

The Journal

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The Auditing Issue



Part of NSF Health Sciences

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welcome



Bob Pietrowski
VP Global
Health Sciences
NSF International

Welcome to the latest edition of our Journal, which is focused on the critical activity of auditing. In this issue...

- NSF-DBA Consultant and former Manager of the UK MHRA's GMP Inspectors, Liz Allanson, tells you the top 10 things that regulatory inspectors look for when inspecting your audit program
- We provide sound, practical advice on how to improve Medical Device corporate audit programs
- We explain how adopting the principles of HACCP, as widely used in other industry sectors like food, can make you a better auditor
- Finally, we proudly announce the first internationally accredited **Pharmaceutical GMP Lead Auditor** training course, designed to ensure that your auditors are properly trained and qualified to perform audits to pharmaceutical GMP standards
- If you don't have the resources to carry out all your audits yourselves, or if you would value assistance from an experienced auditor team, we explain how we can help by undertaking audits on your behalf

Lastly, you will see from the change in my job title that I am leaving NSF-DBA to head up NSF International's Health Sciences division. I shall miss being a part of NSF-DBA, having been here for 23 years, and I would like to take this opportunity to say thank you and goodbye to all those of you I have worked with over the years. I know that NSF-DBA will go from strength to strength in the years to come.

Neil Wilkinson, known to many of you, has now taken over as Managing Partner of NSF-DBA and will be leading the team towards an exciting future as a part of the NSF Health Sciences division.

As the integration of NSF-DBA with Becker and Associates (Washington DC based regulatory consultancy firm) moves forward, we will be realigning our new Health Sciences division into 3 core business units:

- NSF Health Sciences Pharma-Biotech, led by Neil Wilkinson
- NSF Health Sciences Medical Devices, led by Elaine Messa
- NSF Health Sciences Dietary Supplements, led by Ed Wyszumiala

These units will be supported by our Analytical Testing Services and Reference Standards teams.

More about this in our next edition of the Journal.



Neil Wilkinson
Head, NSF
Health Sciences
Pharma-Biotech

Bob Pietrowski
VP Global Health Sciences
NSF International

Neil Wilkinson
Head
NSF Health Sciences Pharma-Biotech

Tech Talk



Bob Pietrowski Explains How Applying the Principles of HACCP Can Make You a Better Auditor

Whenever I carry out an audit, I come away with two nagging questions in my head – “Did I give enough time and attention to those things which are most important?” and “Did I really communicate my concerns effectively to the auditees and are they motivated to make improvements and act on my recommendations?”. Any audit is by definition a sampling exercise – we cannot see everything and challenge everything because we simply don’t have the time. We must use that precious time to focus on those things that really matter. In short, we must apply the principles of **RISK ASSESSMENT**, and apply them to all facets of the audit...

- The planning of the audit
- The allocation of time and attention to the various activities to be audited
- The assessment of the severity of observations
- The way we communicate that severity to the auditee

There are numerous risk assessment procedures that can be used by the auditor to ensure that he/she concentrates on those activities which are most important to assure product quality and safety. Perhaps the most commonly used is **Failure Mode Effect Analysis (FMEA)**, whereby potential hazards (things that can go wrong) are identified and the RISK associated with them is quantified by analyzing and giving a score to...

- The **SEVERITY** of the hazard
- The probability of **OCCURRENCE** of the hazard
- The probability of **DETECTION** of the hazard should it occur

By multiplying together the scores for severity, occurrence and detection (or perhaps more correctly, non-detection) we can obtain an overall score for the risk associated with the hazard and

this can then be used to rank risks associated with any activity. We can use this risk ranking to determine how much time and effort we should spend when auditing this activity and assessing whether the risks, as we see them, are under adequate control.

FMEA is a very useful risk assessment tool, but when auditing I prefer a derivative of FMEA called **Hazard Analysis and Critical Control Points (HACCP)**.

What is HACCP?

HACCP has its origins in the food industry. It was developed in the 1960s by the Pillsbury food company, in collaboration with the US Army and NASA as part of a project to develop foods for the American space program, and in particular to minimize the microbiological risks associated with those foods – no-one wants to suffer from food poisoning in a space suit! HACCP proved to be a great success and has become the process of choice for the assessment and control of microbiological risks in the food industry. But don’t be fooled into thinking that HACCP is only useful for assessing microbiological risk and is applicable only to foods. I and many others have used the principles of HACCP to assess diverse risks in the pharmaceutical and biotech industries – and it works!

In its simplest form, HACCP involves a series of 7 linked steps...

1. Definition of the **product** and the **process**
2. Identification of **potential hazards** and **potential control measures**
3. Determination of **critical control points (CCPs)**
4. Establishment of **critical limits** for each CCP
5. Establishment of a **monitoring system** for each CCP
6. Implementation of a **corrective action plan** to re-establish control when necessary
7. Establishment of **verification procedures** to demonstrate compliance

It is the identification of so-called CCPs and all the steps that follow on from there which make HACCP such a unique and valuable tool, both in terms of controlling risk and as an aid to auditing.

Let us look at each of the 7 steps in a little more detail:

