

«The woman in a man's world»

At the age of 16, Margret Baumann was deciding on a profession. Her parents and her teachers told her to think about college. As she would do throughout her career, she listened to her own instincts and ignored their advice, choosing instead something in the broad field of natural science – as a chemical laboratory apprentice at Siegfried. It was a job that spoke to both Margret's «head and hands».



After completing her apprenticeship she continued her education at a technical university. Focusing on actinide chemistry, Margret then took on a whole new challenge. She entered the renowned Paul Scherrer Institute (PSI) in Würenlingen, Switzerland – a global leader in nuclear research – where she stayed for eight years.



During this time, she also became a teacher, teaching future chemical lab assistants in Aarau. There she met Roland Schürmann, Director of Chemical Production at Siegfried. When Roland invited her to visit the Siegfried facility in Zofingen, she was instantly fascinated with the world of chemical mass production. Without a second thought, she accepted Roland's ensuing offer to manage the TCB production line in Zofingen.

The TCB line – a multi-purpose facility specialized in hydrogenation and comprised of three autoclaves – requires considerable «hands-on» skills. Running the line was demanding and Margret enjoyed the challenge, as well as working with the foremen and shift supervisors, staying in contact with the line personnel, and solving new problems every day. But product launches are what make her eyes light up. Often Margret could be found on the line in the middle of the night, working together with her team to get the processes running successfully. Another challenge was ramping up new systems, such as a state-of-the-art computer-controlled spherical dryer. The department's move to SAP to standardize all processes – and explain the necessity of the resulting fundamental changes to the team – also set high demands for the TCB manager.

«People are creatures of habit. They don't like changes in the way they work,» she adds with a smile. «But the introduction of SAP was a big step forward for Siegfried.»

Today, Margret Baumann is Deputy Director of Chemical Production, a department with more than 140 people. While she remains close to the processes and the line, her contact to the operators and their supervisors is less frequent. «I no longer do the performance reviews with my people,» she explains with a hint of regret. «However, the problems one is confronted with at this level are very exciting.»

But what does Margret Baumann do when she's not optimizing processes at Siegfried? At home in the picturesque village of Lenzburg, she spends as much time as possible with her 5-year-old daughter. Margret also loves the outdoors – skiing and especially, riding on her Harley Davidson.

On another level, twice a month Margret Baumann is a member of the «Swiss Federal Nuclear Safety Commission» to advise the Swiss Government – an important public duty. «Here I am confronted with situations that combine technology, security, and politics. It's extraordinary,» she explains.

Marget Baumann is used to taking on responsibility quickly and easily, even in a male-dominated environment. She is eminently capable of taking charge and knows what she wants to accomplish – without ever being rude, but determined to succeed. It's obvious that manufacturing has remained her passion.

Margret Baumann was interviewed by Peter A. Gehler

Winner of Siegfried Medal

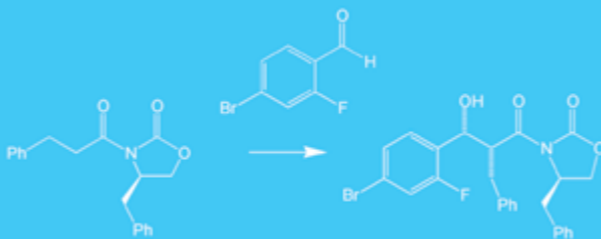
The University of Zurich and Siegfried Ltd are happy to announce that Dr. Joel Hawkins of Pfizer Inc will receive the 2004 Siegfried Medal for his achievements in process chemistry. Key to the selection of Dr. Hawkins are the many facets of chemistry displayed in his approach to addressing problems in process development: 1) Development of new synthetic methodologies; 2) Physical organic evaluation of reaction mechanisms; 3) Automation of process optimization; and 4) Phase targeted route optimization.

Dr. Hawkins' work is exemplified by the remarkably efficient synthesis of **CP-195,543**, a major new therapeutic agent in the LTB4 area. Central to the success of the process was Hawkins' creative implementation of Aldol and Pd-catalyzed C-C bond forming chemistry, guided by his deep understanding of the physical organic chemistry and mechanistic aspects of chemical reactivity. The early adoption of automated computerized instrumentation linked to data-base information technology greatly enhanced his productivity. Such automation allowed systematic monitoring of every process stage and ultimately helped to illuminate the path to success.

