

Siegfried's explorer of new drug production methods

When a friend recently showed him a prescription drug that he was taking, Beat Weber felt proud. The active ingredient was one he had developed himself. "This was the first time that I witnessed first-hand my work making a vital difference to the wellbeing and health of another person. I felt great – it gave me a real sense of accomplishment."

Beat Weber is Director of Process Research at Siegfried, leading an eight-person team formed in the summer of 2002. From the outset his unit has been equipped with the latest in analytical technology. Weber says the launch of his group was a significant moment for the company, marking a fundamental change in the structure of Siegfried's development organization. It also meant a pivotal shift in his own work. From 1994 to 2002 Weber optimized customer processes – squeezing yields and cycle times, as he terms it. "Now we can achieve quantum leaps, using innovative methods and thus adding far more value for clients."

The new process pathways developed by Beat Weber's group must meet exacting standards, particularly when it comes to lead time, cost, and human and environmental safety.

His job is complex. What looks fine in theory, acknowledges Weber, does not always work in practice. That's why he likens process research to walking a tightrope. The line between success and failure is often narrow indeed.

In many cases the work is focused on second-generation processes, in other words, completely new processes for the same target molecule or significant process improvements. For instance, when a custom synthesis product is approaching the end of its patent life time and manufacturing costs must be cut. In such situations, says Weber, clients are willing to accept having to

change the product registration documentation. As for his other activities, Weber works mainly on molecules that are in phase I and II clinical trials.

Asked about typical projects, Weber is not short of examples. Just recently, his team reduced a five-step, highly equipment-intensive process by two steps. It was only this streamlining that made it possible to turn out industrial quantities with the facilities available. In another case he describes the challenge, "the substance had such a strong odor that, even for milligram quantities, workers had to use breathing protection and safety precautions". The new process eliminated this problem. "Since then, the client has already announced three more projects", Weber is pleased to note.

Naturally, Beat Weber also knows where to obtain scientific help. He works closely with Professor Jay Siegel of the University of Zurich, who acts as a scientific advisor. Siegel used to work at the University of San Diego, where he first came into contact with Siegfried representatives. Yet, important know-how comes not only from outside, but also from within the company. "Siegfried has decades of experience in the development of chemical processes. We can draw on this expertise at any time," explains Beat Weber. "My supervisor, Dr. Hansruedi Marti, has been in chemical development at Siegfried for 25 years. I often get hot tips from him."

Asked what his next goal is, Weber says: "In addition to being a process researcher, I am also a kind of missionary. I want to convince our customers that every dollar invested in process research early on is well spent: To begin with, during clinical trials of a new active ingredient, the payoff is in the reliable pilot production of the active substance. Second, when preparing the registration dossier, the benefits are the deeper knowledge of synthesis and side reactions. Finally, at the commercial stage, the active ingredient is synthesized cost-effectively and helps customers and Siegfried to be more competitive."

Beat Weber was interviewed by Peter A. Gehler

«Just recently, his team reduced a five-step, highly equipment-intensive process by two steps.»



Siegfried Biologics GmbH - A biopharmaceutical contract manufacturer offering services from concept to market

Siegfried Biologics GmbH (www.siegfried-biologics.com) the former Alpha Bioverfahrenstechnik GmbH is an established biopharmaceutical contract development and manufacturing company located in Berlin. Siegfried Biologics GmbH provides biopharmaceutical API services from concept to market. The company is a member of the Siegfried Group of companies and was acquired in 2003. Siegfried Biologics GmbH has process development labs and a modern GMP facility with currently two process lines (upstream and downstream) with fermenter volumes up to 300 L. Further expansions are underway. A team of experienced staff manage development, scale-up and manufacturing projects in mammalian cell technology.

Siegfried Biologics GmbH welcomes visitors to its facilities in Berlin.
Michael Bavand, Head Biotechnology

Behind the Scenes Issue 1/04

© 2004, Siegfried Ltd, Zofingen

Newsletter published by Siegfried Ltd

For PDF version: www.siegfried.ch

Comments are welcome. Please send any input concerning "Behind the Scenes" to scenes@siegfried.ch

Editor: Bernhard Küenburg

Siegfried Ltd

Untere Brühlstrasse 4
CH-4800 Zofingen
Switzerland
Tel +41 62 746 11 11

behind

Highlights

Large Hastelloy centrifuge dryer successfully installed and operational at Siegfried

One of the world's largest Hastelloy centrifuge dryers, weighing more than 16 metric tons and with a basket diameter of 130 cm, was installed at Siegfried's manufacturing site in Zofingen, Switzerland. After successful qualification and a testing period, commercial use of this piece of equipment began in early summer 2003. "The power and working speed of this machine combined with the gentle drying of sensitive products is truly impressive" said Peter Küng, production manager at Siegfried.

NAI inspections at 2 sites within 2 weeks produce a fantastic compliance result for Siegfried's manufacturing operations

Following a successful "NAI (No Action Indicated) inspection" at Siegfried's U.S. site in Pennsville in June 2001, the FDA returned in spring 2003 to inspect Siegfried's U.S. and Swiss API manufacturing sites simultaneously. "Both inspections resulted in NAI and demonstrate the high level of compliance at Siegfried, which we regard as integral to the success of our products and services", said David Pulham, head of the compliance board at Siegfried.