Definition of the Product and the Process

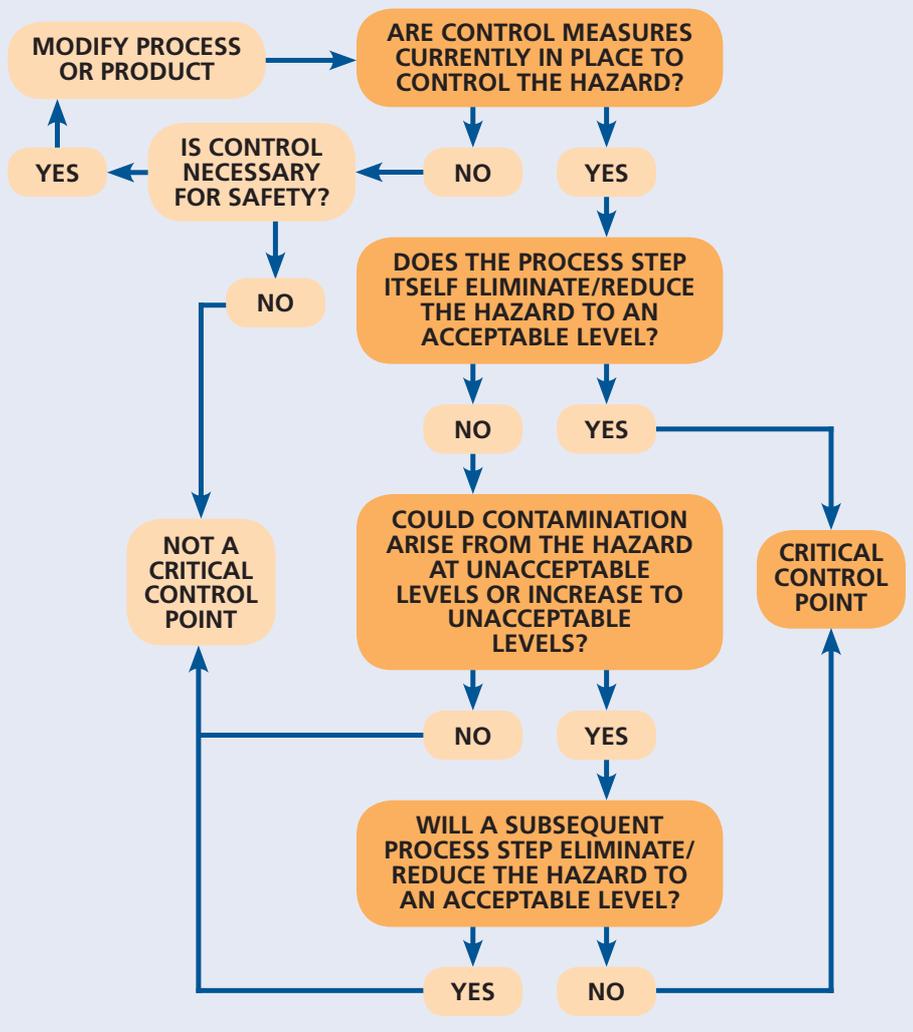
The first and most important step in any risk assessment exercise is ensuring that you really understand the product and the process. The product should be understood in terms of what it is, how it is used and, in particular, its critical quality attributes – those attributes which are essential to the safety and performance of the product. Similarly, it is essential to understand the overall process – all the steps, all the inputs, all the outputs, all the controls, etc. This can best be achieved by formally mapping out the full process.

Identification of Potential Hazards and Potential Control Measures

We can now analyze the whole process and identify those steps which potentially constitute a hazard to achieving the key quality attributes. What we are doing is asking, “What could possibly go wrong and what measures are in place, if any, to stop it going wrong or alert us to the fact if it does go wrong?” This approach allows us to identify the critical control points in the process.

Determination of CCPs

This can be done by using a decision tree as shown in the table below:



Once we have identified those critical steps in the process which must be under excellent control if product safety and quality are to be assured, we can go on to the other critically important steps aimed at achieving and demonstrating control.

Establishment of Critical Limits

For each CCP, a critical limit (or limits) must be established. The limit should be discriminatory – it should distinguish between what is acceptable and what is not. It may therefore be an accept/reject limit or an alert/action limit.

Establishment of a CCP Monitoring System

The establishment of an effective monitoring scheme for each CCP is an essential part of risk management by HACCP. The monitoring system must...

- Be able to detect loss of control
- Provide timely information that permits corrective action to be taken, preferably before product rejection becomes the only option

Things which will influence the effectiveness of the monitoring system include...

- Monitoring frequency
- Sampling points
- Sample size
- Sensitivity of the analytical method

Establishment of a Corrective Action Plan

If monitoring data indicates a loss of control, appropriate action must be taken to regain control. This action should be, wherever possible, pre-agreed and committed to an official procedure and should include the following...

- What action is to be taken and when
- Who is to act
- How the effectiveness of the action is to be verified

Establishment of Verification Procedures to Demonstrate Compliance

Verification procedures may include...

- Trend analysis of data
- Review of deviations, batch rejections, etc, looking especially for repeat occurrences
- Periodic Quality Reviews

Using HACCP Principles to Perform Better Audits

The simple, 7-stage approach of HACCP can be invaluable to the auditor. Applied properly, it can ensure that the auditor...

- Concentrates time and effort on the most important issues (the CCPs)
- Asks the right questions to determine whether the CCPs are under adequate control
- Communicates his/her concerns and the reasons for those concerns
- Makes appropriate recommendations for corrective action

Thus, HACCP principles can bring structure, focus, objectivity and efficiency to any audit. For example...

Planning the Audit – Understanding the Product and the Process and Identifying the CCPs

This is a critical step which is often performed poorly. The auditor must understand the product and the process before he/she can carry out an effective audit. Remember...

IF YOU FAIL TO PLAN, YOU PLAN TO FAIL

HACCP demands that you take the time to really understand the product, in particular the **critical quality attributes**. It is these which will drive the audit and allow the auditor to focus on risk.

For a sterile injectable product, the critical quality attributes will include...

- Sterility
- Apyrogenicity
- Correct dose
- Container integrity

For a tablet product, they will include...

- Content uniformity
- Weight
- Dissolution

and many more.

By analyzing the process and identifying the steps which are critical to achieving those quality attributes, the auditor can identify the CCPs for each attribute. He/she can then allocate

time to ensure that each CCP is adequately audited. Furthermore, the auditor can explain the rationale of the audit to the auditee – where he/she intends to spend time, and why.

Conducting the Audit

During the audit itself, the auditor should challenge each CCP and attempt to get answers to the following questions...

- Does the auditee recognize this as an area of risk (and hence a CCP)?
- Has the auditee attempted to 'design out' the risk?
- Have appropriate limits been set for this CCP?
- Does the auditee monitor at this point and, if so, is the monitoring program sufficient – in terms of frequency, number of samples, sample size, means of analysis and communication of results – to exert control?
- Is the system capable of identifying loss of control or movement towards loss of control?
- Is there a clear, effective corrective action plan in place to regain control?
- Are there systems in place to demonstrate and confirm the adequacy of all these control measures through trend analysis of data, follow-up on corrective actions, change control, periodic review of deviations and other performance indicators?

