

behind

Highlights

Focus on complex customer projects

Dr. Stefan Peterli was asked to increase Siegfried's focus in the area of «Customer Project Delivery». Since the beginning of January 2004, a group of five project managers is responsible for the management of complex customer projects.

«Our goal is to deliver every project on time and within budget - whether it is a new process or 500 kilos for a clinical phase III study.» points out Bernhard Küenburg, Senior Vice President - Sales & Development. «Stefan Peterli is the ideal person for this job. As a Key Account Manager, he already managed numerous complex projects in the past.»

Siegfried Annual Customer Dinner

Siegfried held its traditional customer appreciation dinner during DCAT week at the Rainbow Room in New York City, where the attendees were treated to music and the breathtaking views of Manhattan from the 65th floor of

Rockefeller Plaza. «I was very impressed at how many customers attended, as well as with the quality of the relationship between our customers and Siegfried people. This is proof that Siegfried's strategy for excellent customer relationships works.» said Dr. Markus Altwegg, Siegfried's new Chairman of the Board, who attended the event for the first time.

Targacept CEO in Zofingen

Don deBethizy, CEO of Targacept, Inc. (Winston-Salem North Carolina), visited Siegfried in March to reinforce the strategic nature of the collaboration between the two companies. «We plan to build Targacept's pipeline with a proven chemical development and API manufacturing partner such as Siegfried. The success of the chemical development and formulation projects completed with Siegfried validates our initial impressions.» he said, adding that he was very impressed with the people and facilities at Siegfried's worldwide headquarters in Zofingen, Switzerland.

Editorial



Siegfried

when substance matters

«When substance matters»

In this month's issue I'd like to introduce you to our new company claim. Ideally, a company claim should be short and succinct - and easy to remember. In our claim we aim to express the commitment of our 1'000 employees around the world - and how, every day, the combined creative power of these people brings forth new active pharmaceutical ingredients - to improve the lives of people suffering from disease.

What we came up with is, we believe, the very essence of our company. Last year, a varied group of Siegfried employees - from lab and administrative assistant to the CEO - took part in a series of discussions and workshops to reach a common understanding for our claim. The more we talked and exchanged ideas, the clearer it became. «Substance» in its various forms lies at the heart of Siegfried's activities.

«When substance matters» crystallizes our claim to be pharmaceutical industry's first choice for the development of pharmaceutical and biotechnology-engineered active ingredients in terms of quality, on-time delivery, and overall reliability. «When substance matters» expresses - in just three, precise words - our philosophy, differentiation and strengths.

We hope you will agree, Siegfried - when substance matters!

Bernhard Küenburg
Senior Vice President Sales & Development

Highlights

Upgrading our pipeline with «Science & Technology»

After 25 years as head of our Chemical Development department, Dr. Hans Rudolf Marti took over the «Science & Technology» department this spring to focus on a clear technology position for Siegfried and evaluate Siegfried's new product pipeline. Dr. Regina Thiergardt now heads the Chemical Development department.

«We are fortunate to have both Regina Thiergardt - one of Siegfried's most successful young managers - and Hans-Ruedi Marti - one of the best process chemists in the world - take over these important responsibilities for Siegfried,» says Douglas C. Günthardt, Chief Executive Officer, Siegfried Ltd.

The new «Science & Technology» department will help Siegfried work more closely with universities and technical colleges to stay on the technological cutting edge of chemical process development. In addition, the company draws on the knowledge of Jay Siegel, Professor for Organic Chemistry at the University of Zürich, as a top consultant for our development work. Further, the department will help Siegfried to establish a clear technology strategy, which will allow the evaluation of emerging technologies and the development of specific know-how.

«Of course, my heart is still with our customers and I will continue to work closely with them and evaluate their new projects,» says Marti.



Hans-Ruedi Marti, Ph.D.
Head Science & Technology



Regina Thiergardt, Ph.D.
Head Research and Development
(Chemistry)

«A Day has Only 24 Hours»

A former FDA inspector drives Siegfried's «Quality Policy»

David C. Pulham is not only a recognized former «National Expert for the FDA, but also Chairman of the Siegfried Compliance Board, where he is responsible for the Siegfried Group's Quality Policies. Here Pulham takes a look at the past and the present of drug regulation.

