

Highlights

Siegfried continues to grow

In the first half of 2006, the Siegfried Group (SWX: SFZN) attained revenues of CHF 167.8 million, an increase of 13.9 % over the same period last year. The operating income (EBIT) reached CHF 18.1 million, 1.7 % more than in the first six months of 2005.

The Siegfried Division, encompassing the pharmaceutical activities of the Siegfried Group, showed

revenues of CHF 151 million for the first half of 2006, an increase of 14.4 %. Siegfried Actives, a manufacturer of pharmaceutical ingredients that generates around two thirds of this Division's revenues, continued to work at a good level of capacity utilization.

With operating results of CHF 18.9 million, the Siegfried Division was 6.2 % above the previous year.



«Ko-Lin Feng builds bridges in Shanghai»

**She has seen a lot of the world and is an ideal intermediary between cultures:
Ko-Lin Feng, General Manager of the Siegfried Representative Office in Shanghai.**

Ko-Lin grew up in Taiwan, attended high school on the West Coast of the USA and completed her university degree in Mathematics on the East Coast. Ko-Lin then moved to Switzerland to learn French, signing on with the UNO High Commissioner for Refugees, an experience she looks back on with great fondness.

Before long, Ko-Lin found a job in an US company with international headquarters based in Switzerland where she met Douglas Günthardt, today the CEO at Siegfried. She worked for 10 years in Switzerland, building up offices for the company in Taiwan, then in China. She then became the Commercial Director at Whirlpool, a company with well-known brands such as Bauknecht, and was a driving force in establishing their foothold in China.

When Siegfried decided to open its own offices in Shanghai, Ko-Lin received an offer she couldn't refuse. Why did she accept so quickly? Ko-Lin was very impressed with the excellent teamwork, positive attitude and openness of the management team. And in 2004, she became the General Manager for Siegfried in Shanghai: «Taking on a difficult job is not a problem,» says Ko-Lin, «But having to work with difficult people, that certainly is.» This is why she enjoys her work – every day.

Her tasks as General Manager are diverse and include sourcing of raw materials, ingredients, services and developing regional business opportunities. In the future, she will initiate cooperative development and production partnerships and increasingly investigate further market potential in Asia. As the regional Siegfried representative, Ko-Lin is a key part of all negotiations between Zofingen and any Chinese partners.

Ko-Lin is a person of many interests. Her hobbies include gymnastics, jogging, swimming and travelling, but most of all, she loves to read – anything from novels to poetry. She always packs a book during her many journeys throughout Asia, most recently, all over China. Her last trip took her to Cambodia and all its historical sites. She's already planning her next adventure – to Thailand.

We are thankful that Ko-Lin is with us for our journey into the future.

Ko-Lin Feng was interviewed by Peter A. Gehler

Winner of Siegfried Medal

The University of Zurich and Siegfried Ltd, Zofingen (Switzerland) are happy to announce that Professor Stephen L. Buchwald of Massachusetts Institute of Technology will receive the 2006 Siegfried Medal for his achievements in process chemistry. Professor Buchwald's contributions have effected process chemistry primarily in the synthesis of fine chemicals and active pharmaceutical ingredients, with specific achievements including:

- 1) Design of commercially viable ligand systems to facilitate metal mediated coupling reactions;
- 2) Elaboration of robust synthetic protocols applicable to target synthesis on scale;
- 3) Evaluation of reaction mechanisms to minimize catalysts loadings leading to more environmentally safe chemical processes.

In the area of ligand design, Buchwald is well known for the family of now commercially available biaryl phosphines, which he has used to demonstrate substrate/reactant generality in coupling reactions ranging from arylboronates and arylchlorides in the classic Suzuki-Miyaura reaction to ketones and nitroarylhalides in the synthesis of pharmaceutically important indoles. This ligand mediated chemistry has been used on scale by major pharmaceutical companies; one particular example being the antidepressant MKC-242. The use of metals on scale is only possible if cost, safety and environmental issues can be resolved through mechanistic considerations, Buchwald has been able to optimize these processes to require low catalysts loadings, to be less sensitive to conditions, and to work safely and reliably. This spectrum of achievements from fundamental reaction design to optimized commercially robust process embodies API process chemistry. The Siegfried Medal was established to highlight this kind of multifaceted, scholarly and socially sound approach to chemical research.