Communicating Concerns

It is not enough simply to identify problems and concerns during an audit. The auditee must understand and share the auditor's concerns, otherwise they may not be sufficiently motivated to rectify the problem. Failure to communicate the reasons for concerns is perhaps the most common cause of inadequate follow-up to audits. The structured approach to identification of critical control points and the objective criteria by which the effectiveness of control measures can be judged provide the auditor with an excellent means of discussing concerns and can enable the auditor and auditee to find a common basis for understanding and agreement.

Recommendations for Corrective Actions

Once there is clear understanding of the vulnerability and its scale, the task of making recommendations for corrective action becomes much simpler and more objective. What is more, the auditee will be better motivated to develop effective, permanent fixes for the problem.

In Summary

HACCP represents an excellent way of ensuring that the auditor focuses time and attention on those things that are really important and provides a structured, objective means of challenging the effectiveness of control measures. It is thus a really useful means of assessing risk and of communicating that risk to others. Although developed to address microbiological risk, it is easily adapted to suit any situation. I use it all the time and I strongly recommend that you try it!

Partner with us –

we will do your audits for you!



Mike Halliday, Partner at NSF-DBA, speaks about how NSF-DBA can undertake individual audits, part of, or even your full audit program on your behalf

We at NSF-DBA are very pleased to provide a high quality pharmaceutical sector audit service, using our team of highly experienced pharmaceutical auditors, based in global locations, including Europe, North America and Asia Pacific. Some are ex-EU or FDA regulators and others are experienced industry professionals – but all have tremendous experience in auditing within the pharma industry, its suppliers and contractors. This is quite different from many of our competitors, where pharma experience may be limited.

Each year we conduct hundreds of third party audits on behalf of our wide client base, ranging from start-up firms in clinical development, to virtual companies, to large global firms.

The audits we undertake may be one-offs, to meet a specific client's needs, or we are now providing an audit service for an increasing number of firms, where we undertake part of their audit program to supplement their own audit capability.

There are a number of reasons why firms partner with us to do this – where specific technical expertise is needed, where they don't have geographic coverage, where it fits with their outsourcing strategy or where they are unfamiliar with a local culture, to name just a few!

Feedback from these clients is exceptionally good, noting the support and clear key point of contact within NSF-DBA. When a client expresses an interest in multiple audits on an ongoing basis we assign a key point of contact. We try to ensure continuity by using auditors from a sub-group to service the specific client's needs. We encourage auditor training in the client's audit systems and procedures, as well as getting to know the client's own auditors. Of course we also encourage progress reviews to make sure the service offered meets the client's needs, and that any learning points are actioned.

Key steps to success...

1. A clear brief from client regarding locations, durations, standards and the role of the auditor
2. Assigned key points of contact from all parties
3. Training of auditors in client's systems and procedures
4. Agreeing client report format templates
5. Agreeing a clear technical or quality agreement between NSF-DBA and the parties
6. Use of highly experienced and trained pharmaceutical sector auditors
7. Clear and open communication in setting audit programs and tasks

Challenges do crop up occasionally but are usually accommodated – from short notice audits, auditee cancellations, surprise regulatory inspections during an audit, multiple audits in the same week by different auditors at different locations for the same client, to audits in interesting and varied locations!

The success factors during these challenges rely on the contacts and co-ordination as well as the pool of capable and competent auditors.

One of the clients we are currently working with is Daiichi Sankyo Company Ltd. Daiichi Sankyo have contracted NSF-DBA to work with their corporate GMP audit group to help assess the quality levels at Daiichi Sankyo Group Companies in line with PIC/S GMP standards and to support quality level improvement.



Kenta Goto, Associate Director, Global QA of Daiichi Sankyo said recently of our service, "*We contracted NSF-DBA to complete a number of audits for us. We are very pleased to work with them – they*

have provided a flexible service that meets our needs, along with high calibre auditors. We look forward to an ongoing business relationship".



Kenta Goto

Associate Director,
Global QA of Daiichi Sankyo

If you are interested in understanding the auditing services we can offer, please contact Austin Caudle, our Business Development Manager, at A.Caudle@nsf.org

Loyalty has its benefits

In 2010, NSF-DBA celebrated its 25th anniversary – growing from a small consultancy and training firm based in Kirkbymoorside, UK, which was originally known as David Begg Associates, then DBA, before changing to its current name of NSF-DBA – part of NSF Health Sciences, a global based firm with offices on four continents and consultants capable of delivering services in many local languages.



by Jim Morris,
Partner, NSF-DBA

A strong characteristic of our firm, which bridges the years and office locations, is the strong connection we feel between our associates who assist in delivering our services, our course delegates and our many client companies. Since the early 1990s we have trained over 350 QPs in Europe, many of whom remain close contacts and friends, and an increasing number of quality and technical professionals in the USA. It is in this context that we are pleased to announce a US loyalty program with a single-minded goal of strengthening our connections between course delegates and our contacts at client companies.

The beauty of this program is that it is open to delegates from companies such as Roche/Genentech, Sanofi Pasteur and Pfizer, who have graduated from our modular based in-house educational programs, as well as individuals who have attended our external courses. For instance, if you attended the modular program at Roche/Genentech, you are welcome to attend our free CPD seminars and webinars designed to keep you abreast of key regulatory developments. The only catch is that you must still be with the company who sponsored the in-house program in order to take advantage of this benefit. In addition, if you completed the Quality Leadership Program (QLP) in the USA, you are eligible for continued benefits in recognition of your achievement.

This program is effective as of July 1, 2013. We look forward to hearing from you and realizing the benefit of continued learning and a long term relationship with NSF Health Sciences.

