. During this time the development department was managed by her deputy.

Finally, she returned to Development in 2005. Much has changed since then; the organization has been rebuilt, new people have come on board, processes have been optimized, and the project cycles have been greatly accelerated. "This demands a strong team consisting of different personalities, which is only possible with empathy and a clear idea how to reach your goals," summarizes Regina. "You have to really like people to be successful".

As a child of the ocean breezes of Northern Germany, Regina has come to love the alpine world she lives in today: hiking and skiing in the mountains and enjoying nature. She and her partner spend much of their free time in the Valais in Southern Switzerland, where they have an apartment. After time away from the office, she returns full of ideas and new goals – for Siegfried and our customers a wonderful thing.

Regina Thiergardt was interviewed by Peter A. Gehler

Highlights

Sale of its Sidroga Division

The Siegfried Group sold its Sidroga Division effective April 30, 2007, to Santo Holding AG, a Swiss company based in Zollikon, Switzerland. Sidroga specializes in developing and marketing medicinal and wellness teas and herbal medicines under the Valverde brand name. The company is active mainly in Germany, Austria and Switzerland. In 2006, Sidroga contributed about 11%, or 39.0 million Swiss francs, to the Siegfried Group's total sales. In future, the Siegfried Group will focus increasingly on its core capabilities, namely exclusive synthesis and demanding generics.

Changes Group Management

The Siegfried Group was restructured following the sale of Sidroga. Executive Group Management is now headed by Douglas Günthardt as CEO, and the CFO, Dr. Richard Schindler was named Deputy CEO. Peter Gehler, Chief Communications Officer for the Siegfried Group, was promoted to the Executive Management team. In addition to his current responsibilities, Richard Bruce was appointed Secretary to the Executive Management team.

Siegfried Actives in Zofingen Approved for Highly Active and Allergenic Compounds

In November and December 2006 an inspection was conducted at Siegfried Ltd in Zofingen by the Inspectorate of Northwestern Switzerland (RHI) on behalf of Swissmedic. The inspection became necessary to renew our current license and – even more important – to newly include the commercial production of highly active and allergenic pharmaceutical drug substances.
The inspection focussed on potential cross contamination, personnel and material flow, cleaning, and looked carefully into risk assessments regarding loading and unloading of reactors, the performance of our closed systems approach, transportation, sampling and storage of highly active and allergenic compounds.
In March 2007 Siegfried Ltd finally received the approval by Swissmedic to produce not only classical drug substances, but also highly active and allergenic compounds in Zofingen. This opens Siegfried for a new business segment, which was not accessible until now!

Peter Kiechle
Chief Compliance Officer

Staff Changes

Thomas Cragnolini
Head Engineering

Engineering

Thomas Cragnolini was appointed Head Engineering at Siegfried Actives with effect from July 1, 2007. His predecessor, Hans Baumann, Ph.D., was appointed Head Business Unit Development. In this position he is concerned with Asset Strategy and Operational Excellence.

Gavin Crofts
Business Development Manager

Sales & Marketing

Gavin Crofts was appointed Business Development Manager with effect from July 1, 2007. He will be responsible for the UK market. In November, Thomas Müller, Ph.D., will transfer to the Sales & Marketing department, to further strengthen the Sales and Marketing team in Europe. In the new structure, Gavin Crofts and Thomas Müller will report to Dirk Sator, Ph.D., Head Sales & Marketing Exclusives.

Chemical Development USA

Within the parameters of strengthening the Development Department in the USA, Richard Haldimann, Ph.D., was appointed Head Development Department in Pennsville, New Jersey, USA. He will also serve on the Executive Committee in Pennsville. In addition, Michael Levis, Ph.D., will contribute his process expertise to the Pennsville operations from November 1, 2007.

Behind the Scenes Issue 2/07

For a PDF version: www.siegfried.ch
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