behind the scenes

Newsletter Issue 1/07

Siegfried

Highlights

Siegfried and Celgene co-operate
Siegfried has signed a long-term co-operation agreement with Celgene (NASDAQ: CELG) and sold an active pharmaceutical ingredient (API) asset to the US-based pharmaceutical company. The manufacturing facility has the capability to produce multiple drug substances and initially will be used to produce REVLIMID to supply global markets. Celgene is purchasing the assets for approximately a total of CHF 55,5 million in cash, with an initial payment of CHF 15 million.

Siegfried's new Internet design
The new design of Siegfried's Internet site was ready just in time for the New Year. On the first page (or index page), visitors are given a choice of Siegfried's three business units: Siegfried Actives, Siegfried Generics and Siegfried Biologics. The index page is the platform for all information concerning the Siegfried division. From there, employees, customers and other interested visitors can access the most important company information, such as product data, publications, job offers, or contacts. We are convinced that this fresh and dynamic design meets the expectations of users and gives our company the best possible online presence. www.siegfried.ch.

Editorial

Siegfried when substance matters

Dear business partner,

Many companies have already announced their annual results for the 2006 financial year. The economic upswing has clearly resulted in well-filled order books, especially in Europe.

The situation in the pharmaceutical and chemical sector is not all that conclusive. Companies with a long-term focus maintaining a high quality and performance standard were able to achieve growth. Siegfried is considered to be one of these stable and well performing companies, and we reported positive results for the past financial year.

It is my pleasure to provide you with the following information about our 2006 financial results:

The Siegfried Group posted consolidated sales for the 2006 financial year of 359.8 million Swiss francs, representing a 13% increase over the previous year. Gross profit grew by 10.9% to 120.4 million francs. The operating result is reported at 41.1 million francs, or 4.3% below that of the previous year. The decline is due to extraordinary earnings resulting from a real estate sale in 2005. The Siegfried Division, comprising the pharma activities of the Siegfried Group, increased sales by 13.6% to CHF 320.7 million. The division's product pipeline was successfully expanded by 15 new projects in the field of custom synthesis for exclusives customers in the pharmaceutical industry.

It is absolutely necessary – and expected by our customers – that we develop solutions for our business partners that reflect creativity and innovative power. This makes high demands on us in terms of organizational flexibility and the continued development of our technologies. The article about Spray Drying is well suited to demonstrate these capabilities. This edition again contains the announcement of new appointments to key positions, which we would like to share with you.

The 6th Contract Manufacturing Conference for Pharmaceuticals is scheduled to take place from June 25 – 27, 2007. Siegfried's Chairman of the Compliance Board, David C. Pulham, Ph.D., will chair this important conference. We have enclosed detailed information concerning the conference.

Please accept my best wishes for you personally and for continued success in the course of your business.

Sincerely,

Dr. Hubert Stückler
Head Business Unit Siegfried Actives

Content

Siegfried with fully renovated crystallization plant

A day in the life of
Dirk Sartor, Head New Business Development

Spray drying, a new technique at Siegfried

In the development of an active pharmaceutical ingredient (API) process, it is important to consider more than just the chemical synthesis. New API molecules tend to be more potent and have larger structures. Some of these APIs are closely related to biochemical structures like pseudo-peptides, sugars or antibodies. Manufacturing of these APIs is frequently based on complex multi-step syntheses and is therefore expensive. Bioavailability and physical properties become the focus of pharmaceutical development strategies. We have observed, that with increasing complexity of the API structure, the molecules become more sensitive to chemical and physical process conditions, like temperature, pH or concentration. Siegfried's process chemists have learned to focus equivalently on smart synthesis routes and chemical reactions as well as to develop robust work up & isolation procedures or physical operations. To fulfill the requirements of our pharmaceutical customers, Siegfried continuously improves its knowledge and technical equipment for physico-chemical operations like crystallization [Lit 1], centrifugation, drying, blending and milling [Lit 2, 3].

