

# the scenes

# behind

Newsletter Issue 1/06

## Highlights

### Hubert Stückler speaker at Conference in Kyoto Japan regarding latest GMP situation

The 12th Kyoto Conference on 16th February in Japan was very successful being attended by most Japanese pharmaceutical companies, API manufacturers and engineering companies (about 80 companies and 120 people).

Since a revised Japanese Pharmaceutical Affairs Law has been in effect since April 2005, the companies are hurrying to respond to the change promptly. At the conference, presentations were given such as introduction and future trend of ICH Q8 and Q9, methods for preventing the cross-contamination of high potency compounds and general drugs, isolator as barrier for chemical hazard, and update on current FDA thinking.

Hubert Stückler, President Siegfried Actives, gave a lecture regarding introduction of Siegfried's capabilities such as custom manufacturing for APIs and intermediates under cGMP, the chemical development building featuring cGMP wall to separate the operator's room from the technical installations and «the containment system for closed handling of class 3 compounds». The closed handling system impressed the audience, especially engineering companies.

This Conference is held annually in February by The Society of Chemical Engineers, Japan, Kansai Branch.

## Editorial



### Dear business friends and colleagues,

2006 is underway and we are set to take charge of its challenges and opportunities. Key to these efforts is our open and frank partnership. My colleagues at Siegfried and I would like to thank you for the excellent collaboration between our companies.

As noted in our annual report, the positive growth trend at Siegfried continues and, as you have seen in recent reports,

the consolidation of our industry is accelerating. Many companies have announced facility closings or divestments to focus on core competencies. Since «custom synthesis» is our core business, the ongoing consolidation in the market presents us with opportunities to further strengthen our market position. Our strategic focus provides convincing evidence of the additional benefits of working with Siegfried.

One of the highlights in this issue of our newsletter is winning the Cephalon «Supplier Award». This partnership clearly profiles how customers profit from our combination of API development and production with galenics development and production – all in one location. It also outlines how we can offer development of chemical and galenics processes, together with joint project management and a harmonized quality and regulatory system. An increasing number of our key accounts is interested in this combined service.

In our lead article, «GMPs – an FDA Investigator's Perspective», David C. Pulham, Ph.D. reports on the history, importance and use of GMP. For many years, David Pulham worked at the FDA as an international expert and global trainer for government health agency audits. In 2000, he joined Siegfried as our Compliance Officer and four years later he became the Chairman of the Compliance Board. Our clients greatly appreciate his expertise and advice.

Last but not least, I would like to remind you of the upcoming «Siegfried Symposium» to be held on September 21, 2006 at the University of Zurich.

My best wishes for a continued and successful partnership in 2006!

Sincerely yours,

Hubert Stückler  
Executive Vice President  
Siegfried Actives

## Content



### GMPs

The Perspective of  
David C. Pulham, Ph.D.,  
Chairman of the  
Siegfried Compliance  
Board



### Cephalon Award

Patricia Maxwell, Sales  
& Business Development  
Manager, and Paul  
Zeman, Ph.D., Head  
Pharma Exclusives



### A day in the life of

Tim  
Goodman,  
Site Manager  
Pennsville  
USA



# GMPs – An FDA Investigator’s Perspective



**David Pulham, Ph.D.,**  
Chairman of the Siegfried  
Compliance Board, was an  
FDA investigator for 25 years  
and a National Expert  
Investigator the last 15.

## 1. Introduction

Good Manufacturing Practice (GMP) regulations are a legal codification of sound quality principles that have been used by the pharmaceutical and healthcare manufacturing industries for over 30 years as a means of assuring that products have the identity, strength, purity and quality that they purport to contain. GMPs are in effect in over 100 countries, and GMP compliance a pre-requisite to exporting pharmaceuticals between countries.

Compliance with GMPs is critical to the success of a pharmaceutical company, both from a business and a regulatory perspective. In today's global environment, this frequently means adhering to worldwide GMPs that vary slightly from region to region. The focus of this article is US FDA GMPs, however the principles are applicable to all regions.