Professor Buchwald represents the kind of world-class researcher needed to sustain progress in the field of process chemistry, and he is an exemplary role model for young scientists looking for challenges in chemistry that have impact in fine and API chemical production. The gold medallion and a 10,000 CHF (8,000 USD) prize will be conveyed during the Siegfried Symposium on September 21, 2006 at the University of Zurich.

Highlights



Sandra Siegrist
Marketing Assistant

Sandra Siegrist new Marketing Assistant

On March 1, 2006 Sandra Siegrist began her job as Marketing Assistant at Siegfried Ltd. She took over for Ruth Emmenegger, who left on maternity leave. In her new position, Sandra Siegrist is responsible for all advertising matters, liaison with the specialized media and, among other tasks, for anything going on «behind the marketing scene.»

Siegfried at the <CPhI> Show in Paris, France

From October 3–5, 2006, Siegfried will be at the CPhI in Paris, France. Everyone is invited to visit our boot in Hall 5A, Booth No. 5M06!

Behind the Scenes Issue 2/06

© 2006, Siegfried Ltd, Zofingen
Newsletter published by Siegfried Ltd
For a PDF version: www.siegfried.ch
Comments are welcome.

Please send any input concerning «Behind the Scenes» to

scenes@siegfried.ch

Editor: Hubert Stückler

Siegfried Ltd

Untere Brühlstrasse 4
CH-4800 Zofingen
Switzerland
Tel +41 62 74611 11

the scenes

behind

Newsletter Issue 2/06

Siegfried

Highlights

«No Action Indicated»

This year, the American regulating authority, FDA, inspected both Siegfried plants, in Zofingen, Switzerland, and in Pennsville, New Jersey, USA. The inspections in the API manufacturing plants both ended with the distinction «no action indicated». For Zofingen, it's the second consecutive time, and for Pennsville even the third consecutive time, that the FDA found fault with nothing. This underlines the great importance of compliance to the Siegfried organization.

Siegfried Produces Key Intermediate for Tamiflu

Roche has selected Siegfried Ltd, Zofingen as a manufacturing partner for the flu medicine Tamiflu. Production has already begun and the first deliveries have been made. Roche attests to Siegfried's high degree of flexibility and reliability. Siegfried is proud of its role in the battle against possible pandemics.

Symposium and Siegfried Medal Award at the University of Zurich

Siegfried is proud to announce Prof. Stephen L. Buchwald of the Massachusetts Institute of Technology Cambridge as the recipient of the second Siegfried Medal 2006 in recognition of his outstanding work in practical process chemistry. The Medal will be awarded at the Siegfried Symposium for Process Chemistry at the University of Zurich on September 21.

Registration and information: www.siegfried.ch

Content

Editorial



Siegfried

when substance matters

Dear business friends and colleagues,

By now you have certainly heard the news about Siegfried's selection as a manufacturing

partner for Tamiflu. The quick response by the entire Siegfried team and our excellent collaboration with Roche led to initial deliveries of the key intermediate already within weeks of receiving the commission. This enabled us to start up further processing operations in the supply chain without interrupting production. Once again, Siegfried met the challenge through flexibility, speed and reliability.

Absolute compliance is an important capability for any leading outsourcing partner. This year, the FDA inspected our facilities in Zofingen, Switzerland and Pennsville, New Jersey, USA and issued a «No Action Indicated» (NAI) classification, giving our company the best possible rating. This is important for our customers, too, and enhances their confidence in our projects and products.

Two years ago we built a new milling and blending facility. This year we will complete the total renovation of our crystallization operation, allowing us to guarantee the best possible technical conditions for all production stages.

These efforts are part of our ongoing program to keep our technology and capabilities up to the newest standards. As an API expert, we at Siegfried take pride in our ability to manufacture even highly active substances so they are safe for both our employees and the environment. Naturally, this is completely in the spirit of our company slogan: «Siegfried - when substance matters».

Summer is drawing to an end, signaling the approach of our annual Symposium and the Siegfried Medal Award ceremony. I look forward to seeing you there on September 21, 2006 in Zurich!