	Gold	Platinum	Platinum Core
ELIGIBILITY >	Attended an NSF-DBA course internally or externally	Completed a modular in-house course series of >8 modules internally	Completed the full QLP course series or equivalent
BENEFIT v			
Complimentary copy of The Journal	Yes	Yes	Yes
NSF-DBA LinkedIn Group	Yes	Yes	Yes
NSF-DBA Webinars	No	50% off	No charge
Short courses (1-2 days)	50% off* Within one year from course attendance	50% off* No expiry if with original company sponsor**	50% off*
1 day Continuing Professional Development (CPD) Courses	50% off* Within one year from course attendance	50% off* No expiry if with original company sponsor**	No charge

*Maximum of one 50% discounted course per year, subject to maximum course numbers not being exceeded

**Example: if you complete the course series with Company X and move to work for Company Y, your Platinum membership will expire

The NSF-DBA Loyalty Program is subject to change and NSF-DBA reserves the right to update the Program at any time.

Contact Jim Morris if you require further information at jmorris@nsf-dba.com

Forthcoming Pharmaceutical Courses



What's planned for July – October 2013

Human Error Prevention

NSF-DBA Office, Boston, MA

July 17

This one-day course will provide you with tips that will help you immediately in your workplace. It is developed for people involved in pharmaceutical, biopharmaceutical operations working in production, laboratories, maintenance, and warehouse operations.

The aim of this course is to change the approach followed in conducting investigations where human factors are involved. You will go away with a new way of thinking about human error and tools needed to reduce errors, minimize re-occurring deviations and drive continuous improvement.

Course Fee: \$950.00 (First booking)
\$760.00 (Early bird/additional bookings from same site)

Pharmaceutical GMP Introduction and Update

NSF-DBA Office, Boston, MA

July 23-24

It is a legal requirement that all staff receive regular training in good manufacturing practice and it is extremely important to stay abreast of current GMP requirements and the issues companies are currently being cited for during routine or for-cause GMP inspections. This course is designed to accomplish this for you. We will briefly review the GMP regulations and their history, review latest high level GMP developments and take a deeper dive into those elements of the Quality Management System frequently cited as lacking or out of compliance.

Course Fee: \$1775.00 (First booking)
\$1420.00 (Early bird/additional bookings from same site)

Role of the Quality Leader

Boston Marriott Cambridge,
Cambridge, MA

August 6-8

The responsibility of the Quality Leader today demands a unique skill set of technical, managerial and leadership characteristics. Risk-based decisions are made at a fast pace, issues can quickly escalate when not thoughtfully managed, and good leadership offers strategic advantage to a company. This course will assess your skill set as a leader in the context of pharmaceutical and biopharmaceutical operations and through case studies build your decision making and technical management skills.

Course Fee: \$2950.00 (First booking)
\$2360.00 (Early bird/additional bookings from same site)



Satisfying Regulatory and Quality Requirements in Key Emerging Markets

NSF-DBA Office, Boston, MA

October 8-9

Unprecedented growth in the BRIC markets (Brazil, Russia, India and China) has pharmaceutical companies rapidly aligning their strategies to understand what it takes to do business in these markets.

This course will provide an overview of the regulatory history, climate and cultural drivers in the BRIC countries and other locations such as Turkey, Mexico and key Middle Eastern states. The pace of change and the regulatory trends driven by actions in the BRIC states must be appreciated. These countries are issuing GMP guidances with clear national compliance expectations and are increasingly demanding pre-approval inspections of export markets to gain access.

Course Fee: \$1775.00 (First booking)
\$1420.00 (Early bird/additional bookings from same site)

Sorting out the Myths from the Facts of Supply Chain – Realities for Implementation of EU and US Legislation

NEW COURSE

NSF-DBA Office, Boston, MA

October 15

This course will help you navigate the maze of new regulations, legislation and expectations from global regulators by covering the proposals from the regulators, the responses from the pharmaceutical industry, its suppliers of excipients and APIs and related associations, along with good industry practices for 'end to end' supply chain assurance.

Course Fee: \$950.00 (First booking)
\$760.00 (Early bird/additional bookings from same site)

How Packaging Provides a Competitive Advantage to Ensuring Supply Chain Integrity

NEW COURSE

NSF-DBA Office, Boston, MA

October 16

Packaging Anti-Counterfeiting Measures

This session will provide an overview of the current situation regarding counterfeit pharmaceutical products and a discussion of the use of packaging in detecting counterfeit products, including recent discussions regarding serialization. It will then consider reasonable expectations for an anti-counterfeiting program, types of technologies available, where they are most appropriately used, and what types of protection the features will provide.

Packaging Component Supplier Assurance

This session will first discuss key points for a packaging vendor qualification program. Secondly, it will review specific issues on printed packaging materials, including fundamental information on printing technology, leading to a discussion of the cost of errors, where errors occur, and how they may be prevented or detected.

Course Fee: \$950.00 (First booking)
\$760.00 (Early bird/additional bookings from same site)

Book online at www.nsf-dba.com

Get in touch now to book your place on any of these courses

Call us on: +1 857-277-0060 or email: USinfo@nsf-dba.com

Course details and prices are correct at the time of printing and are published in good faith. NSF-DBA reserves the right to make any changes which may become necessary.



Liz Allanson, NSF-DBA Consultant and former Manager of the UK MHRA's GMP Inspectors, gives us some top tips on what regulators look for when assessing a firm's audit program

AUDITING – WHAT DO THE REGULATORS EXPECT?

There is an increased regulatory focus on audits within the pharmaceutical industry as a result of cases of adulterated materials (eg heparin), the increasing threat of counterfeit medicines, and the introduction of modern quality management systems thinking, based on ICH Q10.

These principles are globally appropriate, irrespective of which Regulatory Agency(s) you get inspected by – as more Regulatory Inspectorates join PIC/S and mature, they will also be looking at the effectiveness of a firm's auditing programs and competency of their auditors. Better to be prepared than caught lacking!

So what are the top 10 things that regulators are looking for?

1. Robust audit systems

Company audit systems (both external and internal) must be part of the written quality management system supported and resourced by the company senior management. Responsibilities should be clearly defined for both external and internal audit systems and performance measures should be in place to confirm that the systems are working correctly and are effective.

2. Decisions supported by sufficient audit evidence

Decisions made, especially by Quality Professionals/Qualified Persons (QPs), are supported by thorough and reliable audit reports.

