

- ISPE – the International Society for Pharmaceutical Engineering
- Industry communities that include the Active Pharmaceutical Ingredients Committee (APIC), a sector group of the European Chemical Industry Council (CEFIC), and many others

To recognize, interpret and implement these requirements demands a good deal of effort, but open and trusting partnerships, such as between you and Siegfried, deliver tangible advantages to the client.

Spotting trends

Currently, “shared audits” – where the audit report of a custom manufacturer is done by a neutral certified auditor and evaluated by different clients – are scheduled to help reduce the overall number of audits. The Active Pharmaceutical Ingredients Committee (APIC) and other private auditors offer such services. While shared audits are often a good idea, confidentiality remains a central issue. A client might need special topics audited for a specific purposes/product, but also wants to keep this information confidential.

Hosting numerous audits and inspections every year helps us spot early regulatory trends. For instance, the FDA recently changed their scope and enforcement strategy once the new commissioner, Dr. M. Hamburg, was introduced. The number of ‘warning letters’ increased significantly and the focus shifted towards shorter reaction times on observations and fewer hurdles for a warning letter. Laboratory controls are also under special scrutiny and analytical methods are looked at very carefully. Impurities play a much more important role, particularly since the Heparin scandal in China. Since the genotoxic impurities guideline was issued in 2008, there is an added focus on potential genotoxic impurities in ppm and ppb levels, especially in Europe. ■

A good thing

Audits are much more than just a review of the Quality Management System of a custom manufacturer. They are an excellent opportunity to exchange information, learn about client expectations, and help develop a more trusting and successful partnership.

Inspections History at Siegfried Actives since 2003

FDA USA: No observations at all by FDA!

Zofingen
Four FDA inspections (2003, 2006, 2007, 2008), all with “No Action Indicated”

Pennsville
Six FDA inspections (2003, 2004, 2006, 2007, 2008, 2009), all with “No Action Indicated”

Swissmedic Switzerland:
Ten inspections at Siegfried in Zofingen since 2003. The License has always been granted including the approval for the production of highly active materials (since 2007).



PMDA Japan:

In November 2009 Siegfried Actives Pennsville successfully passed a PMDA inspection. Siegfried Zofingen and Pennsville are accredited in Japan.



behind the scenes

Siegfried



Customer Audits

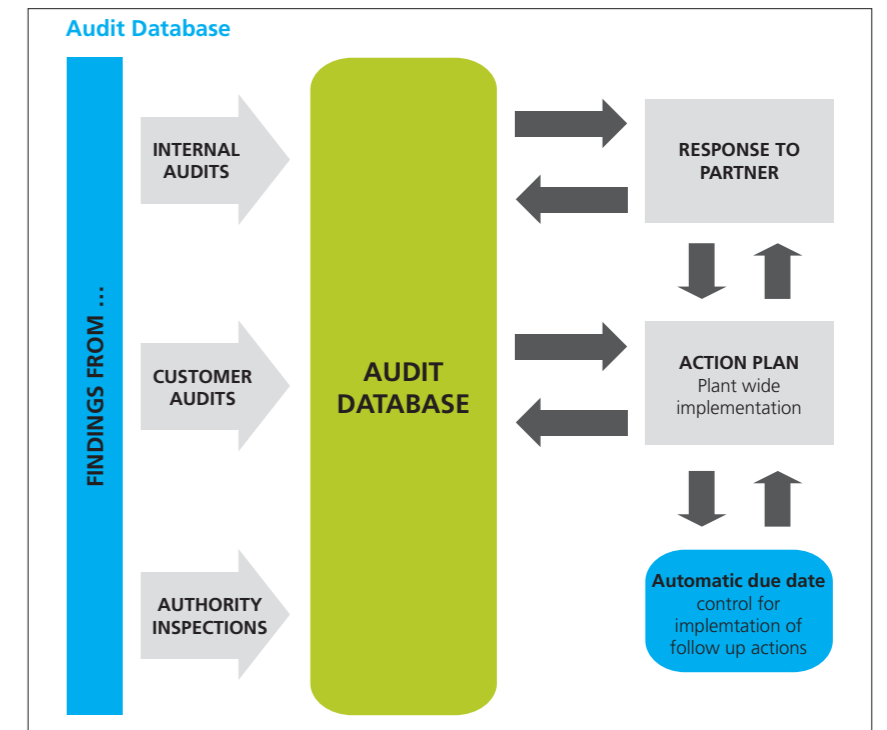
Obligation or Opportunity for a Trusting Relationship?

Sometimes both contract givers (client) and contract acceptors (custom manufacturer) see audits as an inconvenient and expensive exercise. However, audits can be a key opportunity to closely analyze your custom manufacturer and, from the custom manufacturer’s side, it’s the perfect moment to review the client’s expectations. “It’s the occasion to gauge the ‘give and take’ between two partners,” adds Peter Kiechle (Chief Compliance Officer).

Purpose and Expectations

First off: audits are a legal requirement. The ICH guideline Q7 states there should be a contract in place to allow the client to audit the custom manufacturer facilities for GMP compliance. Regular audits are expected, usually every other year. These audits can be routine, due diligence-like audits or audits to prepare for pre-approval inspections (PAI). For on-cause audits are also possible when unexpected incidents occur.

Besides the legal aspects, there are client expectations that include quality management issues and knowledge of key personnel capabilities at the custom manufacturer. In turn, the custom manufacturer can confirm compliance with all GMP requirements, a comprehensive Quality Management System, and gen-



eral competency – all characteristics of a reliable partner.