Sincerely,

Dr. Hubert Stückler
Head Business Unit Siegfried Actives



Winner of the second
Siegfried Medal
Prof. Stephen L. Buchwald



New Challenges for the Supply
Chain of Siegfried Actives
Peter Küng, Head Scale-up
(and co-authors)



A day in the life of
Ko-Lin Feng
General Manager of the Siegfried
Representative Office in Shanghai

New Challenges for the Supply Chain of Siegfried Actives

High Potent Active Ingredients in the Pharmaceutical Industry

High potent active ingredients have long been known in medicine, and the pharmaceutical industry has been producing them for quite some time now. At the end of the 1950s, a newly marketed sleeping aid and tranquilizer, Contergan, gained infamy when its teratogenic side effects became known. The drug's active ingredient, thalidomide, clearly a high potent molecule, was rediscovered in the 1990s in connection with the treatment of a leprosy-like disease and was again brought onto the market. Being aware of the potential of thalidomide, the conditions imposed for its manufacture, sale and application are extremely restrictive. In today's fight against cancer, increasing attention is being paid to the broad palette of high potent molecules. Likewise, because these components also play an increasingly important role in custom synthesis, we wanted to meet the challenge of getting involved with these APIs and their intermediate stages, of testing them and later on, also synthesizing them. A general overview of the situation can be gleaned simply by searching the Internet for high potent active ingredients, where one can read the following general description:

«...(A) High Potent Active Ingredient (HPAI) is an active pharmaceutical intermediate or ingredient that has a specific Occupational Exposure Limit (OEL) at or below 10 micrograms per cubic meter of air as an 8 hour time weighted average. Basically, it means the particular compound is a potent and toxic compound. Currently, high potent active ingredients are gaining importance due to their efficient toxic effect over various diseases. Also, their ability to kill cancerous cells is an important factor that is giving momentum to the widespread usage of high potent active ingredients in oncology related treatments. This potent capability is also of interest for other diseases warranting research and development for producing such high potent active ingredients by leading pharmaceutical companies.

A major contributing factor for innovating pharmaceutical companies to look for potent compounds is the increasing shift in disease treatment trends across various therapeutics. More and more drugs available in the market aspire to have functional properties such as low dosage and high potency. This is due to the emerging attitude of an effective drug which is patient friendly, treatment friendly, offers lower dosage options, and provides a sure shot cure at a faster rate than other drugs, which otherwise requires a long dosage time and less effective....»

Requirements for the Supply Chain of Siegfried Actives

In order to meet employee-friendly manufacturing practices, a Task Force was formed whose basic function was to establish limiting values, manufacturing conditions, and corresponding safety standards (in industry, classes and thresholds are anything but uniformly defined).

The creation of a classification system, which also included contributions by renowned external experts, was of central importance. The Classification Committee now meets regularly when projects and products are being evaluated, thereby ensuring that these are assigned to the appropriate and corresponding Siegfried Exposition Class. What is important here is the identification of so-called Class 3 products (OEL 1-10 $\mu\text{g}/\text{m}^3$); these must be manufactured under special, controlled conditions in the production and in the pilot plant, and also handled with special care in the lab.

Siegfried Exposure Classes

Exposure Class	Occupational Exposure Limit
1	> 500 $\mu\text{g} / \text{m}^3$
2	10 – 500 $\mu\text{g} / \text{m}^3$
3	1 – 9 $\mu\text{g} / \text{m}^3$
4	< 1 $\mu\text{g} / \text{m}^3$

Challenges in Chemical Development

At the beginning of a project, the chemical and technical documents from a particular customer must be assessed. According to the phase of the project, the documents available to us present varying levels of detail and stages of processing. Depending on the standard of knowledge, the chemical syntheses can be listed in great detail. However, because most of our projects are still being developed by our customers, there is often hardly any, or only very inadequate, toxicologic information available, especially for the intermediate products. In the past few years, the focus on high potent medications has further intensified; correspondingly, the portion of Class 3 substances has likely greatly increased. In the laboratory area, this class of substances has to be processed with particular care and the personal protection of the employees must be the main concern.

When work in the lab involves Class 3 substances, open communication with all employees and corresponding training in properly handling these compounds is assigned the highest priority. For this reason that training is carried out at the beginning of the lab work. This training informs the worker about the dangers of the substances to be processed and the associated personal protection required by the employees. The training documentation is available to the employees at all times.

Critical points to be emphasized include protective clothing, the handling and disposal of trash and waste materials, and the labeling of the substances as Class 3. The proper procedure to follow should an accident occur is defined before the project begins.

Weighing, isolation and drying have been identified as the most critical steps in the laboratory synthesis of Class 3 substances. Suitable weighing stations enclosed in fume hoods with special fine particle filters have therefore been installed. Likewise, in order to avoid contamination during unloading and removal, drying is carried out in specially designed drying cabinets located in fume hoods. After the successful completion of the laboratory phase, the instruments and fume hoods used are cleaned according to the relevant guidelines.