When asked how he came to be an FDA inspector, Pulham has a cut-and-dry answer: «I like numbers and facts, not fiction.» Pulham's love of the rational has resulted in an impressive - and surprisingly action-packed - 26-year career with the FDA. In the beginning, fresh out of college with degrees in Mathematics and Medical Technology, he first worked in a hospital laboratory. This did not last long because he was looking for a challenge with a wider scope to the whole industry. In 1975 he applied at the Food and Drug Administration (FDA) and was immediately hired.

Man of the world

After only nine months on the job, Pulham was already on his way to Ireland and France for the FDA. He considered this a great honor, as only a total of 10 inspectors within the FDA were qualified for overseas work at that time. The obvious reasons for his selection were his education and language abilities - Pulham speaks fluent French - but there was also another reason. At that time it was important for the FDA to have skilled and culturally competent people that would help maintain a positive image of the agency around the world while ensuring safe and effective imports to the US.

Those that have had the privilege of personally meeting David Pulham can attest to the wisdom of the FDA's decision. After his first 10 years at the FDA, Pulham was promoted to National Expert, a select group of inspectors that help establish FDA policies, train the other inspectors, and work with national regulatory organizations around the world to standardize compliance. It was as a National Expert that Pulham first came into contact with Switzerland.

«Right from the start, the Swiss were reassuring in their level of competence and motivation to «do the job right,» recalls Pulham. Unfortunately the industry was somewhat out of date with respect to FDA expectations. This resulted in a painful growing experience, but ultimately in Swiss regulations and compliance that are now aligned with the FDA's expectations.

A Caribbean adventure

Pulham has many stories from his 26 years with the FDA, but one of the most memorable adventures was being sent to Haiti in the mid 1990s by the US government. His job was to find out why almost 200 children - all under 6-years old - had mysteriously died in a short time.

«This was hard work, in a country that was horribly under-developed and had virtually no drug regulations,» describes Pulham. «Finally, we tracked down a local factory that was producing a deadly medication. There was hardly any infrastructure and we had to think fast - and creatively - to prevent even more deaths.»

Working closely with the Haitian government, Pulham used radio broadcasts and an informational campaign for the «foot doctors» across the whole country. The government was impressed with the efficient and knowledgeable way this American inspector managed a tragic situation, and asked Pulham to stay to help build an organization and processes similar to the FDA. He began intensive training of the government officials - but was called to the next FDA emergency before he could complete the project himself.

Pulham continued to derive great satisfaction from his work; especially when he would see companies readily implement needed solutions to critical issues in his inspection: «For many smaller companies these were

often costly measures. Despite even tough inspections, many companies would welcome me back any time as they recognized the value of the inspection observations in raising the quality assurance level of their products.»

Career change

After almost three decades with the FDA, Pulham decided to make the switch from government to industry. Was the change difficult?

«Not really difficult, but full of surprises,» laughs Pulham.

Being on the other side of the fence made him aware of the confusion that still reigns in the industry about the expectations of the FDA: «I have learned more about what FDA requires after I left FDA than during the 26 years with the FDA,» jokes Pulham.

However, once he began at Siegfried, he quickly set up detailed competency goals that give each department within the company a clear set of parameters to achieve the expected performance levels.

Pulham sees a positive - but clear - trend in the current development of the FDA and its regulatory efforts; «Today, the FDA increasingly expects drug companies to analyze their own risks on an ongoing basis, and to implement the corresponding solutions.»

This also means that it's a high-risk option for companies to wait passively until the FDA issues an official «Warning Letter». Being the target of an FDA complaint can compromise a company's reputation - and create a significant problem for its marketing department.

Staying on the move

When asked if he had any regrets looking back on his career, Pulham responds instantly: «That there are only 24 hours in a day!»

Those of us that have worked with David Pulham - and have experienced his boundless energy as he inoculates the Siegfried organization with a comprehensive understanding of «100% quality» - believe him immediately.

David C. Pulham was interviewed by Peter A. Gehler

Compliance Board

Siegfried's Compliance Board consists of the highest level of management within the organization. The Board is responsible to establish quality policies that are aligned with regulatory requirements as well as state-of-the-art practice throughout the Siegfried Group. Pulham's FDA background helps ensure that both these goals are met.