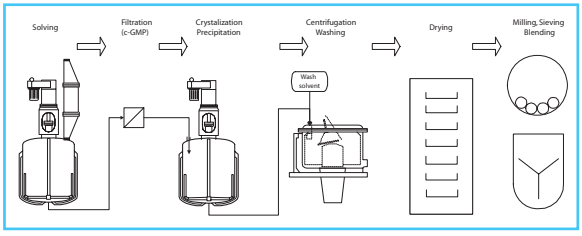
The crystallization process

Overview of dryer types used for API

Dryer type	Shelf	Double Cone	Paddle	Spherical	Filter*	Centrifuge	Spray Dryer***
							
Approx. loading capacity (m^3)**	0.3	1.0	1.0	2.0	0.08	0.4	continuous
Drying batch cycle time (h)	12 - 60	8 - 18	9 - 12	2 - 6	5 - 12	0.2 - 2	2.5kg/hr max.
Drying technique	vacuum	vacuum	vacuum	vacuum	vacuum	hot nitrogen	hot nitrogen
Agglomeration	yes	yes	no	no	no	no	no
Delumping equipment	-	-	crusher	crusher	stirrer	-	-
Loading / unloading	open	closed	closed	closed	closed	closed autom	closed
Closed syst. Cleaning in Place	no	yes	yes	yes	yes	yes	yes
Construction material used	stainless	glass-lined	stainless	Hastelloy	Hastelloy	Hastelloy	stainless
at Siegfried	steel + Hastelloy	steel	steel + Hastelloy	C22	C22	C22	steel
Rotation / stirring speed (rpm)	-	2	10	25	30 - 40	1,200	n/a

* Kilolab scale only ** 20%-80% of volume ***continuous mode 60kg/day; centrifugation and milling not required; particle size adjusted by operational settings

A very important step on the way to producing a solid API with defined physical and chemical properties is the drying step. Drying is not only the removal of water or organic solvents, but also a significant part of the last process steps in production; therefore drying influences the quality and cGMP compliance of the final API. Within the recent years we have both updated our capabilities in «classical» contact drying and we have implemented a new drying technology with mild drying conditions for one of our projects. To meet our customer's tight schedule for the production of an API, we have established a spray-drying unit within a short amount of time at our US plant in Pennsville, NJ.



Conventional drying, contact drying or indirect drying

In the manufacturing of APIs we mainly use multi-purpose equipment in a batch mode. APIs are mostly dried batch-wise as well and the optimum drying equipment for universal batch drying is indirect contact dryers [Lit 4]. Indirect contact dryers are sealed vessels with heated walls; heat is transferred from the walls to the product. The heat is needed to vaporize the solvent, so that it can be removed via the gas phase. Most of the time vacuum is used to assist in solvent evaporation.

To compensate for evaporative cooling effects, the heat needs to be transferred continuously to the powder. Because this conductive heat transfer is not very effective for organic solids, which behave nearly like insulators, the powder may be mixed by using stirrers, blenders, or even with in-line choppers.

By constantly changing the contact surface, these devices assist the conductive transfer of heat and help to optimize drying times. Siegfried has a broad variety of indirect dryers like vacuum-shelf dryers, conical (double-cone) tumble dryers, paddle dryers (e.g. the Glatt Inox/ Rosenmund Universal dryer and Rosenmund spherical dryers), filter dryers, or a centrifuge-dryer [Lit 3]. With the wide range of equipment at our disposal, we can adapt drying conditions to the physico-chemical requirements of the substance.

Sometimes quality and safety aspects restrict the drying conditions. The maximum heat, that we can apply to a system should not induce decomposition. Hot spots, caused by friction from mechanical stirrers, have to be avoided. Because organic powders behave quasi-adiabatically 1 – 2 cm from the surface (no heat transfer to the environment), the maximum jacket temperature has to be restricted for safety reasons.

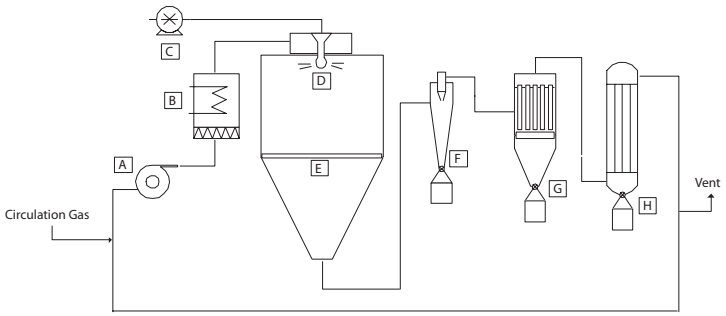
Therefore some substances are not suitable for classical, indirect drying and we need to apply direct drying techniques like spray drying, fluid bed drying, or microwave drying. Because these techniques are generally continuous processes, they are not very popular in the pharmaceutical industry. Spray drying is a relatively expensive unit operation because of its energy consumption, equipment, and peripheral costs (i.e. nitrogen). Nevertheless, it is a common process used to produce tons of dried substances in the food industry under mild conditions. Capitalizing on the advantages of the technique, spray drying has also found applications in the pharmaceutical and fine chemical industry.

