The Journal

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The Auditing Issue

NSF DBA℠

Part of NSF Health Sciences

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welcome

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VP Global
Health Sciences
NSF International

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

- NSF-DBA Consultant and former Manager of MHRA'S GMP inspectors, Liz Allanson, tells you the top 10 things that regulatory inspectors look for when inspecting **your** audit programme
- We provide sound, practical advice on how to improve Medical Device corporate audit programmes
- We explain how adopting the principles of HACCP 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
- But 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. Sarah Richardson and Gill Gibbeson describe the challenges and rewards that come from organising and executing worldwide contract audits for multi-national and small start-up companies, including Daiichi-Sankyo

All your favourite sections are here as ever – the regulatory update and the full listing of upcoming courses. We hope you find it a good read!

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.

Bob Pietrowski
VP Global Health Sciences
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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 analysing 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 programme, and in particular to minimise 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 critical control points (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

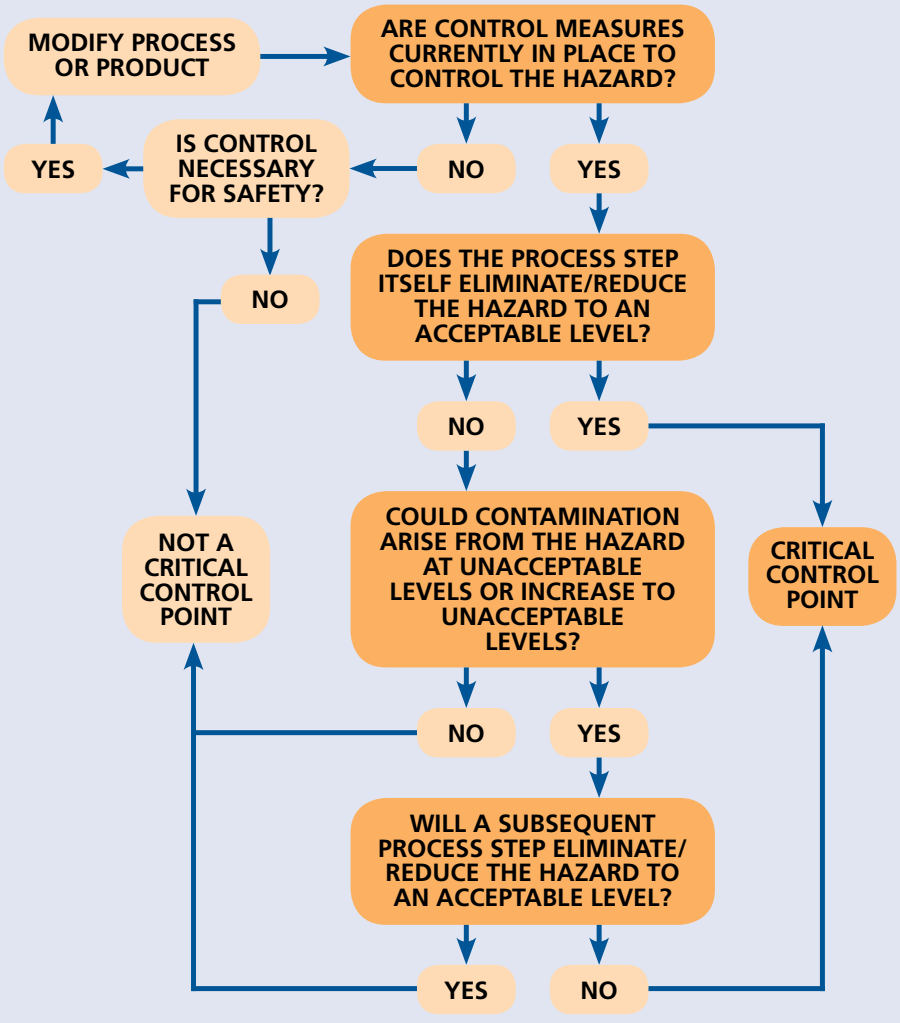
The first and most important step in any risk assessment exercise is ensuring that you really understand the product and the process. The product should be understood in terms of what it is, how it is used and, in particular, its critical quality attributes – those attributes which are essential to the 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 analyse 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 indicate 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 analysing 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 recognise 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 programme 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!

The Face of Contract

Mike Halliday, Partner, speaks about the contract au

We at NSF-DBA are very pleased to provide a contract auditing service using a team of over 20 auditors based in the UK, mainland Europe, North America and Asia Pacific. Some are ex-regulators and all have tremendous experience in auditing within the pharma industry and its suppliers and contractors.