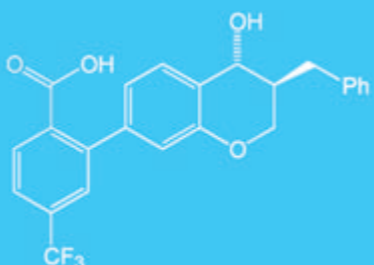
In addition to displaying an elegant fusion of creativity, analytical insight and technical accomplishment, the final optimized synthesis circumvented several dangerous procedures and reduced the use of hazardous chemicals, making for a safer, more environmentally friendly process.

The Siegfried Medal was established to highlight just this kind of multifaceted, scholarly and socially sound approach to chemical research. Dr. Hawkins represents the kind of world-class researcher needed to sustain progress in the field, and he is an exemplary role model for young scientists looking for challenges in chemistry that have immediate and direct impact on society. The gold medallion and a 10,000 CHF prize will be conveyed during the Siegfried Symposium on October 14th at the University of Zurich.

For the synthesis of CP-195,543 Joel Hawkins used newly devised titanium Aldol conditions. It gave him a yield of 94% with 98% of the desired diastereomer:



This new method was used to synthesize Pfizer's CP-195,543 compound lead, which is an LTB4 receptor antagonist for inflammatory diseases:



Max Widmer, Ph. D.
General Manager Siegfried Actives

Highlights

Dr. Max Widmer took over the responsibility for Siegfried Actives in May 2004

Max Widmer has been with Siegfried for 25 years and was manager of the global supply chain before he became general manager of the business unit Siegfried Actives. «I am very honoured to have been given this responsibility» says Max Widmer. «My focus will be on improving efficiency in our two production sites in Zofingen, Switzerland and Pennsville, USA. This will be achieved while at the same time increasing our flexibility to yet increase our focus on our customers and to be able to provide custom designed solutions.»

Dr. Axel Müller joined Siegfried as General Manager of Siegfried Generics in April 2004

«It is very exciting for me to work for the pharmaceutical service company that possesses both, chemical as well as formulation capabilities», says Axel Müller. Siegfried is well known for its high quality dossiers and a very reliable supply chain with integrated solid dosage form development and manufacturing capacity.



Axel Müller, Ph. D.
General Manager Siegfried Generics

China Purchasing office in Shanghai

Siegfried started a sourcing office as part of its China operations in mid 2004. «It is our intent to actively source raw materials and advanced intermediates from selected partners in Asia», says Douglas Günthard, CEO of Siegfried Ltd. «We believe that establishing an area of excellence in sourcing raw materials as well as intermediates from the far east will support our continued drive to provide the optimal, most cost effective supply chain solution to our customers world wide. It is therefore with great pleasure that we announce that Ko-Lin Feng has joined Siegfried to start up and head our China office in mid 2004»



Ko-Lin Feng
China Purchase Office Shanghai

Highlights

Symposium and Siegfried Medal at the University of Zurich

«We are thrilled to announce that Joel M. Hawkins from Pfizer was selected by our international jury as the winner of the first Siegfried Medal for his outstanding work in practical process chemistry. And we are excited that Dr. Hawkins will be joined by other top speakers from industry and academia in Zurich on October 14th, 2004 for a class leading Symposium», says Bernhard Küenburg, Head Marketing & Development at Siegfried. Registration and information: www.siegfried.ch Find more details on page 6.

Editorial



Outsourcing of API's – Where is the path leading to?

Over the past few years I have come across an increasing number of articles bemoaning the state of the pharmaceutical custom manufacturing industry. It feels like you can't open a trade journal without finding articles on the overcapacity within the industry and news about custom manufacturing companies downsizing or restructuring. Yet it is only a few years ago (end 1999 beginning 2000) that industry analysts predicted double-digit revenue growth for the foreseeable future! So what happened? Is it a passing industry malaise, caused by the unusual low number of approvals of NCEs since 2000? Or, is the path to outsourcing pharmaceutical active ingredients (APIs) no longer leading to the US and Europe but to Asia? We believe that it is a combination of the above. Clearly the cGMP custom manufacturing industry of tomorrow will look decidedly different than it does today. However, there will remain an attractive space for manufacturers of APIs in the western hemisphere for the following reasons. **First:** compliance is still a major issue and with an excellent compliance philosophy and a team of senior compliance experts we can build a basis for competitiveness in this business. I am, therefore particularly happy to feature an article by Dr. Peter Kiechle, chief compliance officer of Siegfried Ltd about “changing of equipment in validated processes” in this newsletter. **Secondly** instead of fighting the emerging Asian markets we need to integrate low cost manufacturing in our overall service concept. If we continue to produce all intermediates only out of western platforms, it is likely that we will have trouble staying competitive. In