Inside view of a paddle dryer

Spray drying

In cases where mild drying conditions are needed or where it is necessary to have a liquid feed to the drying step, spray drying can be the optimum unit operation. In a spray dryer (Figure 1), the drying gases (air or nitrogen) are heated from 100°C to as much as 300°C and fed by a blower to the conical drying chamber. The chamber is designed for optimal gas circulation and minimal product holdup. The liquid feed is pumped to an atomizing nozzle in the drying chamber. Raising or lowering the feed rate controls the outlet temperature. The temperature gradient between the inlet and the outlet of the dryer establishes the drying rate.

Spray Dryer Schematic



A. Circulation Fan
B. Heater & Filter
C. Feed Pump
D. Centrifugal Atomizer
E. Drying Chamber
F. Cylcone
G. Baghouse
H. Condenser

The minute droplets mix with the heated gases, solvents are evaporated, and the droplets are rapidly dried and transported out of the chamber at the bottom. A cyclone is used to separate the solid product from the «humidified» carrier gases. Collection of fines may be achieved by the addition of a baghouse. Spray drying is a very mild technique; because solvent evaporation cools the droplets, the temperature of the powder remains very low, so that even in a hot gas stream (>100°C) the effective temperature of a powder can be less than 30°C. Other advantages are that the amount of organic solid in the heated drying chamber is low and the contact time is short. This reduces the overall thermal process safety risk even when high drying temperatures are needed.

Spray dryer Pennsville

Different spray dryer designs may be applied to optimize production rate, yield, and quality [Lit 5, 6]. In an open circuit design the gases are vented and air is generally used as the drying gas. In a closed circuit design, nitrogen is used as the drying gas and is recycled in the system. To reduce the moisture in the circulating gas stream, a heat exchanger is used to condense the liquid.

The spray dryer flows may be cocurrent, countercurrent, or mixed. The most common configuration for heat sensitive materials is cocurrent with the drying gas. This gas sweeps over the feed nozzle and rapidly carries the dried particles from the chamber, minimizing contact time. A mixed flow configuration has the product flow impinging into the drying gas flow but exiting in the same direction from whence it came. This configuration is also useful in developing larger particles. Countercurrent flow is typically used when products are not heat sensitive.
There are three methods for atomization of the feedstock: pressure, two-fluid, or spinning disc. In the pressure method, the feed is pushed through an atomizing nozzle, with the resultant particle size inversely related to pressure applied. A similar relationship exists with the two-fluid method; the pressure source comes from the air or nitrogen that mixes with the feed in the nozzle and entrains the liquid. The spinning disc nozzle is a popular method where the feed is centrifugally expelled through the nozzle. Increasing the speed of the spinning disk results in finer particles.

Spray drying has some very distinct advantages over some other forms of drying. Atomization of the feed allows perhaps the highest ratio of surface area to weight of feed of any drying process. Due to the short residence time in the drying chamber, there is minimal exposure of the product to the heated gases. The minimal product heating preserves properties of even biologically active substances. Operationally, spray dryers are mechanically simple; the systems have minimal moving parts. Particle sizes can be regulated through control of atomizer speed or pressure. Fine powders may be produced, resulting in the elimination of milling steps. Many substances are engendered in an amorphous state, which may be an advantage for the bioavailability of the API. In cases where additional filtration (e.g. sterile filtration) is required, a filter may be easily inserted into the process at the feed step. The final product is by nature very homogeneous.

While it has several advantages, in relation to other drying methods, spray drying is less economical than conventional dewatering/drying combinations. Highly viscous solutions (>250 cP) are not easily atomized and result in stringy particles; lowering the concentration typically lowers the viscosity but raises processing time. For materials with low ignition energy, leading to a tendency for dust explosions, or with organic solvents in the liquid phase, the air-fed, open circuit systems are limited to temperatures below threshold values. These safety concerns are mitigated by switching to the nitrogen-fed, closed circuit configuration. Comparing spray drying to lyophilization, another popular liquid feed drying process, spray drying is more energy efficient with lower processing times than freeze drying; however, freeze drying does offer advantages when dealing with particularly heat sensitive compounds. Another disadvantage is that spray drying has no purification effect like isolation and classical drying. Therefore the substance needs to be isolated using a filter or a centrifuge and then has to be re-dissolved to be applied to the spray dryer.