Each year we conduct over 100 contract audits, mostly for 3 key clients who use our services regularly to supplement their own audit capability.

Feedback from clients is exceptionally good, noting the support and clear key point of contact within NSF-DBA. That's great news for us, being one of the areas we try to continuously improve. When a client expresses an interest in multiple audits on an ongoing basis we assign a member of the client administration team to be a key point of contact. We try where possible to ensure continuity by using auditors from a sub-group to service the client's needs. We encourage auditor training in the client's audit systems and procedures as well as getting to know client 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 role of the auditor
2. Assigned key points of contact from both sides
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 client parties
6. Use of highly experienced and trained auditors
7. Clear and open communication in setting audit programmes and tasks

Challenges do crop up occasionally but are usually accommodated – from short notice audits, auditee cancellations, surprise regulatory inspections during a contract 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 coordination as well as the pool of capable and competent auditors.

Daiichi-Sankyo

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."

> *"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."*

Kenta Goto
Associate Director,
Global QA of Daiichi Sankyo

For more information about the contract auditing service off

Auditing at NSF-DBA

uditing service offered by NSF-DBA

> *We have been working with Daiichi Sankyo for nearly a year now and during that time I have been responsible for coordinating 6 audits for them – and we are currently planning the 7th!*

Sarah Richardson
NSF-DBA

Sarah Richardson is the key point of contact for Daiichi Sankyo and describes below the work that she has been completing with them…

"We have been working with Daiichi Sankyo for nearly a year now and during that time I have been responsible for coordinating 6 audits for them – and we are currently planning the 7th!

My role covers the whole of the audit process. The client sends in a request for an audit with their preferred dates and I liaise with the auditing team to schedule it with the most suitable auditor. We have a very large team of auditors who are based worldwide so 99% of the time we are able to meet the client's preferred dates. Having such a huge resource of auditors available means that if audit requests are very last minute we are able to fulfil them and still provide the excellent service that our clients come to expect of NSF-DBA.

Whilst working with Daiichi Sankyo, I have arranged for auditors to go far and wide – from London to Brazil, Ireland to India – and have coordinated each audit, from the initial scheduling, to the report, to the CAPA review. Every audit completed by NSF-DBA for every client that we work with is different and we treat it that way. The service that you receive from me and my colleagues is truly personalised and we work with you to maintain the flexible service and excellent business relationship that Kenta Goto of Daiichi Sankyo speaks about."

Gill Gibbeson has been working closely with one of our clients for whom we have been providing a contract auditing service for the last 4 years…

"Over the past year or so I have had the challenge of arranging approximately 65 audits in various parts of the world including India, North Africa, the Middle East and Siberia and many in Europe. I am fortunate to work with a team of intrepid and highly experienced auditors who are willing to travel to some inaccessible places and catch a plane at very short notice, which does make my job easier and allows us to provide an excellent service to our client.

We put together a team of very experienced auditors, who are then given the opportunity to meet our client and to receive training in their procedures and documentation. Our client values the opportunity of meeting our team as this helps to build up a rapport between us, something which is very valuable when providing this type of service. Once the team has been approved my contact provides me with a schedule of the audits required. These cover API, third party and contract manufacturer audits on a variety of dosage forms. I do also get requests for urgent short notice audits and, as a team, we do our very best to fulfil these requests.

I work with my client contact to allocate the most suitably experienced auditor to each audit and then I deal with all the arrangements, liaising with the various sites to be audited, arranging travel, requesting necessary documentation etc. Once the audits are completed I ensure that the reports and supporting documentation are with our client as soon as possible.

It has been a very successful partnership with excellent relationships being built between me, our auditors and our client."

> *Over the past year or so I have had the challenge of arranging approximately 65 audits in various parts of the world including India, North Africa, the Middle East and Siberia and many in Europe.*

Gill Gibbeson
NSF-DBA

For legal reasons some of our clients prefer not to be identified and we have been unable to name them in the article.

ered by NSF-DBA contact Mike Halliday at **mch@nsf-dba.com**

Forthcoming Courses

What's planned for June – September 2013

Risk-Based Decision Making in Sterile Products Manufacture

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

10 – 13 June

Manufacturing sterile products is easy – until things go wrong! When things go wrong catastrophically, decision making is relatively straightforward. However, things are rarely so 'black and white'. The biggest challenge facing anyone in sterile products manufacture is to deal with the 'grey area' problems which arise almost daily. This unique course is designed to help YOU do just that!