The Siegfried Symposium 2004

Process chemistry drives much of the chemical industry but receives fewer than its shares of highlights. Siegfried in collaboration with Prof. Jay Siegel at the Organic Chemistry Institute at the University of Zürich has invited high level speakers for a symposium to be held at the University Campus on October 14, 2004. Representatives of the world's leading pharma companies will present various case studies of important methods in process development.

Final invitation to this symposium will be sent out in June 2004. Please also reserve October 15th for a customer day at Siegfried in Zofingen, Switzerland. If you are interested in receiving more detailed information on this free symposium, contact

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The Siegfried Medal

The University of Zürich is accepting nominations for the **2004 Siegfried Medal** Award in Chemical Methods, which impact Process Chemistry. This distinguished award has been established at the University of Zürich by Siegfried Ltd of Zofingen, Switzerland to recognize original research in chemical processes, carried out in academic and/or industrial laboratories and influencing the way process chemistry is conducted. The medal will be awarded biannually and consists of a **gold medal** and an honorarium of **10'000 CHF**. The award will be presented at the **Siegfried Symposium** scheduled for **October 14, 2004 at the University of Zürich**. The selected winner will get the opportunity to present his results. A full description of the Siegfried symposium can be found at **www.oci.unizh.ch/zurichem** and **www.siegfried.ch**.

Content



Milling/blending, key steps in modern API manufacturing
Hans Rudolf Schlatter, Ph.D.
Project Manager



A day in the life of
David C. Pulham, Ph.D.
Chairman of the Siegfried Compliance Board



First Siegfried Medal, Symposium in conjunction with the University of Zürich
Prof. Jay Siegel

Milling and blending - Key Steps in Modern API Manufacturing

Our new milling/blending plant (Building 631) went into operation in March 2004 at the Siegfried headquarters in Zofingen, Switzerland.

Pharmaceutical companies need to package their active ingredients (APIs) in administrable forms such as tablets, capsules, coated pills, etc. To make the packaging step run smoothly and reproducibly, the dried active ingredients (cf newsletter 1/04) need to meet customer-specified particle size distribution, homogenously throughout an entire batch of up to several hundred kilograms. To meet these criteria consistently APIs are routinely milled or sieved, then thoroughly blended.

This is a most exacting process step, given the rigorous compliance and safety regulations concerning contamination and cross-contamination of active ingredients, plus personnel safety and protection. The same equipment may be milling and blending different products from one day to the next, so flexibility and cleaning are of crucial importance.

Let's take a look at how those challenges are addressed, using the example of Siegfried's state-of-the-art milling/blending plant that opened in March 2004 in Zofingen, Switzerland.

Design

The new plant uses closed circuit operation with a stringent control of dust escape. Thus external contamination, or cross-contamination is prevented effectively.

Moreover, the plans called for a pair of multi-product installations (milling lines) including a charge unit, feed hopper, doser, blender, and discharge/filling section (see diagram), that would also be reasonably easy to clean.

One of the lines is designed for free-flowing products, so it can dispense with agitators in the hopper and the blender. The second, higher-capacity line is also capable of handling products of high density and reduced flowability, a product property that calls for forced conveyor systems at the feed hopper and blender. Various mills or sieves can be inserted in either one of the milling lines for maximum flexibility in processing the 60-plus active ingredients that Siegfried produces. With required particle sizes mainly in the low- μ to 200 μ range, the plant is equipped with a battery of milling systems: impact mills, universal mills, and/or sieves.

Floor diagram

The 5th floor of the factory building (not shown) houses the plant infrastructure: ventilation and cooling installations, air conditioning (humidity, temperature) and air filtering, mill exhaust air extractors, and the hot water supply.

Dry APIs are fed into the bulk container on the 4th floor: drum tilting / docking device for the sealed entry through the grinder and into the feed hopper.

The 3rd floor houses the hopper discharge equipment: a delumper and double helix dosing system.

The 2nd floor contains the heart of the train: a mill or sieve that can be connected via flexible piping to the system above and the blenders below. Monitoring of the milling/screening process is possible through manual in-process control sampling.