EU QPs have been known to sign GMP declarations for active pharmaceutical ingredients, based on minimal information, and in some cases no audit report at all – NOT an acceptable practice!!

3. Competent auditors

An audit is only as good as the auditor who performed it. Regulators are looking for evidence that auditors are trained in the skills and techniques of auditing and have a good level of GMP knowledge and experience, and that they know the standards that must be applied.

A recent EMA communication on audits of API suppliers indicates that auditors should have sufficient scientific and technical experience to ensure their audits of API manufacturers are 'adequate and thorough'. Whilst this communication focused on APIs, the principle is equally applicable to other technical areas in the pharma sector.

Auditors must be trained and assessed in their knowledge of EU GMP and in auditing techniques in general, with full documentation of such training and experience.

Where a proposed auditor lacks an appropriate level of direct experience in the field of manufacture, he or she should undergo a documented training and assessment program in the areas relevant to the audit, taking into account the auditor's anticipated role in the audit and the technologies that are likely to be encountered during the audit.

4. Relevant audit standards applied

Audit evidence must demonstrate that the correct standards have been applied as audit criteria – eg ICH Q7, EudraLex Volume 4, 21 CFR 210/211, PIC/S GMP, ANSI/NSF/IPEC 363, and all relevant guidances.

5. Sufficient time for the audit

Adequate time must be allowed for each audit and must be appropriate for the scope of the audit. Time allocated must include preparation and follow-up time.

6. Risk-based audits

Audits must not be tick-box compliance audits. The auditor should constantly understand and assess the risks posed to the patient by the operations being audited.

7. Good supplier audit reports

The focus and concern associated with global supply chains has resulted in regulators taking a much more robust stance as evidenced by legislation changes such as FDASIA in the US and FMD in the EU, and API supplier audit reports are being routinely reviewed by EU inspectors. The detail should support the final conclusion or recommendation.

Regulators are rightly skeptical about the value (if any) of solely relying on 'Questionnaire Audits' and expect physical audits to be undertaken of API/excipient manufacturers and their associated supply chains by the firm, or on behalf of the firm by appropriately qualified auditors.

8. Good use of audit information

A good audit system will have formal mechanisms for sharing audit reports and findings with others who can then make informed decisions and use the data to improve other aspects of the business.

9. Follow-up

There should be a formal procedure for following up on the audit observations. Confirmation is expected that deficiencies have been rectified by effective CAPAs, which should be available for review.

10. Continual improvement of audit systems and of systems audited

All audits should produce improvements, including improvements to the audit processes and systems that the auditor is following.

Do you really know how your excipient is made?

by Janeen Skutnik

Stories regarding adulterated and contaminated ingredients can be found almost weekly, and yet some companies continue to turn a blind eye to supplier qualification, auditing and monitoring.

Even today some rely on a paper audit or paper questionnaire and think that is good enough! So I ask, when was the last time someone wrote in response to a questionnaire "There is paint peeling above reactor A" or "We segregate our storage and quarantine areas with chairs"? It is impossible to ask in a paper questionnaire every conceivable question that could arise. Even well seasoned auditors are surprised by the interpretations some companies have of cGMP – which they would never conceive of asking on a questionnaire. It is also impossible to assess on paper a company's quality culture and commitment to quality. It is important to recognize that auditing is only ONE PART of the overall supplier qualification and monitoring program.

Can you answer these questions?

- Do you know how your excipients are produced?
- Do you know if your excipient supplier sub-contracts out any portion of the manufacturing?
- Do you have full transparency and traceability of your excipient supply chain?
- Do you know how your excipient supplier qualifies their suppliers?
- Do you know if your distributor audits their suppliers?
- What evidence do you have to substantiate these answers?

The auditing of excipients is a very important aspect of the overall assurance of the quality of the finished dosage form. Excipients, after all, comprise a large portion of the overall dosage form. While excipients are required to comply with appropriate GMPs, there currently is no universal

guideline that details the expectations. The International Pharmaceutical Excipients Council (IPEC), which had developed a GMP Guide for Pharmaceutical Excipients, has partnered with NSF to develop ANSI NSF-IPEC 363 GMPs for Pharmaceutical Excipients. This guide provides the necessary expectations and requirements for excipients that can be used in audit programs. Because excipients are so widely used by so many companies, the use of second or third party auditing and/or third party certifications should be considered. Consider this: a pharmaceutical company desires consolidation of inspections so that 15 different countries do not all show up at different times to inspect the same facility. An excipient supplier may have more than 200 customers; is it reasonable to expect they should host 200 audits a year?

The finalization of NSF 363 will provide a standard for auditing and certification of excipients to appropriate GMPs. NSF-DBA can be a valuable partner in your company's supplier qualification program by providing audits of your excipient suppliers.



Contact Janeen Skutnik at jskutnik@nsf-dba.com for more information on the NSF 363 standard or excipient auditing



Regulatory Update

EU Pharma News

The Falsified Medicines Directive (FMD)

Implications for Importation of APIs

The FMD (Directive 2011/62/EU) requires that from July 2, 2013 all APIs imported into the EU have to be certified as meeting EU GMP by a Competent Authority of the exporting country unless they have been assessed by the European Commission as having acceptable regulatory controls in place and have been listed as an acceptable country.

The situation regarding the issuing of API certificates, or requests for listing on the Commission's approved countries list, was summarized by the EC Pharmaceutical Committee at a meeting on March 27, 2013. The report of this meeting detailed the current position with the top 18 countries who export to the EU, which account for 97% of all API imports into the EU. This was the situation at the time...