While compliance with GMPs is critical, it is virtually impossible to achieve without a thorough understanding of the origin and intent of the requirements. GMPs as defined in US regulations 21CFR210.1 are "minimum current GMPs." FDA stated in 1976 when the present version of GMPs was drafted, that the regulations are 'dynamic' and expected to evolve with new technologies and concepts. Thus, GMPs are referred to as 'umbrella' or 'current GMPs' (cGMPs). Since they apply to a myriad of systems and processes, they are broad in nature and subject to interpretation. The vagaries of the GMPs have been frustrating to industry and to FDA Investigators, as any interpretation is subject to question and criticism. Guidelines add clarity, however judgment is still required to tailor GMPs to a particular situation if they are to be applied appropriately.

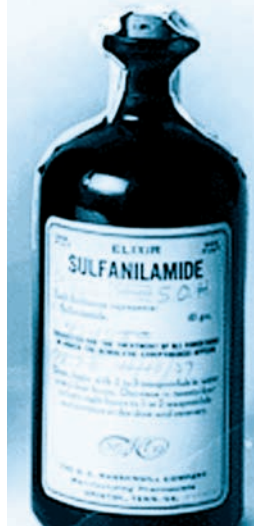
Only if the origin, intent and evolution of GMPs are understood, can they be correctly interpreted and applied and an appropriate level of compliance established and systems implemented to facilitate and monitor compliance. This approach results in a value-adding, compliant quality system so critical to the safety and efficacy of the product and to the company's success.

## 2. Origin

GMPs are based on altruistic, truly catastrophic events. Sulfanilamide, a synthetic antibacterial drug used to treat streptococcal infections was praised in the 1930s as the first drug to successfully treat bacterial infections. It was manufactured as tablets and as a parenteral, injectable product while companies struggled to liquefy the product so it could be marketed for children and patients who preferred medication in liquid form. In 1937 it was discovered that diethylene glycol (DEG) could be used as a dissolving agent for sulfanilamide. The resulting 'Elixir Sulfanilamide' with raspberry flavoring was marketed primarily for children. Unfortunately neither DEG, a deadly toxic chemical cousin of antifreeze, nor Elixir Sulfanilamide was tested for safety before 600 bottles were shipped to pharmacies and 700 to physician offices. "Elixir Sulfanilamide was essentially slapped together without a thought to testing, without a thought to assessing its toxicity, or certainly without a thought to even looking into the literature to see what you were putting into the product," said Food and Drug Administration (FDA) historian John Swann. Within days, many patients who were taking the medication became gravely ill and several died of kidney failure.

Another catastrophic event leading to the initiation of cGMPs occurred in December 1940 when sulfathiazole tablets contaminated with phenobarbital were distributed causing hundreds of deaths and injuries. FDA's investigation into sulfathiazole production, and the Agency's efforts to retrieve the drug from the market, disclosed numerous control deficiencies in the plant and serious irregularities in the firm's recall attempt. The incident prompted FDA to require detailed controls in sulfathiazole production and throughout the industry, an approach that became the basis

## Sulfanilamide



Sulfanilamide and its derivative sulfa drugs are bacteriostatic, gaining their effectiveness by interfering with the enzymatic systems of bacteria and inhibiting their ability to grow or multiply. Due to the capacity of some bacteria to adapt in such a way that makes them resistant to this bacteriostatic action, a tremendous number of the sulfa drugs that originally appeared to be effective, no longer exhibit antibacterial action.





for production control standards for all pharmaceuticals.

Finally, an incident in the 1950s and '60s occurred that further reinforced FDA's growing concern over inadequate control in pharmaceutical manufacturing. Pregnant women used the drug thalidomide to treat morning sickness. Before scientists discovered the teratogenic danger of thalidomide, as many as 12,000 children outside the US were born deformed, some with missing arms or legs. The FDA won praise for keeping the drug out of the United States and on August 7, 1962 a grateful President John F. Kennedy awarded the Distinguished Federal Civil Service Award to FDA's Dr. Kelsey for her leadership in this issue. The thalidomide tragedy led to increasing FDA authority to regulate drugs.

The Nation's reaction was emotional. "To realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that that medicine which I had used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm: well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive. I have known hours when death for me would be a welcome relief from this agony." (Letter by Dr. A.S. Calhoun, October 22, 1937).