that spirit I am happy to announce the opening of the Siegfried sourcing office in Shanghai. **Thirdly** we see a switch from the pure outsourcing model to a more sophisticated partnering model, especially for APIs and late stage intermediates. With all the time and money involved to get a new drug registered, pharma companies become reluctant to have a strict vendor relationship, there is simply too much at stake to stay distanced. Supply interruption due to technical issues or compliance issues are very costly. As a consequence more and more energy is put into supplier qualification. Diligent supplier qualification, however, does not make a project successful: it is the experience of working together and personal relationship from the management through to the scientists that ensures speedy communications and successful project handling. This cannot be achieved at an arms length. **And fourth,** you need skills, innovation, and science. Without top-level experts a supplier will have a hard time explaining its value to a customer. Therefore we are more than happy to again emphasize the Symposium for “Innovation in Process Chemistry” and the Siegfried Medal on October 14th at the University of Zurich in collaboration with Prof. Jay Siegel. Enjoy the September newsletter and join us in thinking about attractive business models for the future of the chemical pharmaceutical industry in the western world.

Bernhard Küenburg
Senior Vice President Sales & Development

Content



Winner of the first Siegfried Medal
Joel M. Hawkins, Ph. D.



Never change a winning team/train
Peter Kiechle, Ph. D.



A life in the day of
Margret Baumann, Deputy Director of Chemical Production

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Never Change a Winning Team/Train!

Changing trains* in validated process steps

In the GMP environment of producing Active Pharmaceutical Ingredients (APIs) we all know that - beside all chemical know-how and other important pieces - commercial production is possible only if the following requirements are fulfilled:

1. **the train, in which the process step is being produced, has to be qualified** and
2. **the process step has to be validated in the qualified train**

By that, we ensure that the material is reliably produced in adequate quality. The material has the same quality day-by-day, kg-by-kg and ton-by-ton.

For **monoplants** which are dedicated to only one product this may be cumbersome and may need a lot of planning and preparation. But if it is finally and successfully finished, it satisfies the GMP requirements for several years as long as no major changes of the equipment or the process are made.

On the other hand, Siegfried Ltd as a midsize contract manufacturer of Active Pharmaceutical Ingredients (API's) and key intermediates, has only few products, which have the volume to utilize and fill **monoplants** year-round. Therefore, we are widely using **multipurpose trains** for different compounds. That said, it might be very well possible that a train, where a particular process step has been successfully validated, is not available for use at the needed time since it is occupied by a different compound. This means that we have to move to a different train, i.e. we have to 'change the winning team/train'.

*A train is a group of immobile reactors, equipment, instruments, and devices which build a 'family' for a certain step in production.

What does it mean in terms of the validity of our process step? At first glance, it could mean that the process has to be validated on the new train from scratch again. But are there also different approaches like cross validation possible? Do we always have to revalidate when changing a train? Guidelines don't give clear answers. They just state, that the process has to be validated before a material can be sold as commercially.

Siegfried's approach is to decide and work along **three different scenarios**:

1. The new train is **equal** to the originally qualified train (keyword: like-to-like changes).
2. The train **is not equal, but the difference between the originally qualified train and the new train is not relevant for the particular process step under discussion.**
3. The new train is **significantly different** form the originally qualified train.

But what is equal and what is different? The responsible persons from chemical production might see it differently in comparison to the responsible in the quality department. Therefore, a clear set of criteria is needed to judge it on a solid basis. At Siegfried Ltd the following elements have to be considered, when making this decision:

- Reactor type (material, condensors, pipes, coolers etc.)
- Reactor volume, operating pressure/vacuum
- Agitator type
- Heating/cooling system
- Charging system
- Others; Filters, hoses, receivers etc.