Course Fee: £2400.00 plus VAT

Modern Approaches to Process Validation

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

10 – 13 June

This course will focus on the modern approaches to process validation, including the design of facilities and the qualification of equipment and utilities. It will provide practical advice on implementing the 2011 FDA guidance and the 2012 draft EU CHMP guidance on process validation. We will explain how process validation must link to patients' needs and the changing regulatory requirements. We will explain how tools, such as risk management, statistics and change management, are used to accomplish this. We will show how this modern approach can add real value to your business and provide better protection to patients.

Course Fee: £2100.00 plus VAT

GMP for Clinical Trials Manufacture and Supply

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

10 – 13 June

The implementation of Directive 2001/20/EC has brought profound changes to the way clinical trials are conducted in the EU and equally important changes to the way IMPs are manufactured and controlled.

- What 'standard' of GMP is appropriate at the various clinical trial phases?
- Validation – how much, how soon?
- What exactly is a Product Specification File?
- In the case of split manufacture, whose QP should release?
- What is the role of the QP when IMPs are imported?
- Where does GMP end and GCP begin?
- How do QPs deal with comparators?

All of these questions and many more will be addressed in this intensive four-day training course.

Course Fee: £2400.00 plus VAT

Active Pharmaceutical Ingredients

Durham Marriott Hotel Royal County, Durham, UK

17 – 20 June

The quality of a medicine depends in no small part on the quality of its ingredients, and in particular the active. Thus, the QP and other key professionals in dosage form manufacture must have a thorough understanding of how the manufacture and control of the active and its supply chain may influence the fitness for use of the finished product. This is recognised by the regulators, especially in Europe where the adoption of Directive 2004/27/EC has put the responsibility for assuring the quality of the active firmly on the shoulders of the dosage form manufacturer, with certain expectations specifically for the QP. This course is designed to provide you with the knowledge and understanding to fulfil your responsibilities.

Course Fee: £2560.00 plus VAT (First booking)
£2048.00 plus VAT (Additional bookings from same site)

Good Distribution Practice

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

11 – 12 July

Maintenance of the cold chain is essential for products such as vaccines and other biopharmaceuticals. The effectiveness of the cold chain is a major area of concern during regulatory inspections and adverse inspection observations are common.

Regulators have now broadened the emphasis of temperature control to include all products where defined temperature bands exist, including 'room temperature' or 'ambient temperature' products. This course is designed to help you avoid regulatory criticism and to assure the quality of your products from factory to patient.

Course Fee: £1400.00 plus VAT

The Role & Professional Duties of the Qualified Person

York Marriott Hotel, York, UK

22 – 25 July

This course provides essential guidance, not just on the legal duties of the Qualified Person, but also on how the QP should organise themselves, their colleagues and the quality system to ensure that they fulfil their duties with skill and professionalism. We include a review of the UK QP assessment process and a simulated QP assessment interview. This course is essential for the new QP, but is also a great refresher for the QP looking to bring about change in their organisation.

Course Fee: £2560.00 plus VAT (First booking)
£2048.00 plus VAT (Additional bookings from same site)

Visit www.nsf-dba.com for more information on all our courses

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.

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Deviation and CAPA Systems – Best Practices

Amsterdam Marriott Hotel, Amsterdam, The Netherlands

16 – 17 September

Your Deviation and CAPA system is a crucial part of your quality system. It should protect your patients against poor quality medicines and drive continuous quality improvement by stopping inefficient, wasteful and often dangerous practices. This course is not just about how to conduct a root cause investigation. It will provide you with proven tools and techniques to simplify your deviation management system and improve the effectiveness of your CAPA system, saving you time and money whilst improving regulatory compliance.

Course Fee: £1400.00 plus VAT

Human Error Prevention

Amsterdam Marriott Hotel, Amsterdam, The Netherlands

18 – 20 September

Human error is often thought to be the cause of many product recalls, customer complaints, batch rejects, deviations and adverse audit findings. In most cases, however, human error is not the root cause, just a convenient excuse. The good news is that such costly and risky mistakes can be prevented. The objective of this course is simple – to provide you with very practical advice and guidance on how to significantly reduce so called 'human error'. Error reduction will potentially save you £millions and improve your regulatory compliance. Don't allow yourself to fall behind your competitors!

Course Fee: £1800.00 plus VAT

Mathematics & Statistics

York Marriott Hotel, York, UK

16 – 19 September

Perhaps the only statistics course aimed directly at the pharmaceutical industry! Given the increasing importance of PAT, QbD, trending of in-process data and analysis of data for product reviews, all pharmaceutical professionals need to ensure that their understanding of, and ability to use, statistical routines is well developed.