Out of these and other catastrophic events evolved FDA regulations and GMPs. The initial intent was to ensure the safety and efficacy of the nation's drug supply. GMPs focused on the control of critical operations and critical parameters based on scientifically sound principles and best industry practices. Controlling critical raw materials, qualifying critical equipment and validating critical analytical methods and processes were the original focus. For example, aseptic filling operations for small volume parenterals required validation because sterility could not otherwise be assured and terminal sterilization was not possible. These were widely recognized to be sound good business practices resulting in reliable, reproducible product quality.

### 3. Evolution

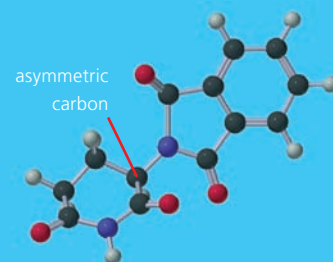
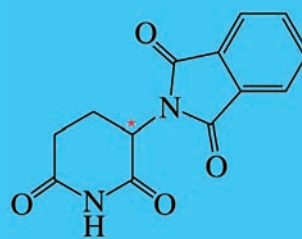
From this focused beginning, GMPs evolved considerably. Validation of critical aseptic filling operations has been extrapolated to validation of manufacturing processes for non-critical excipients for active pharmaceutical ingredients (APIs). From validation of complex computerized systems controlling complex API crystallization profiles, to validating hand calculators and wall clocks used to measure mixing times against a specification of 5-20 minutes. From validating mixing parameters of suspensions during filling of syringes to ensure uniformity, to validating mixing times of true aqueous solutions in bulk. From validating cleaning procedures for steroids and potent chemicals in tortuous transfer lines, to validating smooth, flat, 4-inch spatulas used to sample inorganic non-critical raw materials.

Good Manufacturing Practices have grown not only in pharmaceutical manufacturing, they have also been transferred to Good Laboratory Practices, Good Clinical Practices, Good Engineering Practices, Good Documentation Practices, and ...GxPs.

GMPs evolved from their original intent for many reasons; some are justified and value-adding. A major contributing factor continues to be defective distributed product. For example eye drops with caustic acid causing severe injury in the 1970's. A company with 60% of a batch of topical ointment returned as defective, yet not recalling the remaining 40% in the 1980's. A company rewriting sterility reports for small volume parenteral batches that failed as passing and shipping the product in the 1980's. An infant cough syrup tainted with up to 30% diethylene glycol in the 1990's, and a young teenager deprived of life by contaminated LVPs and SVPs in a hospital in California in the 1990's. Beyond these personal experiences, the infamous Generic Drug Scandal of the 1980's heightened concern about FDA's control of the pharmaceutical industry in the past 3 decades.

Also contributing to the evolution of GMPs is a lack of understanding and misinterpretation of FDA requirements. FDA presenters at conferences and seminars

### Thalidomide



are construed by industry as presenting official FDA policy. Frequently these presenters offer their own opinion and interpretation of requirements. Similarly, industry interprets FDA-483 observations as the Agency's official position, although the Form clearly states 'This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance.' Because of these misinterpretations and misunderstandings, I state in jest, 'I have learned more about what FDA requires since I left FDA, than during 25 years teaching and enforcing GMPs as an FDA Investigator.'

In addition to irresponsible companies and misinterpretation of FDA presentations and FDA-483s, the FDA 'system' encourages expansion and elaboration of GMPs beyond their original intent. FDA's success and funding is based in part on the number of enforcement actions taken. Similarly, FDA Investigators are recognized and promoted based on the number of actions they initiate, e.g. Warning Letters, Seizures and Consent Decrees. This negative reinforcement encourages FDA to continuously search for new 'issues' and interpretations of the GMPs. Not only does this expand interpretation of the GMPs, it has an economic impact on the industry and ironically decreases FDA oversight of quality and compliance. Significant FDA regulatory actions frequently result in companies closing plants in the US, relying on their facilities outside the US, or contracting work to offshore suppliers. This results in decreased FDA oversight as non-US based firms are inspected less frequently and to a significantly less extent due to funding and time constraints. Therefore, FDA's attempt to closely regulate some firms and products actually results in significantly less control.