Challenges in Quality Control

An increasing number of pharmaceuticals contain high potent active ingredients. This is a major challenge not only to chemical-pharmaceutical development and production, but also to analytical control laboratories. Once a compound has been classified (e.g. Class 3) a risk assessment is carried out:

Which process steps are critical? Which methods and instruments are used? What can go wrong? What are the risks for the operator, for the co-workers in a lab, for the environment?

Consequently specific safety measures and technical solutions are defined, followed by the evaluation and purchase of the necessary equipment including their installation and qualification, the selection of adequate personal protection equipment, and finally the training of the operators.

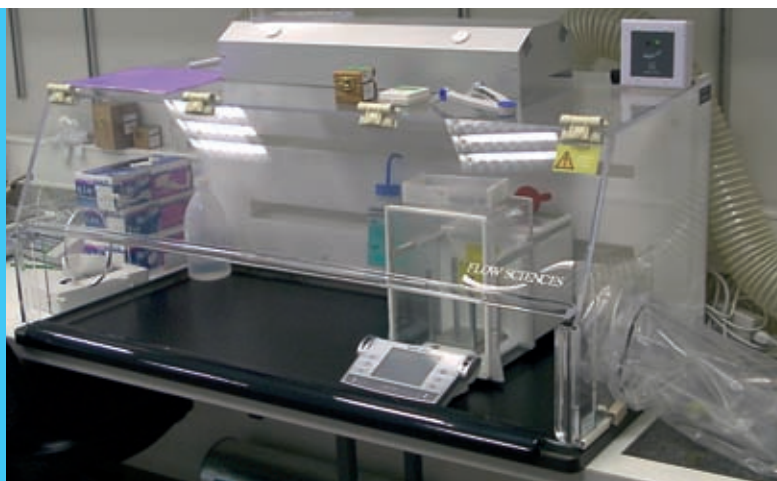
Since high potent compounds bear potential health risks, an early and regular flow of information to employees is important for them to become familiar with the rationales of such «dangerous» projects and to build up trust in their future tasks.

In analytical labs only small quantities of high potent compounds are handled, nevertheless facilities, equipment and work practices have to be adapted to the specific needs. Typical manipulations in QC are weighing and diluting of analytical samples and reference substances as well as transferring of samples e.g. from the sample preparation lab to the analytical instrument lab for which we created special transport containers. Exposition to powder and dust is most critical and has to be avoided by all means. For this reason we installed special safety workbenches equipped with special dust filters. The laminar airflow protects the analyst from getting contaminated by the substance during weighing or diluting. Disposal of contaminated consumables is performed by a litterbag system mounted to the safety bench. Written procedures give details about actions to be taken in case of spills. One of the safety workbenches features a vacuum drying oven seamlessly attached to the bench, which ensures the safe transfer of a sample directly into the oven without leaving the protected environment.

But with all the fancy installations, the most sophisticated equipment and elaborated processes, one needs to focus on the skills and diligence of the operators. A comprehensive (hands-on) training program was therefore established to familiarize the analysts with the new work practices.

In the course of establishing Class 3 readiness a most welcome side effect resulted from the various discussions, the technical evaluations and the trainings: we noticed a growing safety awareness in our department.

Thanks to very knowledgeable and cooperative analysts the handling of Class 3 compounds has almost become a routine operation in QC and we are proud that our efforts have contributed to the expansion of Siegfried's product portfolio towards high potent compounds.



Before special process optimization instruments are employed, such as the reaction calorimeter, the automatic parallel synthesizer or the automatic laboratory synthesizer, a cleaning concept that guarantees the certain decontamination of these complex devices must already be in place.

The synthesized Class 3 substances are stored in tightly sealed vessels and labeled with easily recognizable stickers. In particular, the samples used for determining the analytical purity must be conspicuously identified so that they are clearly distinguishable from the normal samples.

With the identification and classification of Class 3 substances, the implementation of a safe work routine in the lab, and personal protection precautions, a concept was established that ensures safe handling in the lab. These procedures guarantee that Siegfried Actives is well prepared for the future.

Challenges for Production

During the last quarter of 2005, after successful developing and pilot phase testing, the Siegfried Actives department introduced its first high potent active ingredient in chemical manufacturing on a technical production scale.