Course Fee: £2560.00 plus VAT (First booking)
£2048.00 plus VAT (Additional bookings from same site)

Free Seminar for Prospective QPs and Sponsors

York Marriott Hotel, York, UK

17 September

Interested in becoming a QP? Why not attend this free seminar to find out more about what we can offer? Learn about what is required to become a QP and see one of our training modules in action.

This seminar is open to sponsors and prospective sponsors of candidates currently studying or planning to study with NSF-DBA or any other training provider.

Course Fee: FREE

Effective Pharmaceutical Audits and Self-Inspections

York Marriott Hotel, York, UK

23 – 27 September

Faced with industry and regulatory pressure, NSF-DBA was actively encouraged to successfully redesign an existing, popular course and reintroduce it with this, the first International Pharmaceutical Quality Management Systems Auditor/Lead Auditor certification. The course, certified by IRCA (www.irca.org), the world's largest international certification body for auditors of quality management systems, meets the requirements of the new Pharmaceutical Quality Management System. The course has been specifically designed to provide delegates with education, understanding and development to meet today's pharmaceutical pressures, including the auditor skills and toolbox of auditing techniques needed by the successful pharmaceutical lead auditor. Given the course focus, content and delivery of EudraLex Volume 4 Chapters 1 to 9, ICH Q10 as the combined QMS, the team at NSF-DBA sees this as the first truly certified GMP auditor training course available globally today.

Course Fee: £2600.00 plus VAT

Risk-Based Decision Making for Quality Professionals and QPs

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

24 – 25 September

The toughest task facing any Qualified Person or Quality Professional is to take decisions regarding the suitability for release of materials when things go wrong. This course is designed to provide you with proven risk management techniques which will help you to make sound, risk-based decisions which benefit the patient, your company and you! Packed with real-life scenarios for you to work on, this course is not to be missed.

Course Fee: £1400.00 plus VAT

Get in touch now to book your place on any of these courses
Call us on: +44 (0) 1751 432 999 or email: courses@nsf-dba.com

Liz Allanson, NSF-DBA Consultant, Tells Us The Top 10 Things Regulators Look For

There is an increased regulatory focus on audits within the pharmaceutical industry as a result of cases of adulterated materials, eg heparin, and the increasing threat of counterfeit medicines.

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 Qualified Persons (QPs), are supported by thorough and reliable audit reports. 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!!

3. Competent auditors

An audit is only as good as the auditor that 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.

4. Relevant audit standards applied

Audit evidence must demonstrate that the correct standards have been applied as audit criteria.

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 and supplier audit reports are being routinely reviewed by inspectors. The detail should support the final conclusion or recommendation.

8. Good use of audit information

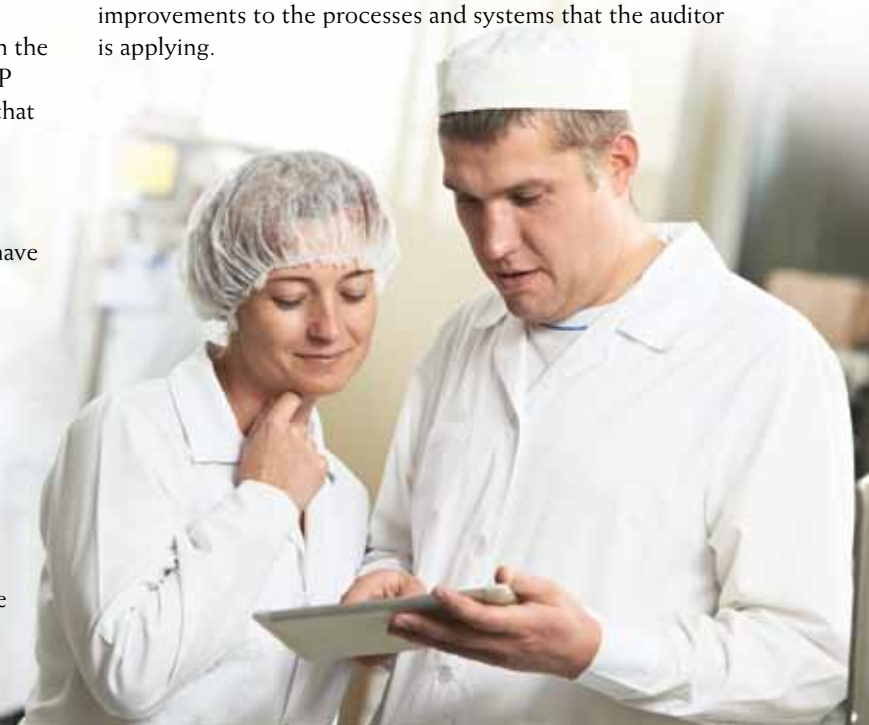
A good audit system will have formal mechanisms for sharing audit reports and findings with others who can then make informed decisions and use the data to improve other aspects of the business.