New Chief Compliance Officer at Siegfried – Peter Kiechle joined in July 2003

On July 14 Peter Kiechle, former head of global analytical research and development at Novartis Pharma, joined Siegfried as new Chief Compliance Officer. He will report to CEO Douglas Günthardt and will manage the two compliance organizations in Zofingen, Switzerland and Pennsville, New Jersey. "My global analytical and compliance experience at Novartis gives me an excellent background for this demanding job and I am very excited to join a dynamic service organization like Siegfried", Peter Kiechle said.

SAP successfully implemented and validated at Siegfried in Zofingen

SAP has gone live at the Siegfried headquarters in Zofingen, Switzerland. "It was a huge challenge, but after one year of intensive project work, we were able to switch from our old system to SAP on July 2" said Jürg Amman, Chief Information Officer at Siegfried. Two months after the system's launch, the validation report was finalized. After initial difficulties, SAP is now running smoothly.

Content

Editorial



Welcome to behind the scenes.

In an age when information is available almost anywhere, at any time, and in overwhelming quantity, it seems especially important to receive the right information at the appropriate time and presented in a professional manner.

That need inspired the creation and design of this newsletter from Siegfried. As a multi-faceted, leading provider of services for the development and production of active pharmaceutical ingredients, as well as for formulation, quality control and registration, we have an inside line on the latest developments in many areas. In addition, we would like to provide glimpses into the everyday activities of our company.

We are launching this newsletter partly as a contribution to the discussion of issues that are specific to our industry. With the same commitment to the highest standards of quality that we maintain in our products and services, we will strive for excellence in the technical content and design of this publication.

Leading off in this first issue is Dr. Stefan Peterli, key account manager and expert for process technology, with a look at the sensitive subject of drying technolo-

gies for pharmaceutical intermediates and drug substances. Siegfried has invested significantly throughout the past years to upgrade this final operation step to the latest technological and compliance standards.

We also introduce specialists from Siegfried and tell you about occasions and events related to our business. For example, as Siegfried has to permanently focus on innovation and process improvements, we accompany the head of our process research group through a workday to make readers familiar with his daily challenges and successes.

I am pleased to present the first Siegfried Newsletter "Behind the Scenes". Enjoy the read!

Bernhard Küenburg

Senior Vice President Sales & Development



New Drying Technology to lower API cost
by Stefan Peterli,
Key Account Manager
See inside.



A day in the life of
Beat Weber, Director of Process Research at Siegfried.
See last page.



Siegfried Biologics GmbH
Michael Bavand, Head Biotechnology, welcomes visitors in Berlin.
See last page.

New Centrifuge Dryer Reduces Batch Cycle Times in API Manufacturing

At its headquarters in Zofingen, Switzerland, Siegfried has recently completed installation of a new centrifuge dryer which helps in reducing batch cycle times and therefore cost in API manufacturing.

Siegfried has been manufacturing active pharmaceutical ingredients for APIs for 130 years. The final steps in this manufacturing process include solid-liquid separation, drying, milling and blending (see fig. 1) resulting in a drug substance, which is then converted to the pharmaceutical dosage form, e.g. tablets or capsules.

Drying is a critical physical operation in API production since there is no purification possible afterwards and the residual solvents depend on the drying process. There are numerous dryer types suitable for APIs. While some dryers have been in use for a long time, more recently combined equipment such as a centrifuge dryer has become available. This article gives a brief overview of the equipment used at Siegfried to dry APIs, comparing drying principles and assessing advantages and disadvantages. The operating principles of the centrifuge dryer are explained and the influence of drying technology on batch cycle time and product cost is evaluated.

Fig. 1 Final steps of API manufacturing



Overview of dryer types used for APIs

Table 1 gives an overview of dryer types and compares their advantages and drawbacks.

The vacuum shelf dryer is used at Siegfried on a kilo-lab scale and occasionally in the manufacturing of solid pharmaceutical dosage forms for the drying of tablet granulates.

The double cone dryer is based on vacuum contact drying with slow vertical rotation. While the loading capacity is high and loading, discharging and cleaning is possible in a closed system, agglomerates are frequently observed and the drying process is slow.

The tube-shaped paddle dryer with its horizontal stirrer paddle and built-in crusher eliminates agglomerates efficiently. High loading capacity combined with a reasonable batch cycle time makes this an attractive drying option.

More recently, two spherical dryers (essentially paddle dryers in spherical geometry) have been installed. The combination of the spherical geometry, fast stirrer and efficient vacuum system lead to shorter drying times of as little as two hours per batch. Use of Hastelloy C22 as the construction material allows drying of corrosive HCl salts. The spherical dryer is equipped with a vertical closed system for loading and discharging under controlled air conditions using HEPA filtered air, thus minimizing environmental and product contamination. Rooms for loading and unloading are only accessible through double air locks. With operators using full protective gear with a fresh air supply when necessary, it is possible to handle toxic compounds.