- Only one country has been approved by the Commission and will not be required to issue GMP certificates – Switzerland
- Six countries have applied to go on the list of acceptable countries – Australia, Brazil, Israel, Japan, Singapore and USA. Of these...
 - ♦ Israel and Singapore are considered not acceptable at this time and will be required to provide GMP certificates
 - ♦ Australia, Japan and USA are still being assessed. The Commission is confident that Australia and USA will be approved by July 2 and will not have to provide GMP certificates
 - ♦ Brazil still has to submit the paperwork needed to start the assessment process
- As for China and India, who together have over 60% of overseas sites exporting to the EU, there is still significant uncertainty as to whether they will be able to issue APIs exported to the EU with the necessary certification by July 2, 2013

More Questions and Answers

On April 5, 2013 version 4 of the Commission's Q&A regarding the importation of APIs from outside of the EU was published. This version contained three new questions and answers:

- Question 2a asks **“Does the written confirmation apply to blood plasma?”** The answer is “no”. However, substances isolated from blood plasma are considered active substances and in this case written confirmation is required
- Question 10a asks **“Do starting materials that undergo additional purification or chemical synthesis in the production of an active substance require written confirmation if imported into the EU?”** The answer is “no”. Starting materials such as those that undergo additional purification or chemical synthesis do not meet the definition of materials that require a written confirmation
- Question 11b asks **“If the manufacture of finished dosage forms is intended for export only, is API certification still required?”** The answer is “yes”. The API that is incorporated into a finished dosage form, manufactured in the EU but intended for export only, does require written confirmation

ACAA with Israel

An 'Agreement on Conformity Assessment and Acceptance of Industrial Products' (ACAA) between the EU and Israel came into effect on January 4, 2013. The ACAA applies to medicinal products for human and veterinary use including chemical, biological, immunological, radio-pharmaceuticals and herbal medicinal products, active pharmaceutical ingredients and excipients. It does not apply to investigational medicinal products (IMPs), homeopathic products, medicinal gases, veterinary immunologicals, advanced therapy products or products based on human tissues, blood and cells. There is provision to extend the ACAA to cover IMPs, veterinary immunologicals and products based on human tissues, blood and cells at a later date.

The EU and Israel also will share information on the regulatory status of manufacturers and importers, with the EMA managing a GMP database to facilitate the exchanges. Inspection reports are to be forwarded to the other party in 30 days or less, with an additional 30-day extension allowed in cases where a new inspection or product re-evaluation is carried out.

The ACAA brings Israel into the EU's rapid alert system for product quality defects and recalls. It also grants Israel access to EU training sessions and the GMP-related working groups.

As far as the need for re-testing on importation and QP certification is concerned, the EMA's understanding is that the same interpretation applies as for other Mutual Recognition Agreements (MRAs); ie that there can be an exemption from the need for re-testing on importation but that certification by the QP is still required.

EU Good Distribution Practice Guideline

On March 7, 2013 the European Commission published the final version of the EU Good Distribution Practice (GDP) Guideline. The structure of this final version is the same as the draft that was published in 2011, although the wording has been improved in several places. The new guideline becomes effective on September 7, 2013.

This version provides a very significant expansion compared to the current 1994 GDP Guide that had just four pages. The structure and content are now very similar to part 1 of the GMP guideline. The same themes run through this revised GDP guideline as have been made more prominent in recent GMP revisions; ie

- Quality Management Systems
- Management Responsibility
- Quality Risk Management
- Supply Chain Controls

The new guideline consists of ten chapters:

1. Quality Management
 2. Personnel
 3. Premises and Equipment
 4. Documentation
 5. Operations
 6. Complaints, Returns, Suspected Falsified Medicinal Products and Medicinal Products Recalls
 7. Outsourced Activities
 8. Self-Inspections
 9. Transportation
 10. Specific Provisions for Brokers
- plus a Glossary

The personnel section defines the requirements for 'Responsible Persons' and lists 12 routine duties of the RP.

There is a section on falsified medicinal products that states:

- If identified or suspected must immediately inform Competent Authority
 - must have an SOP to this effect
- Must immediately segregate
- All activities must be documented

The new section specifically for brokers builds on the new requirements for brokers in Directive 2011/62/EU, which requires brokers to be registered and lays out the requirements to become a broker. The revised guidance requires brokers to have quality and documentation systems and to keep records of what they sell and manage between other parties to ensure that those products are authorized for sale within the EU. These records must be kept for a minimum of five years.

FDA News

Tablet Scoring: Nomenclature, Labeling and Data for Evaluation

In March 2013 the FDA issued final Guidance for Industry on Tablet Scoring: Nomenclature, Labeling and Data for Evaluation.

This guidance provides recommendations for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) regarding the criteria that should be met to facilitate the evaluation and labeling of tablets that have been scored. Specifically, it recommends:

- Guidelines to follow, data to provide and criteria to meet and detail in an application to approve a scored tablet
- Nomenclature and labeling for approved scored tablets

The final guidance states that 15 tablets with a 'score' to facilitate tablet splitting should be tested to ensure products meet the proposed hardness range. The tests, all of which are to be provided to the agency for evaluation, aim to ensure a loss of mass of less than 3.0% between the individual segments. The draft that was issued in 2011 did not include a testing protocol for ensuring mass loss specifications for scored drugs.

Draft SUPAC Manufacturing Equipment Addendum

In April 2013, the FDA released a draft guidance of scale-up and post-approval changes that combines and supersedes the following previous SUPAC guidance documents:

- SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum
- SUPAC-SS: Non-sterile Semi-solid Dosage Forms, Manufacturing Equipment Addendum

The FDA stated that the new draft SUPAC Addendum should be used in combination with the other SUPAC guidance documents.

This draft guidance removes the lists of manufacturing equipment that were in the previous guidance documents and clarifies the types of processes being referenced.

Medical Devices News

Recent Developments in EU Medical Device Regulation – April 2013

The debate has started in earnest on the Commission's proposed text (published in September 2012) for a new regulation for medical devices to replace 93/42/EEC and 90/385/EEC.

The EU-Australian Mutual Recognition Agreement (MRA) has had its scope reduced, and the European Medicines Agency has investigated why the new regulation for Advanced Therapy Medicinal Products (ATMP) is so little used.

1. Revision of the medical devices directives

The Commission proposal has been criticized by organizations representing medical insurers and patients for providing insufficient protection against unsafe high risk devices, while the medical devices industry maintains its opposition to the proposed pre-market approval scheme which could affect up to 10% of all devices. The debate appears to be heated, with many different views expressed and no real indication of consensus. A central pre-market authorization agency is unlikely because of the potential costs.