Establishing spray drying at Siegfried

On a recent project, Siegfried was able to use spray drying to solve a difficult drying issue that arose in the commercialization of a process. The material could be dried under mild temperature conditions using a tray dryer with a cycle time on the order of days in pilot scale. Furthermore, the product was very heat sensitive. To produce this product at the plant scale it was absolutely mandatory to implement a technology, which allowed us to produce large quantities in an acceptable time, with the desired quality and homogeneity. It was very obvious, that even with the various drying opportunities at Siegfried, indirect drying was not the preferred option for a fast and economic solution. Therefore we established a spray-drying unit within only two months.

Siegfried worked closely with the spray dryer manufacturer, Anhydro (Soeborg, DK and Olympia Fields, IL, USA), drawing on their years of experience to achieve results in minimal time. Both open circuit and closed circuit dryers were used for pilot testing. The earliest pilot tests were used to establish the inlet and outlet temperatures of the dryer. The closed circuit unit allowed higher processing temperatures, eliminating dangers by operating in a nitrogen environment. Development work also included varying solution concentrations by striking a balance between the viscous limits for the feed at high concentrations and higher processing times at low concentrations.

Before being fed to the dryer, an additional filtration step was inserted to remove insoluble bodies from the solution that were formed in the previous processing step. To achieve the best quality product, different atomization methods and flow patterns were tested. These tests also helped determine a configuration that minimized product holdup, thus improving overall yield. During product development, Siegfried tested other liquid-feed drying methods, but found spray drying to be the best fit to achieve an economical commercial process.

Future prospects

Today spray drying is an established technology in our US plant in Pennsville, where it is used as very effective process technique to isolate this challenging substance. Even with this success, we continue to enhance our knowledge in the use of indirect drying technologies and to be receptive to the application of other modern process techniques, such as microwave drying or freeze drying that will allow us to meet new challenges. It is our intention to use the best-applied technology to design a process that is economic, ecologic, safe and that is capable to manufacture the API under full cGMP conditions with the desired quality and physical properties.

Ira Bradford Graff, Ph.D.
Director, Engineering & Maintenance
Siegfried (USA), Inc.

Michael Karl Levis, Ph.D.
Head Process Optimization Chemistry
Siegfried Ltd, Zofingen

Literature

[Lit 1]: Crystallization - Key Technique in API Manufacturing
by Michael Karl Levis, Ph.D.
Published by Siegfried Ltd in the «Behind the Scenes» Newsletter, September 2005 issue (3/2005)
Copyright: Siegfried Ltd, For a pdf version: www.siegfried.ch

[Lit 2]: Milling and blending - key steps in modern API manufacturing
by Hans-Rudolf Schlatter
Published by Siegfried Ltd in the «Behind the Scenes» Newsletter, May 2004 issue (2/2004)
Copyright: Siegfried Ltd, For a pdf version: www.siegfried.ch

[Lit 3]: New Centrifuge Dryer Reduces Batch Cycle Times in API manufacturing
by Stefan Peterli
Published by Siegfried Ltd in the «Behind the Scenes» Newsletter, January 2004 issue (1/2004)
Copyright: Siegfried Ltd, For a pdf version: www.siegfried.ch

[Lit 4]: M. Lattmann, R. Laible Batch drying: The indirect solution to sensitive drying problems, Chemical Engineering Magazine, November 2005

[Lit 5]: A. Frank, The Basic Technical Aspects of Spray Drying, APV Anhydro AS, [February 1997]

[Lit 6]: APV Dryer Handbook, 2nd Ed., Invensys APV, [August 2002]

Highlights

New Sales & Marketing Analyst hired for Zofingen

Jane Plaxton began her position as Market Analyst for Multiclient Products on 1st November, 2006. She was born and raised in Yorkshire, England and attended the University of Huddersfield to obtain a Bachelor of Science in Applied Chemistry and the University of Durham to obtain a Master of Business Administration. Jane had worked for several international organizations, in Europe and Asia, before joining Siegfried. Her main duties include detailed analysis of the global market, provision of market intelligence and identification of potential cooperation partners. Jane is based in Zofingen.

Important personal changes in Zofingen

Peter Küng has been promoted as new Head Chemical Operations Zofingen effective January 1, 2007. Before he was Head Pilot Plant. Urs Bucher has been appointed as new Head Pilot Plant.

Karin Knobloch has been promoted as new Head Phyisical Operations Zofingen. She formerly held responsibility for Quality Assurance at Siegfried.

Business Development Associate, Midwest/Southwest Region US

Lindsey Pruitt joined Siegfried in January as a Business Development Associate. Lindsey is responsible for generating leads and establishing new customer relationships with selected national Big Pharma accounts and emerging pharmaceutical companies in the Southeast and Midwest regions of the United States. This includes the biotech corridor from Maryland to Research Triangle Park in North Carolina. In addition, she will support the Business Development Director by implementing key business objectives at selected accounts. Prior to joining Siegfried, Lindsey worked as a Sales & Marketing Analyst for Chattem Chemicals, Inc. She received a Bachelor of Arts in Psychology with an emphasis in pre-medical studies from Lee University in Cleveland, Tennessee.