Essentially, as a service provider, the custom manufacturer must satisfy client expectations. Siegfried works with approximately 60 different clients with 60 different interpretations of GMP – and very specific service expectations. That makes an open and trusting partnership of crucial importance. Despite the challenge of having to meet a wide variety of quality management parameters, Siegfried QM experts strive to provide a high level of service to consistently meet client expectations.

Preparing and Conducting Audits

Quality management is only one aspect of a successful audit; careful preparation is also important. Every year, Siegfried hosts out 40-50 audits and inspections, virtually one audit every week. With such a full agenda, planning is key, which normally begins about three months before a scheduled audit date. Large pharma companies usually look to the end of the calendar year for their audits, when planning for the next year. While this helps to put audits in a proper sequence, unexpected inspections by authorities often mix up the order. Fortunately, all pharma companies are familiar with this problem and understand that even the most thoroughly planned audit can sometimes be postponed on short notice when the authorities show up.

The audit agenda is another issue that may vary from audit to audit. However, certain topics are always important: the quality management system, deviation handling, change control, a facility tour, review of batch log records, etc. Specific people need to be available and scheduled in the agenda – for the specific topics. This ensures the necessary support for the auditors. There may also

Siegfried Standard Agenda for a One Day Audit

Participants:	Lead Auditor	
	Auditor	
	(Specialists)	
Participants Siegfried	Auditee Team	(full time)
	Auditing & Contracts	
	Business Development	(part time)
	Product Management	
	Project Team	(part time)
	Project Manager	
	Warehouse	(part time)
	Head Warehouse Management	
	Sampling	(part time)
	QA Raw Materials and Sampling	
	Production	(part time)
	Head Chemical Production	
	Head Physical Operations	
	Chemical Development	
	Product Chemist	
	Development	(part time)
	Head Development	
	Quality Assurance	(part time)
	Head Quality Assurance Actives	
	Manager Quality Assurance Actives	
	Stability Manager	
	Quality Control / Analytics	(part time)
	Head Quality Control	
	Group Leader Quality Control	
	Analytical Project Leader (APL)	
	Utilities, HVAC, Monitoring	(part time)
	Responsible Personnel as needed	
	Computerized Systems & Doc. Mgt.	(part time)
	Manager Documentation Management	
	Manager Computerized Systems	
	Engineering	(part time)
	Head Engineering Actives	

be further issues that will need scheduling, such as viewing the product on-site during production. Splitting up the audit team is rarely done, as this can lead to redundant efforts and coordination difficulties, such as a Siegfried expert that may be needed for several issues at the

same time. Also, because daily work has to continue during an audit, it would make larger audit groups (>4) harder to manage properly, even if such groups are an exception. Sometimes pharma company audit groups are composed of auditors from different sites. This has led

Time (appr.)	Item	Participants Siegfried*
08:30 – 09:15	Introduction Meeting Overview of the site and Presentation of Siegfried's Quality Management System	Core Team
09:15 – 11:30	Warehouse – Walk through -Incoming Goods Area, Storage Area -Sampling Area	Head Warehouse Mgt. QA Raw Materials and Sampling
	Production – Walk through -Chemical Operations -Physical Operations	Head Chemical Production Head Physical Operations Chemical Development Product Chemist
11:30 – 12:30	Quality Control Laboratories - Presentation of QC - Lab Tour, incl. Stability Chambers	Head Quality Control Analytical Project Leader Stability Manager
12:30 – 13:30	Lunch	
13:30 – 16:45	Quality Management - Deviation, Complaint Handling - Change Control System - Qualification, Maintenance - Process and Cleaning Validation - Batch Records and Release Procedure - Product Quality Reviews - SOP and Training System, etc. - Utilities / Technical Systems - Other items as defined by auditor	Head Quality Assurance Actives Manager Quality Assurance Actives Manager Documentation Management Manager Computerized Systems Head Engineering Actives Other Responsible Personnel as needed
16:45	Preparation for wrap up Meeting	Auditors
17:15	Wrap up Meeting	All participants

*The hosting team is always present

to confusion and several audits running in parallel, which is neither efficient nor good auditing practice. At Siegfried, we strive to have the client to designate one reference auditor to conduct a single audit for all sites.

Siegfried uses a standard audit agenda based on our previous experience and PIC/S inspection guidelines. In April 2009 an inspection by four European PIC/S inspectors at Siegfried strictly followed the PIC/S topics; it went very well for both sides.

Maintaining high standards

With so many audits and inspections every year, Siegfried maintains daily work processes at a high standard that bear scrutiny of an audit at any time. This is quite a challenge but avoids the complications of any special preparation ('polishing') before an audit and maintains awareness among the Siegfried teams. The high frequency of audits is different from pharma companies that essentially have only inspections (with the necessary lead time to prepare).

A high number of audits is an excellent opportunity to understand current industrial expectations and audit/inspection trends (that go beyond the guidelines and regulations). This helps us better interpret guidelines in different countries and organizations, and also understand the relevant so-called industrial practices. Part of an unstated but expected rule of thumb, an inspector or auditor may want the custom manufacturer to provide a solution applied in general practice by other contract acceptors, which is not explicitly stated in the guidelines. Discussions during audits also help give a sense of such new practices and expectations, which often demands additional resources or adds costs that are not set by any regulations.

In addition to audit practices, there are many different organizations and regulatory bodies that influence the quality management system within a company:

- WHO – the International Conference on Harmonization (ICH)
- FDA – the Food and Drug Administration (USA)
- EMEA – the European Medicines Agency
- Swissmedic – the Swiss medicines agency
- Local country authorities