The other major issue to be addressed by the revision is the competency of Notified Bodies (NBs). Team-NB, the NBs trade association, has produced a draft code of conduct in an attempt to pre-empt most of the criticisms made of NBs, including that they are aligned too closely with industry rather than member states and (by implication) the patients. Among other matters, the code of conduct attempts to set out a practical method of implementing the controversial provision for NBs to make unannounced inspections. NBs have also produced a position paper proposing an enhanced audit regime to authorized representatives.

Consequence for manufacturers and recommended action

The revision will have a significant effect on all aspects of CE-marking pre- and post-market, but especially with regard to high risk or novel devices which are likely to become more difficult to bring to market and to have enhanced post-market surveillance requirements.

Manufacturers are recommended to keep in touch with developments of interest via journals, the Commission website, trade associations, MHRA, and their NB. They should also plan for longer approval times while the new system beds down.

2. Many high risk medical devices are excluded from the EU-Australia MRA as from 1 January 2013

This development will remove a relatively easy method of getting device approval for Australia based on its CE-marking for all Class III devices, implantable intra-ocular lenses, intra-ocular visco-elastic fluids and barrier contraceptives. It appears to echo the lack of confidence in the CE certification shown by some EU stakeholders. These devices may be reinstated in the MRA after a 'confidence building' period. Transition arrangements will be put in place in the meantime.

Consequence for manufacturers and recommended action

Manufacturers of high risk products sold in Australia via the MRA are advised to consult their NBs on next steps.

3. European Medicines Agency is expecting more marketing authorizations for ATMPs in the future

The EMA has carried out a survey to find out why its ATMP certification procedure is not more widely used by SMEs. They found that the SMEs did not clearly understand how the certification procedure fitted in relative to CE-marking (for medical devices) and product licencing (for drugs). Specifically, the link between their ATMP certification procedure and marketing authorization was seen to be unclear.

Consequence for manufacturers and recommended action

Potential manufacturers of ATMPs should consult the EMA early in their product development in order to gain the best possible understanding of the regulatory process.

For more information on the new developments and regulations in the Medical Devices Industry, go to nsf-dba.com/articles/view/122 for the NSF-DBA Study Day on the New Medical Devices Regulation.



Certified Auditor Training – The Story Continues

In early 2012 we told you that NSF-DBA had gained approval from IRCA (International Register of Certificated Auditors) for the first pharmaceutical auditor course based on pharmaceutical standards rather than the ISO 9000 series of quality management standards. This was possible due to the adoption of ICH Q10 (Pharmaceutical Quality System) by key regulatory agencies including FDA, EMA, PDMA, as the basis of a Pharmaceutical Quality Management System, and as a gap analysis between GMP and a range of other QMS standards.

Now, with the adoption (as a legal requirement) of key elements of ICH Q10 into the EudraLex GMP guides, we are in the process of evolving our PQMS certified auditor course further and retitling the certification as '**Pharmaceutical GMP Lead Auditor**'. This is stop press news and should be confirmed in the next few weeks from IRCA. Updates will be placed on our website.

The prime qualification and standard we should expect of our pharmaceutical sector auditors to satisfy ourselves, our patients and our regulators should be GMP – FDA CFR 210/211, EudraLex Volume 4, PIC/S being the key GMP standards.

There are also challenges to our suppliers and to our auditors to ensure that appropriate application of GMP is applied across our supply base and NSF-DBA offers additional auditor training to help with some of these areas – eg for excipients (see our 'How to Audit' program).

The journey with IRCA to develop the PQMS certification and now to adopt the change in emphasis to GMP has been challenging, enjoyable and very rewarding and we at NSF-DBA feel we have learned from IRCA and have shared our extensive knowledge of the pharmaceutical industry with IRCA in return. We are looking forward to the future and the establishment of the Pharmaceutical GMP course and auditor certification.

Our currently entitled '*Effective Pharmaceutical Audits and Self-Inspections*' course, which leads to IRCA certification as a Pharmaceutical Quality Management Systems auditor, will be rebranded once the course criteria are finalized with IRCA to

Pharmaceutical GMP Lead Auditor

This means that, for the first time, we will be able to offer what our industry and our regulatory agencies have wanted for years. GMP is an expected standard for auditing within our industry sector, and the skill and training of the auditor help with application of appropriate levels of GMP to suit the products concerned.

Do bear in mind the course was specifically designed to use GMP as an audit standard and is not just an ISO 9000 course with a pharma 'bolt-on', as offered by other providers.

THIS COURSE IS A TRUE GMP AUDITOR COURSE AND NOT A REBRANDED ISO AUDITOR COURSE!

We believe our auditor training course is unique and special for a variety of reasons and, while you may have choices in training provider, our ideas in origination of the scheme and the pharmaceutical focus we bring will continue to have this course stand out from those who follow. You will then have choices as to how you train your auditors and spend your valuable training budget to maximum benefit. Before you decide, consider the following...

- We have been teaching pharmaceutical auditing skills for the last 25 years. Our current training course is the product of those 25 years of experience and constant improvement
- Our tutors are all highly experienced pharmaceutical GMP auditors – including several former GMP inspectors. The structure of the course allows them to share stories and practical experiences, which will make you a better auditor
- The NSF-DBA tutors all go through specific education in training skills to prepare them to deliver this highly interactive course
- We can offer the course in-house at firms (subject to numbers) as well as via our external courses
- Since we launched the IRCA certified auditor training course two years ago, we have trained over 250 pharmaceutical auditors from Europe, the Americas, South Africa, China and Singapore. We have even trained the GMP inspectors of a PIC/S member state
- The IRCA certification of our course gives this course the credibility of being recognized by an independent expert body
- We are establishing an Alumni association for people who have attended our course so that they can benefit from networking with other NSF-DBA pharmaceutical GMP auditors and, of course, our tutors long after their training is complete
- We are also developing follow-on courses to provide Continuing Professional Development for the pharmaceutical GMP auditor. These will range from in-depth training courses from our Pharmaceutical Quality and GMP programs to our 'How to Audit...' workshops, providing essential guidance on auditing specific products, processes and activities

Different types of auditor certification

If you successfully complete the IRCA Pharmaceutical Auditor and Lead Auditor course this satisfies the training element for:

- Pharmaceutical provisional internal auditor
- Internal auditor
- Provisional auditor

For more information on these courses or on becoming a Pharmaceutical Auditor please contact Gill Gibbeson at gg@nsf-dba.com

g ues



- Auditor
- Lead auditor or principal auditor

Applicants then need to additionally demonstrate the desired level of education, work experience and post-course practical audit experience to meet the appropriate pharmaceutical auditor grade requirements as defined in IRCA document 1000. Check our website (www.nsf-dba.com) for links to relevant IRCA documents.