Director – Sales & Marketing

Effective January 1st, 2007 Milton Boyer is promoted to Director – Sales & Marketing for the Siegfried (USA) sales team. In his short tenure Milton has demonstrated a broad skill set, working internally to build relationships with manufacturing, externally brokering key customer transactions, and serving as a change agent for new initiatives. In this new capacity, Milton will continue to focus on the commercialization of the opiate product line as well as assume broader Marketing responsibilities for the US sales group.

Director – Business Development

Effective January 1st, 2007 Scott Powers is promoted to Director – Business Development. Scott has the longest business development tenure within the USA Sales. His strong manufacturing background and pilot plant experience have been invaluable in the implementation of exclusive synthesis projects in Pennsville and Zofingen. He has effectively managed many projects from inquiry to commercialization including the most complex project the company has undertaken.

Siegfried with fully renovated crystallization plant

Following two years of intensive planning and construction work, the crystallization plant is now operational again with a new airlock system. Full production in building 630 was started at the beginning of 2007. The second stage of conversion was completed in November 2006 and the finishing work executed in December.

Highest priority is given to safeguarding the closed handling of solid materials. Eight so-called clean rooms were installed on the 1st and 2nd floors of building 630 in accordance with Siegfried's zone concept. Access to these clean-room areas has been sealed off and fitted with staff and material airlocks working on a pressure zone concept. All clean rooms are fitted with pharma terrazzo floors, HEPA (High Efficiency Particulate Air Filter) filters and metal clad walls and ceilings. They correspond to Class D with fewer than 100,000 particles per cubic foot. These construction measures ensure safe handling for both staff and product, and the risk of possible cross-contamination has been minimized. Production of sterile active substances is now possible with the existing infrastructure. The two buildings, 630 and 631, now conform to the highest requirements of our customers and the authorities as now the processes of crystallization, drying, centrifugation, grinding and mixing are all carried out in Zone D. With this project Siegfried meets the compliance requirements in building 630 for the coming years and, therefore, remains a highly qualified and reliable partner in manufacturing chemical and pharmaceutical active substances.

Further information: www.siegfried.ch

Behind the Scenes Issue 1/07

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 62 746 11 11

Dirk Sartor: Siegfried's Hunter

It's my job to help shape the future of Siegfried, that is, to look for projects that are a good fit for us. By observing market developments and keeping a close eye on the pipelines – everything from start-ups to the «big pharma» companies – I jump into action when I see a potential need for outsourcing. But thanks to our reputation in the industry, we often get companies that come knocking on our door. I meet with them, analyze their needs and nail down the technical issues so I can prepare a quote.

This is called «New Business Development.» It also means that I'm on the road a lot, all over the world, but mostly in Europe and Japan. I like to travel, even if it means not having a lot of time with my family in Germany. When I'm not on the road, I work in Zofingen during the week with a place in a village (Küngoldingen) close by, where I can sleep. On the weekends I'm home with my wife and our two kids, Sebastian and Saskia.

Traveling long distances is OK for me. I just need to be well organized and make sure I've done as much as I can for the family, as my wife ends up alone with the kids most of the time. We live on a farm in a beautiful area close to Heidelberg. We inherited it from my parents 10 years ago and had it totally rebuilt; it's a good place for me to relax and «recharge my batteries.»

To get my mind off work, I like to be outdoors, to take care of the fields and trees around the house. Where I live is also perfect for mountain bike riding, and hunting, which is a family tradition and one of my passions. I enjoy being out early in the morning and observing nature. It's a fantastic feeling to experience things that most people (who are still asleep at this hour) seldom get to see.

My passion for hunting carries over to my job as well, where I depend on my instincts and intuition to find the right projects. Then you need patience, because it's important to find the right moment to strike. When talking to a customer I can sense if a project is ready to be outsourced. It always feels great to see how a customer trusts me enough to talk about their plans. I see myself as a partner rather than a salesperson, and the customer does too; communicating well is important.

I also enjoy being in touch with colleagues in Zofingen and at our Pennsville facility. You have to be a bit of an individualist and idealist at my job. I like to travel alone, but need the connection to my family. I call them daily when I'm on the road so that we are part of each other's lives – despite the physical distance. And I am very grateful that my wife runs the home, otherwise I could never do this job.