#### **4. Origin, Evolution and Intent**

Compliance with the intent of the GMPs is critical to the safety and efficacy of pharmaceuticals. GMPs require a review of the quality characteristics of each product annually based on a number of parameters and a re-evaluation of the controls and production process to identify ways to improve the process and monitor the product's quality. This has evolved in some cases to devoting hundreds of hours collating data annually into a professional presentation ready for auditors and investigators to review if desired. This is outside the original intent of the requirement. Rather, an in-depth review after each campaign should be performed so immediate action can be taken before the next campaign, adding value to the process and quality of the product. These post-campaign reviews can then be collated annually in one day and reviewed for annual trends.

Another example of applying the intent of the GMPs in a value-adding manner is to evaluate the equivalence of manufacturing equipment when a process is moved from one equipment train to another. Rather than merely re-validating the entire process on the new equipment, a scientific evaluation of the equivalence of the two trains may be performed adding value to the assessment.

Companies for years have calibrated all measurement instruments associated with a piece of equipment because they are there, rather than evaluating which parameters are critical to the operation and the associated instruments that require calibration. This was recently highlighted in FDA's Risk Based Approach to GMPs for the 21st Century that mandates a rigorous assessment of the equipment, and identification of critical parameters. Similarly, process validation should include critical parameters, not merely all parameters that can be measured although they add no value.

Another example of obscured GMP intent is to incorporate all raw material specifications from a given supplier into raw material acceptance criteria merely because they are provided. Later when changing suppliers and the second supplier does not monitor the same parameters, the question arises why the original parameter was incorporated in the specification. An assessment of the important parameters of the raw material should be made and only those parameters followed, not all parameters merely because they are available.

#### **5. Conclusion**

The intent of GMPs is critical to product quality, reproducibly and reliability. When GMPs are applied in a thoughtful manner, to control important processes and parameters, they add value and increase quality at reduced cost.

Cephalon handing over the award  
«Partner in Growth» to Siegfried.

From left to right:  
Nilay Vashi\*  
P. Zeman  
F. Gautschi  
H.-R. Schlatter  
T. Röhrich  
M. Späne  
D.C. Günthardt  
A. Gloor  
M. Pfänninger  
B. Grünenfelder  
Satya Bhamidipati\*  
H. Stückler  
\* Cephalon



## Highlights

### Cephalon awards Siegfried as «Partner in Growth»

Since 2003 Actives and Generics have worked successfully together to enable the US based company Cephalon to market a product both in EU and US. The three years of intensive collaboration were fruitful. As of November 29, 2005 Siegfried is an approved supplier of Gabitril tablets containing tiagabine as the active drug both in the United States and in Europe!

Cephalon, a US based mid-sized pharmaceutical company is one of the top 10 US biopharmaceutical companies. Gabitril was launched by Novo Nordisk in EU in 1996/1997 and by Abbott, a Novo Nordisk licensee, in the United States (US) in 1997 as adjunctive therapy in adults and children 12 years and older in treatment of partial seizures. Sanofi acquired the Gabitril license for rest of the world (EU) in 1997. Cephalon purchased the rights to Gabitril from Abbott for the US in 2000 and from Sanofi for the rest of the world in 2001/2002. Siegfried first manufactured tiagabine for Novo Nordisk in the early 1990's. Cephalon is evaluating potential uses of Gabitril for treatment of other indications.

After purchasing Gabitril and tiagabine marketing rights, Cephalon approached Siegfried to manufacture both the active drug ingredient and tablets for the European and US markets. Siegfried's prior experience with tiagabine was helpful in this decision. By mid-2003 Siegfried had secured supply agreements for the drug substance, tiagabine HCl as well as tablet manufacturing for Gabitril.

The first challenge was to get Siegfried approved as a Gabitril manufacturing site for EU using a formulation to match the US Gabitril. The next challenge was to get Siegfried approved as an alternate Gabitril manufacturing site for the US. There are four EU dosage strengths and seven US dosage strengths, each with a different color.