What prior training or experience do I need to attend the course?

As this is a pharmaceutical industry-based course, a good working knowledge of pharmaceutical GMP is important – we teach you how to audit against GMP requirements; we don't teach you the principles of GMP. Ideally, therefore, we believe the trainee auditor should attend a comprehensive GMP training course (the NSF-DBA GMP course is designed to complement and lead delegates into the course) or have about two years' experience working in a GMP environment prior to attending.

What is in it for me?

Becoming a certified pharmaceutical auditor or internal auditor provides you with the skills to perform professional and insightful audits which will benefit your company and its patients and will satisfy the increasing demands of the regulators that auditors be appropriately trained. But more than this, there is evidence that the qualification can be important in your career development...

- Some professional GMP auditors go on to lead audit teams and departments
- Some professional GMP auditors go on to train as Quality Professionals/QPs using the knowledge and experience gained in auditing in their everyday decision making process
- Some professional GMP auditors go on to become senior leaders in their companies



Mike Halliday
NSF-DBA tutor



Neil Wilkinson
NSF-DBA tutor



David Selby
NSF-DBA tutor



Liz Allanson
NSF-DBA tutor

Pharmaceutical GMP Lead Auditor,

Quality Leadership Program (QLP) Update

The NSF-DBA QLP, a 12-module program over two years, modeled on the content of our Qualified Person's (QP) training in Europe, will complete Series 2 in the US this Fall as a public course. <http://nsf-dba.com/pages/qlp-training>

We have an excellent delegate group once again and interest in the program continues to get an enthusiastic response from delegates currently enrolled, and also from people inquiring about the future program. We realize that the US industry, whilst not having the same legal requirement for QPs as Europe, recognizes that the education program given to QPs by NSF-DBA is highly valued (as evidenced by the number of US-based firms that run in-house Quality Professional programs with us).

We strongly believe there is an industry need for a publicly available program in the US, and before we move forward with our next program we wish to seek the views of our customer base on exactly what the US pharma-biotech industry needs are in the area of the Pharmaceutical Quality Professional, so we can evolve and continually improve our program.

To this aim we are currently conducting a detailed survey about this program with industry colleagues and key stakeholders.

Our goal is to ensure that this program, while already very well received by those who have attended, will have a lasting and positive impact on the US industry. Whilst we see great value in the core elements of the QP program we don't necessarily wish to simply copy the NSF-DBA Qualified Person's (<http://nsf-dba.com/pages/qp-training>) training model for the US market. If you haven't received the survey by August 1 and wish to provide us with your input, please send an email to jmorris@nsf-dba.com. If you completed the survey, thank you for taking the time to do so. We definitely value your input!

Medical Device Corporate Auditing

Corporate regulatory audits are a fundamental business monitoring and measurement tool that provide an organization with the necessary early warning systems to identify and manage a whole series of business critical situations.

Whether you are a large, global, multi-product company or a small/medium enterprise, a well designed, implemented and managed corporate audit program can also provide the tools to further support an organization's values, policies, objectives and continual improvement programs.

Here are a few tips from our Medical Devices team to ensure that your corporate audit is successful:

Ensure that your programs interact with your risk management activities so that you can monitor trends, weaknesses and vulnerabilities and adapt your audit focus. Furthermore, ensure you incorporate your corporate audit findings into these risk registers.

Have self-assessment tools and checklists with data collection and analysis tools capable of providing you with a drill-down into current risks and vulnerabilities within your processes.

NSF-DBA has created a whole series of questionnaires and tools that enable you to prepare for development projects, manufacturing processes, analytical and quality activities as well as plant and equipment specific questions. Examples include our Orthopedic Product Risk Management checklist, our Sterile Medical Device Sterilization Process checklist and our Process Validation checklist.

Utilize these checklists as self-assessment tools so that you can quickly encourage your design authorities, manufacturing facilities and sales and distribution affiliates to think about what they should have in their processes and enable them to declare whether they comply (or not!).

Assign competency codes to your audit engagements to ensure you have the right people on the audit team, eg expertise in wound care, clinical investigation planning, microbiology, etc.

Create excellent audit teams. Well trained auditors will plan, conduct and conclude effective audit engagements and provide maximum benefit to the organization.

Ensure that each audit engagement has a clear scope so everyone understands the purpose and intent as well as the likely outcomes. Corporate audits should look at identifying vulnerabilities and risks as well as identifying best practices which can be shared. Don't fall into the trap of just being a mock FDA inspector or a mock notified body auditor! (It may not always be what your board needs...)

Be prepared – have intelligence processes that furnish the team with the necessary information about new risks, new regulations, new process failures, new product failures BEFORE THE AUDIT! Go to the FDA warning letter database and review the regulatory failures and their reasons so that you can see whether your processes are vulnerable to the same findings.

NSF-DBA Medical Devices is capable of providing audit monographs to prepare your auditors for various device types so that you know the most common risks, issues, process vulnerabilities and technical expectations within the development, manufacture, supply and post-market surveillance activities.

Have a desktop review from experts before, during and after the audits. Have a specialist internal or external (for example NSF-DBA) expert review your audit program and plan. With Biocompatibility, Microbiology, Sterilization, Mechanical Engineering, Human Factors, Clinical Investigation, Packaging, Electronics and Software experts to hand, we are sure to furnish your corporate audit program with the necessary advice and information to reassure you and prepare you for your audit.

Ask the experts! At NSF-DBA we have medical device auditors with a combined audit experience of over 200 years. We are able to ensure that your corporate auditing program is effective, focused and value for money. To learn more visit nsf-dba.com/pages/medical-devices