9. Follow-up

There should be a formal procedure for following up on the audit observations. Confirmation that deficiencies have been rectified and CAPA plans implemented should be available.

10. Continual improvement of audit systems and of systems audited

All audits should produce improvements and this includes improvements to the processes and systems that the auditor is applying.



Regulatory Update

EU Pharma News

The Falsified Medicines Directive (FMD)

Implications for Importation of APIs

The FMD (Directive 2011/62/EU) requires that from 2 July 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 summarised by the EC Pharmaceutical Committee at a meeting on 27 March 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 2 July 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 2 July 2013

More Questions and Answers

On 5 April 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

Regulatory Update

ACAA with Israel

An 'Agreement on Conformity Assessment and Acceptance of Industrial Products' (ACAA) between the EU and Israel came into effect on 4 January 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 7 March 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 7 September 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 authorised for sale within the EU. These records must be kept for a minimum of five years.

NSF-DBA will be holding a two-day course entitled 'Good Distribution Practice' in Manchester on 11 and 12 July. We will provide you with the up-to-date situation and give you our opinion on how to comply with the latest regulations and guidance in a practical and cost-effective way. See our website www.nsf-dba.com for more details.

FDA News

Tablet Scoring: Nomenclature, Labelling and Data for Evaluation

In March 2013 the FDA issued final Guidance for Industry on Tablet Scoring: Nomenclature, Labelling 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 labelling 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 labelling 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 criticised by organisations 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 authorisation 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 authorised 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 authorisations 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 authorisation 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 Trainin – The Story Contin

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 issuing of ICH Q10 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 of key elements of ICH Q10 into EudraLex GMP guides we are in the process of evolving our PQMS certified auditor course further and retitling the certification as a **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.

While there will always be a need for recognition of other standards within the suppliers to our industry, the prime qualification and standard we should expect of our auditors to satisfy ourselves, our patients and our regulators should be GMP. This will bring challenges to our suppliers and to our auditors to ensure that appropriate application of GMP is applied. We at NSF-DBA are offering additional auditor training to help with some of these difficult challenges (see our '*How to Audit*' programme).

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 GMP certification.

Our course, currently entitled '*Effective Pharmaceutical Audits and Self-Inspections*', which leads to IRCA certification as a Pharmaceutical Quality Management System auditor will be rebranded in due course once the course criteria are finalised 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 suppliers to our industry 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 uses GMP as an audit standard and not ISO 9000 series and as such…

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 from the UK's regulatory agency. 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
- 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
- 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 MSc programme 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
- Auditor
- Lead auditor or principal auditor

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

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Applicants 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; the course doesn'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 this course.

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 QPs using the knowledge and experience gained in auditing in their everyday QP decision making process
- Some professional GMP auditors go on to become leaders in their companies
- For those wanting a Masters Degree level GMP course we do offer a Pharmaceutical Quality and GMP course in conjunction with the University of Strathclyde

Liz Allanson
NSF-DBA tutor

Mike Halliday
NSF-DBA tutor

David Selby
NSF-DBA tutor

Peter Monger
NSF-DBA tutor

rmaceutical GMP Lead Auditor,

NSF DBA℠

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Leadership | Change Agents
Quality and Technical Professionals

Medical Device Corporate Auditing

Corporate regulatory audits are a fundamental business monitoring and measurement tool that provide an organisation 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 programme can also provide the tools to further support an organisation's values, policies, objectives and continual improvement programmes.

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

Ensure that your programmes 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 Orthopaedic Product Risk Management checklist, our Sterile Medical Device Sterilisation Process checklist and our Process Validation checklist.

Utilise 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 organisation.

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 programme and plan. With Biocompatibility, Microbiology, Sterilisation, Mechanical Engineering, Human Factors, Clinical Investigation, Packaging, Electronics and Software experts to hand, we are sure to furnish your corporate audit programme 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 programme is effective, focused and value for money. To learn more visit **nsf-dba.com/pages/medical-devices**

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