The 1st floor contains the blenders, a 2'000 l rotating container blender, dockable with double lids, or a permanently installed 4'000 l conical screw blender.

The ground floor is where the discharged product is automatically filled into customer specified packaging, using a closed system with an inliner and a continuous bag.

Automatic closed-circuit sample withdrawal for final product analysis.

Avoiding contamination

Technical measures like drum tilting/docking device and low-contamination split (butterfly) valves (Buck® valve) with dust extractors allow straightforward operation of the plant while minimizing powder contamination. The substance being processed is confined within a closed system at all times; sample extraction points are also designed to discharge a quantity of sample material while maintaining closed-circuit conditions.

Product discharge and filling uses a continuous bag system, which again minimizes the escape of dust. Critical zones are in a controlled environment, under defined air pressure, temperature and humidity. Access is strictly via separate personnel and material airlocks, while clear, simple hygiene and clothing rules afford maximum protection for the product and plant personnel alike.

Plant cleaning

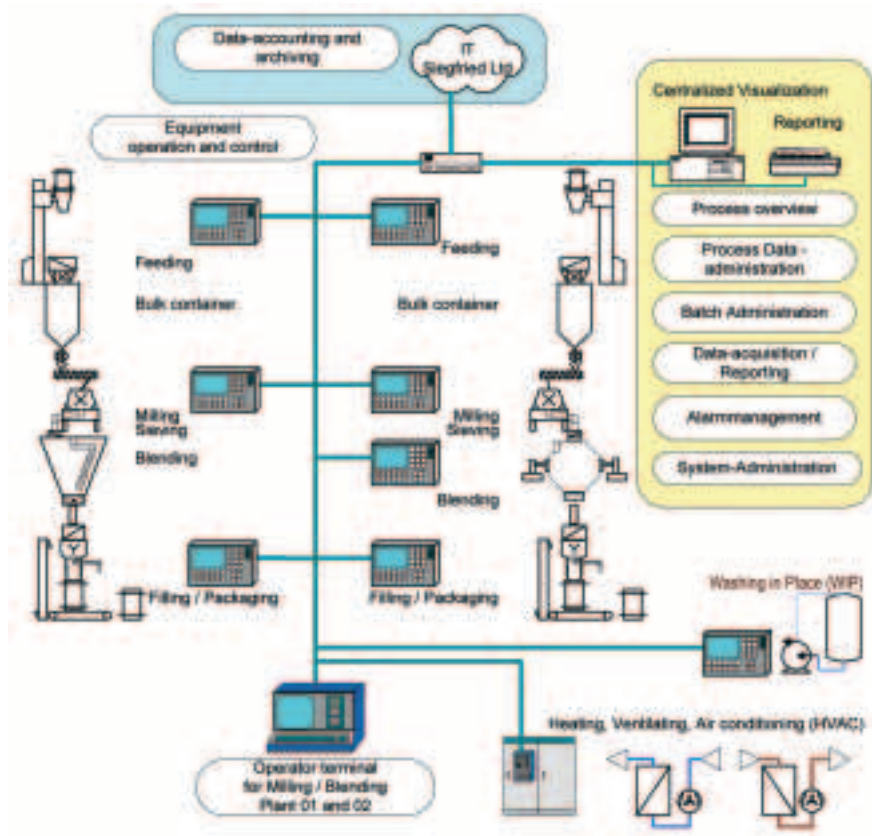
Plant cleaning uses a simple WIP (washing in place) system. During the cleaning cycle, cleaning agent - usually purified water or a purified ethanol/water mix - is distributed under pressure to a network of fixed washing nozzles. Blind spots are largely avoided by careful placement of the nozzles, allowing for a thorough cleaning of most of the equipment. Pressure washer guns are used to clean larger vessels. Manual cleaning tasks are limited to just a few small parts like lids, split valves, sieves, mill rotors, and certain items in the discharge/filling section. At the end of the cleaning cycle the equipment is dried in a stream of air and nitrogen.