With the manufacturing of this substance, the protection and safety of the co-worker was of top concern: all operational sequences had to be carefully considered and newly evaluated. This especially applied to the following topics:

- Personal protection and safety of the operators
- Contamination by the active ingredient
- Cleaning and decontamination
- Procedures to be followed in case of accident
- Training

In the following section the complex problems encountered and the corresponding solutions implemented will be discussed:



Personal protection and safety of the operators

We strove for a closed operation mode throughout, to protect the operators. All hose connections were replaced by solid pipe installations. The loading of powdered starting materials into the reactors and, likewise, the unloading of intermediate products and the product itself from the centrifuges proved to be especially challenging problems. In order to carry out these operational sequences as closed processes, special Drum Containment Systems (DCS) were procured and introduced (Glove Box principle). Additionally, all potential sampling sites in the process had to be defined and equipped with systems that would enable closed sampling.

Contamination by the Active Ingredient

A zone concept was designed complementary to the closed operational procedure. Zone 1 includes the reactors with their constructional systems (super structural parts) and the procedures described above. Zone 2 includes the reaction chamber, i.e., the reaction set-up. This installation is physically separated from its surroundings and equipped with a separate ventilation system, which ensures a pre-defined airflow direction. The operational and functional reliability of the ventilation system is continuously monitored during the process. The incoming and the outgoing air is purified using special dust filters. The source air and process exhaust air are channeled over absorbers, and the wastewater is then collected. In order to prevent an uncontrolled contamination the active ingredient is chemically transformed to an inactive form and the process wastewater as well as all waste streams are treated, as necessary.

Cleaning and Decontamination

Special importance is attributed to the simple and rapid cleaning of the specific installation as well as to the decontamination of contaminated infrastructure parts, such as vacuum pumps and/or exhaust filters. For this, the cleaning of the installation was described in detail and documented in relation to the manufacturing process. Additionally, scenarios for the repair of potential wearing parts were compiled in close collaboration with the engineering department. The effectiveness of the cleaning procedure chosen was verified with placebo batches. Finally, the parameters for release of the whole equipment after cleaning were defined in cooperation with Quality Assurance.

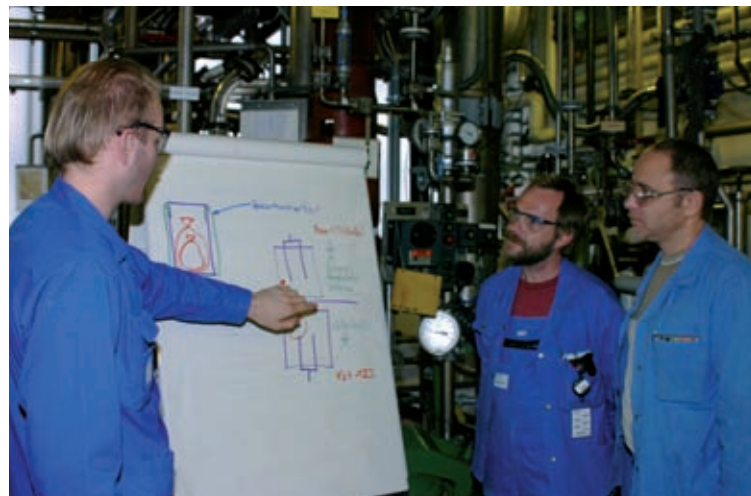
Procedures to be followed in Case of Accident

As part of planning for all eventualities, possible accident scenarios were developed and practiced in collaboration with Siegfried's emergency services. Thus, for example, the procedure on how to handle an unplanned leak was practiced. In this exercise, special full protective clothing was worn and the subsequent decontamination was practiced.

Training

A great deal of effort is devoted to ensuring that all employees involved receive appropriate training. The new technical systems, the newly established Standard Operating Procedures (SOP) as well as sensitive reaction steps are drilled using placebo runs in chemical production. Training of employees is not strictly limited to the chemical production, but also continues along the material and sample flow. Thus, for example, the logistic employees are schooled in the proper and safe handling of the active ingredient.

The manufacture of high potent active ingredients is a complex process and offers many new challenges. The successful introduction of the first active ingredient of this substance category into manufacturing impressively verifies the efficiency of all areas within Siegfried Actives. Meanwhile, at Siegfried, there are several projects and products where the Class 3 philosophy is already being used, and it appears that, after last year's introduction of the first representative of this product class, our future portfolio will include many such substances. The anticipated introduction of the next two products is scheduled for the end of the year 2006 and the beginning of the year 2007.



Siegfried Ltd

Chris Kleiner

Head Operations Actives

Thomas Müller

Head Chemical Development

Stefan Geisshüsler

Head Quality Control

Peter Küng

Head Scale-up