Concurrently, as tiagabine HCl had not been manufactured since mid 90's, the manufacturing process needed to be revalidated to meet current regulatory standards. The first challenge was to get these manufacturing changes approved in the EU followed by getting Siegfried approved as an alternate supplier of the drug substance in the US.

Communication between Siegfried and Cephalon, as well as between groups within Siegfried was a critical driver for success. Between 2002 and 2005 Cephalon has been experiencing a tremendous growth. When our discussions began Cephalon had 700 employees. Today less than 3 years later there are over 3,000. Nevertheless we have lived up to the motto «What does not kill me makes me stronger». Today our relationship is stronger than ever. In recognition of this, Cephalon awarded Siegfried a plaque that presents Siegfried and Cephalon as «Partner's in Growth». This is displayed in the Entry Hall of the Siegfried Main Building in Zofingen. The most «tangible» result of our common success is that Siegfried has been given the opportunity to bid for new Cephalon projects.

Though Gabitril is not the leader in the therapeutic category, Cephalon believes that there is a huge market for Gabitril in other conditions. Presently Cephalon is conducting clinical trials for generalized anxiety disorder (GAD), the results of which are expected in 2006. Filing for GAD in the US is slated for later in 2006.

Other business opportunities to maximize financial opportunities for both Cephalon and Siegfried are being considered and collaborated on.

Patricia Maxwell  
Sales & Business  
Development Manager

Paul Zeman, Ph.D.  
Head Pharma Exclusives

## Highlights

### Siegfried Group Reports Strong Second Half Year

Following a strong second half year, the Siegfried Group reports group sales of CHF 318.3 million for the 2005 financial year (2004: CHF 321.4 million). Accordingly, consolidated net profit jumped from CHF 16.4 million in 2004 to CHF 36.8 million. Operating profit for 2005 is reported at CHF 43.4 million, considerably above the CHF 33.4 million (before special items) last year.

While the Siegfried Group showed a sales decline of 14.8% for the first half year in 2005, lost ground was nearly recovered thanks to a strong performance during the second half year. The sales increase is due mainly to the Siegfried Division's core business with active pharmaceutical ingredients. At the end of the year, the sales decline amounted to only 0.9% when compared to the previous year and expressed in Swiss francs, or 1.1% when expressed in local currencies. Net profit more than doubled.

## Tim Goodman – a team player by conviction

Tim Goodman's professional career is closely connected with the production of active pharmaceutical ingredients. Today he manages Siegfried's Pennsville, New Jersey, plant. After completing a bachelor's degree in engineering, Tim joined the US Air Force as an officer for 9 years of military service. After several years of employment with Eastman Kodak, Tim helped build and validate an active pharmaceutical ingredients production and process development plant for Roche in the USA. He subsequently joined Siegfried's US team and was soon appointed general manager of the Pennsville plant.

Tim married his wife, Denise, 25 years ago, and the couple has three children, two of whom are already grown-up and have left the home. In his leisure time, Tim jogs long distances and sometimes participates in competitions (5 and 10 kilometers, half marathons and a marathon). He also enjoys playing golf – for a change and for relaxation.

Ask Tim about his most important task in the company, and he will soon mention the team. His management philosophy is based on teamwork and focuses on the team. When he talks, he rarely mentions individual persons. His absolute favorite task is to coach people, and accordingly, one sees him in the production plant often.

And you can sense that Tim trusts his people, and they trust him.

What Tim does not like is the feeling that his management team doesn't pull together at times, which will quickly result in lively discussions. And when asked about his most pleasant experience in the company, he mentions a story that happened only recently. In order to continue with a project that needed to be finished under great time pressure and not to disrupt the process, a team drove to work at midnight to implement a test and release the process as quickly as possible. Although a snow storm passed through New Jersey that night, the team still showed up. Tim's other experiences at work are all connected with dedication and commitment and with goals achieved.

Many of Tim Goodman's personal goals concern safety and environmental protection. His aim is to prevent industrial accidents by means of appropriate training and the right attitude. He is rightly proud, for instance, of the fact that Pennsville last year surpassed its quality and production targets.

Tim Goodman was interviewed by Peter A. Gehler.



Tim Goodman  
Site Manager Pennsville USA

**Siegfried**

when substance matters

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