High throughput by combining product isolation and drying

Combining product isolation (separation of the solid from the mother liquors) with drying of solid product in one machine, eliminates labor intensive unloading of the centrifuge and loading of the dryer. Also, potential product contamination by physical handling is further reduced.

In a nutsch filter dryer (used at Siegfried on a kilolab scale) the product is dried in a stream of hot nitrogen. Its disadvantages include a residual filter cake which needs to be removed at the end of the campaign.

Centrifuge dryers have been used more recently in API manufacturing, with separation by centrifugation and drying carried out in one apparatus. Construction from chemically inert Hastelloy C22 make this dryer suitable for use under a wide variety of conditions (both acidic and basic solvents).

The product is dried in fluidized bed mode, using a stream of hot nitrogen at a pressure of 5.5 bar and temperatures of 25-150°C. The unloading of wet product is not necessary, thus reducing batch cycle times and eliminating product contamination. Automated loading and discharge procedure and fully automated cleaning in place means that there is no operator exposure to solvents and no environmental contamination.

The cooling effect of the solvent evaporation gives gentle drying with no local overheating.

The centrifuge dryer (see fig. 2) features a horizontal centrifuge with a 130 cm basket combined with a closed nitrogen circulation loop (equipped with condensers to remove the solvent). The process takes place in six sequential operation steps, with all parameters adjustable for achieving optimal results.

For the solid-liquid separation, the centrifuge is filled with product slurry through the hollow drive shaft. A sintered metal filter basket allowing retention of particles as small as 10 microns has been installed in the equipment in use at Siegfried, which can process batches up to 400 kg in weight and up to 800 liters in volume. In the washing step, the washing liquid is introduced through the hollow drive shaft and the variable centrifuge speed gives an optimal washing effect. The filter cake is then dislodged using nitrogen blasted through segments in the filter basket.

The next step is fluidized bed drying (see fig. 3). The filter basket retains small particles and the cooling effect of the solvent evaporating gives gentle drying with no local overheating. Weight cells allow monitoring of the drying process. In the final step, dried product is pneumatically discharged by opening the seal plate and applying nitrogen pressure. The technical set-up of the centrifuge dryer allows complete discharge of the equipment after each batch.

Fig. 2 Centrifuge dryer schematic diagram



Fig. 3 Fluidized bed drying



Table 2 Comparison of drying technologies: Batch cycle time versus cost

Isolation / Drying Technology	Centrifuge/ Paddle Dryer	Centrifuge/ Spherical Dryer	Centrifuge Dryer
Batch cycle time [h]	5+12 = 17	5+6 = 11	6
Productivity [batches/week]	10	15	28
Approx. relative product cost per kg [%]	100	75	< 50
Capital expenditure centrifuge [CHF million]	1.5	1.5	3.0
Capital expenditure dryer [CHF million]	1.0	1.5	0

Comparison of isolation/drying technologies: Batch cycle time vs cost

Table 2 compares three combinations, the centrifuge with a paddle dryer, the centrifuge with a spherical dryer and the centrifuge dryer. Looking at a typical isolation and drying process run at Siegfried, the shortest batch cycle time is achieved in a centrifuge dryer. This equipment enhances productivity considerably; almost three times as many batches are possible per week compared to the centrifuge/paddle dryer combination.

In the case of the centrifuge dryer, the approximate relative cost per kg of dried product is less than 50% of the combination centrifuge/paddle dryer, while capital expenditure for each of the three options is fairly similar. This comparison clearly demonstrates that investment in technologically advanced equipment can easily pay off by reduced batch cycle times and product per kg cost as well as enhanced productivity and batch-to-batch reproducibility. While the number of operators is considerably reduced due to the high degree of automation, process set-up and optimization require a thorough understanding of all parameters involved. The traditional manual centrifuge unloading will therefore be replaced by the programming of approximately 100 parameters for the automated centrifuge dryer.

Investments such as our new spherical dryers and the centrifuge dryer enable us to provide pharmaceutical originators with high value added APIs at an optimal cost. In a market which has come under worldwide intense price pressure, Siegfried commits to take the lead through use of advanced technology.

Stefan Peterli
(Parts of this article have been published in the August 2003 issue of sp2 magazine.)

Table 1 Overview of dryer types used for API

Dryer type	Shelf	Double Cone	Paddle	Spherical	Filter*	Centrifuge
Approx. loading capacity [m³]	0.3	1.0	1.0	2.0	0.08	0.4
Drying batch cycle time [h]	12 - 60	8 - 18	9 - 12	2 - 6	5 - 12	0.2 - 2
Drying technique	vacuum	vacuum	vacuum	vacuum	vacuum	hot nitrogen
Agglomeration	yes	yes	no	no	no	no
Delumping equipment	-	-	crusher	crusher	stirrer	-
Loading / unloading	open	closed	closed	closed	closed	closed autom
Closed syst. Cleaning In Place	no	yes	yes	yes	yes	yes
Construction material used at Siegfried	stainless	glass-lined	stainless	Hastelloy	Hastelloy	Hastelloy
Rotation / stirring speed [rpm]	-	2	10	25	30 - 40	1,200

* Kilolab scale only