Safety

Fast-running mills and airborne fine powder present a potentially dangerous combination, with a significant risk of dust explosions. It was therefore decided to run the milling trains under a completely inert (nitrogen) atmosphere. The trains are only allowed to operate at oxygen concentrations below 6%, a figure that is easily achieved by flushing with nitrogen. Exclusion of Oxygen is achieved by following an inertisation protocol. As a side benefit the inert atmosphere also affords effective product safety. Moreover, the plant incorporates extensive anti-explosion fea-

Automation

The two milling and blending trains are automated for efficient, reproducible processing. Certain third-party units like the drum tilting device, container blenders, and discharge/filling equipment have their own Siemens S7-300 PLC controllers. A server with two workstations sets up and manages milling jobs, provides central operating controls, logs alarms, visualizes plant operation using WinCC, and maintains a short-term operational data archive. A facility-wide long-term archiving system (PharmaRapid) is set to go into operation within the year.



Technical specifications

Building:	Height	25.21 m
	Plan area	10 m x 20 m
	Total area	1'400 m ²
	Volume	6'000 m ³
Clean room areas:	Level 3	272 m ²
	Level 2	158 m ²
Ventilation:	Air volume	20'000 m ³ / h fresh air
	Air renewal	10 - 15x / h
	Temperature	21 - 26°C
	Humidity	40 - 60%
	Pressure differentials	10 - 20 Pa
Processing equipment:	Milling line 1	2'000 l with container blender
	Milling line 2	4'000 l with conical screw blender

Processing equipment in detail:

Conical Screw Blender	
Mills	Frewitt impact mill Bauermeister universal mill
Sieve	Allgaier ultrasonic rolling sieve Sieve, agitated
Drum Tipping Device for 200 l vessels	
Delumper	
Double helix dosing system	
Continuous bag filling system	
WIP system (washing in place) with spray nozzles	
WinCC process management system, local SPS Operational data archiving	

tures (e.g. electrical installations to EX standards, electrically conductive floors, antistatic grounding cables) to further reduce the safety hazard in the event of dust contamination or a solvent leak.

Plant construction

From design to qualification it took 18 months to complete the 25 meter tall factory including its HVAC (heating, ventilation and air-conditioning) infrastructure and automated processing technology.

The zone concept defined in the master plan made it possible to limit the areas necessitating a class 100'000-controlled atmosphere. Such energy intensive air handling is only required in the plant feed area where containers are loaded and unloaded, for the sampling points at the point of milling, and for the packaging area for the discharged milled and blended product.

The interior of the building is designed for efficiency and for full compliance with cGMP regulations. Controlled zones and airlocks are state-of-the-art; anodized aluminium clean room walls and false ceilings, separation walls to shroud technical infrastructure and pipe work. The conductive Pharma Terrazzo floors and controlled air circulation guarantee easy cleaning and a state-of-the-art hygiene level.

A central air conditioning plant provides a 10–15x air renewal rate throughout the building, with guaranteed air temperature and relative humidity of 21°–26°C and 40–60% respectively. Critical zones, ante-rooms and airlocks are isolated by pressure differentials of 15 Pa.

Putting the plant into service

The plant was planned, built and put into service in accordance with a master validation plan, as outlined by applicable GMP guidelines (i.e. Q7A §12.3, PIC/S PI 006-1 §5). IQ, OQ, and PQ were largely concluded after 4 months. In parallel with the qualification process the plant's future operators were trained. Next, each product's optimal milling parameters were determined, and the corresponding process and plant cleaning cycles validated. Only then could commercial operation get underway.

This milling, blending and packaging plant for active pharmaceutical ingredients was a specific investment for meeting high-end cGMP requirements. The internal compliance organization, our customers and government inspectors all keep a diligent watch over the handling of purified active ingredients. This is an area where close cooperation is just as essential as technical expertise in milling, blending and powder handling.

Product and personnel safety

- Closed-circuit plant
- Low-dust product feed
- Low-dust sampling
- Low-dust product packaging
- Inert nitrogen atmosphere inside plant equipment
- Closed-circuit plant cleaning using water and ethanol (Working in Place)
- Separate air-locks for materials and personnel
- Air conditioning with controlled air volume, pressure, temperature and humidity
- Personnel hygiene rules
- Fire alarm and sprinkler system
- Product safety tests

Blender in rotation between «split butterfly valves» (Buck®-type)



Packaging unit with automatic weight control and continuous bag system



Centerpiece of Mill