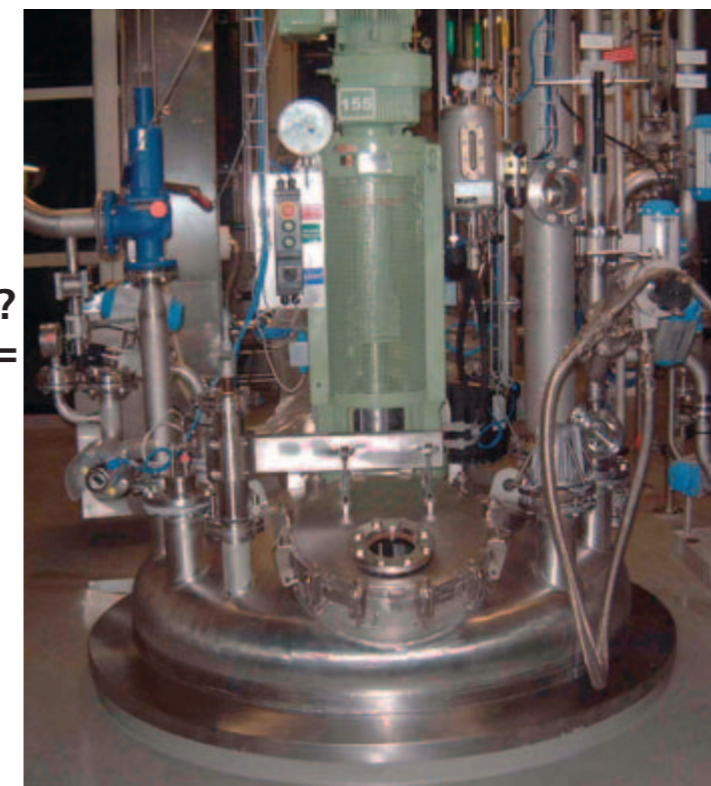
Scenario 1

The new train is equal to the originally qualified train (keyword: like-to-like changes): If the above mentioned criteria are fulfilled, different trains are considered as equal, the manufacturing process can be considered as validated on the new train.

Scenario 2

The train is not equal, but the difference between the originally qualified train and the new train is not relevant for the particular process step under discussion: If the above mentioned criteria are not met, i.e. the trains are 'somehow' different, an assessment of these differences with respect to the specific process step has to be made. Discussing and documenting whether the existing differences between the originally qualified train and the new one may cause a different quality or are not likely to influence the process step is a Risk Assessment, which needs the know-how from the chemists, the engineers, the physical chemists, the physicist (if applicable) and the validation experts of the Quality unit. This team evaluates the impact of the technical differences. Technical trials may be necessary to clearly judge the relevance of the differences. In case of a judgment that there are technical differences but that they are **not significant for the particular process step**, the validity of the process step at the new train is not automatically granted. Validation has to be conducted as a cross validation against the quality of the material produced in the original train. What does this mean? The process step will be performed at the new train and the quality of the resulting intermediate is analyzed and compared with the quality of the original set-up. In addition, the intermediate from the new train will be held separately and synthesized through to the final product. There again, the quality will be compared with the originally validated quality. In the case of equivalent quality, the process step on the new train is considered as validated.

If not equivalent, investigation of the root cause is necessary.



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Scenario 3

The new train is significantly different form the originally qualified train: The third and most easy scenario to judge is the use of a new train, which is clearly different compared to the originally used one. In those cases a **validation from scratch is unavoidable.**

The discussion of the different scenarios clearly shows that changing a train in most cases costs time in evaluating it's impact (Risk Assessment) and even more time in cross validating (scenario 2) or full new validation (scenario 3) on the new train. In addition, it needs careful planning of the available resources.

Further more, other arguments have to be taken into consideration:

- Is the original train mentioned in the registration documents?
If yes, using a new train requires at least notification of the regulatory bodies if not a prior approval.
- Is the original train fixed by contract with the customer(s)?
Does a Quality Agreement state something special about changes of trains?
If yes, an agreement with the customer(s) prior to this change is needed.

Summary: Changing trains in a GMP environment needs careful scientific and technical consideration prior to the change. The equivalency of the trains and the impact of the differences between trains determine the scenario, which has to be applied. Also the filed process and the requirements by the customers set narrow boundaries for changing trains. Therefore, the best is to 'Never Change a Winning Train', but the real world of a contract manufacturer like Siegfried Ltd is different and it is therefore essential to deal with necessary changes in a smart way to serve the customer with an adequate price at adequate GMPs.

Peter Kiechle, Ph.D.
Head Compliance Officer

Siegfried

Flowchart for Process Validation in Case of Changing Trains:

